“Men who are occupied in the restoration of health to other men, by the joint exertion of skill and humanity, are above all the great of the earth. They even partake of divinity, since to preserve and renew is almost as noble as to create.”

– Voltaire
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Front cover
Electron micrograph showing the interior of an islet of Langerhans of the pancreas, with cells in different stages of activity

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Editorial Correspondence
Dr. Jayanta K. Panda, Editor
Asst. Professor, Medicine, SCB Medical College
Mob.: 9437028282, Email: drjayantpanda@gmail.com
IMA House, Medical Road, Ranihat, Cuttack - 753007, Orissa
Ph.: 0671-2413060, 2121125, Email: imaoorissa@imaorissa.com, ima@ortel.net Website: www.imaodish.com
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Dr. Jayanta K. Panda
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Ph : 0671-2413060, 2121125,
Email : imaorissa@imaorissa.com, ima@ortel.net,
Website : www.imaodisha.com

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Dr. Jayanta K. Panda, Hon Editor, OMJ
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DIABETES: CHALLENGE OF THE MILLENNIUM

History of Diabetes is history of mankind, and we are trying to fight it out from time immemorial, from detecting ants in urine, discovering insulin to promising β-cell transplantation. Inspite, about 285 million people, worldwide, 51 million in our country, have Diabetes now, with an increasing trend in prevalence, making it one of the most common non communicable disease globally. The significant rise is observed in regions with rapidly developing economics and urbanization and we Indians are more vulnerable to be worse sufferers in future days alongwith our Chinese neighbors.

Not only the rising aging population in most countries, has contributed significantly to this rise in prevalence, but the age of onset of Diabetes is decreasing giving rise to an increasing proportion of young people being affected by the disease, may be mostly due to westernized food & life style.

Diabetes is associated with approximately two fold increase in mortality & morbidity associated with microvascular and macrovascular complications. It accounts for 75-90% of excess CAD risk and enhances the effects of other CV risk factors. Upto 50% of older patients with type-2 Diabetes are at risk of foot problems and upto 85% of lower limb amputations are preceded by foot ulcers, diabetes being the most common cause of non traumatic amputation. Prevalence of erectile dysfunction in men with diabetes is about 35-50%. One third patients of Type-2 Diabetes and two third patients of Type-1 Diabetes develop sight threatening diabetic retinopathy and require laser during their life time. Again one third of people with diabetes will progress to proteinuria and be at high risk of end stage renal disease (ESRD) and will be affected by Distal Symmetrical Sensorimotor Polyneuropathy.

So let us equip ourselves with knowledge, arms and ammunitions for intervening the greatest challenge of the millennium to Medical Science – The Diabetes & loose the battle to China to be the Diabetes Capital of the world.

Jag带"rata Kumar Panda
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– Hon Editor.
Human leukocyte antigens (HLAs) are the glycoproteins residing on the surface of almost every cell in the body which is to serve as recognition molecules in the initiation of an immune response. It refers to the major histocompatibility complex (MHC) in humans, first observed by Jean Dausset in 1952. There are six major loci on the chromosome No.6, where the genes that produce HLA antigens are inherited. These are mainly HLA- A,B,C encode Class I MHC molecules and HLA – DR, DQ, DP encode Class II MHC molecules. The HLA genes are most polymorphic in the human genome with a large number of allelic variants at each locus.

There are a few methods for determining individual HLA polymorphism, otherwise called ‘HLA typing’. Over 2000 alleles of class I and II of HLA systems are known till now. Methods for HLA typing are either based on detection of specific anti-HLA antibodies to HLA antigens (serological typing) or DNA based method (Molecular typing). Serological typing is conventionally done using live lymphocytes (Microlymphocytotoxic test). This has been replaced by Molecular method like sequence specific DNA typing using polymerase chain reaction (PCR), which is economical, rapid, precise and technically simple.

While HLA typing is important for organ transplantation, presently it is also worked out for genetic susceptibility to many autoimmune diseases. People with certain HLA antigens are more likely to develop definite autoimmune disease, type1 diabetes mellitus (T1DM) being one of them. Consequently HLA typing, particularly DNA typing, has led to some advancement in the diagnosis of T1DM. In T1DM there occurs destruction of the insulin producing β cells of the pancreas resulting in deficiency of insulin, mostly from an early age.

The HLA region is the most important genetic contributor to T1DM susceptibility. Human MHC gene cluster occupies a region on the short arm of chromosome 6 in its distal part. Studies on the structural organization of MHC molecules revealed a total of 224 gene out of which 128 are assumed to be functional and 96 are nonfunctional. These genes make the proteins which are important in immune system.

Auto-immunity of T1DM begins with an inflammatory process probably of infectious or environmental origin. The inflammatory cells in the pancreas produce cytokines like gamma interferon, tumor necrosis factor-α (TNF-α) and Interleukin-1 which induce the expression of HLA type-II molecules on pancreatic β cells together with lymphocytic infiltration. Class II HLA expressed on the pancreatic cells may function as antigen presenting cells (APC) for their own cellular proteins which are recognized by auto-reactive T and B cells. Subsequently it leads to the destruction of β cells through different processes including apoptosis. This hypothesis says that the inflammatory process mostly starts with a viral infection or environmental trauma. Although it is not exactly proved in humans, circumstantial evidences with certain viral infections like mumps, cytomegalovirus, rubella and influenza virus favour this hypothesis.

The most important gene in diabetes is the DR molecule on HLA inherited from both parents. Two forms of DR, designated DR3 and DR4, are most important. In general population, 50% of people have DR3 or DR4 and 1% have both. In comparison, T1 DM patients have 95% of DR3 or DR4 and 30% have both. Although both put a person at risk for developing the disease, there are some differences as follows:-
(1) Diabetics who have inherited only DR3 develop the disease at an older age which tend to have antibodies against β cells of pancreas (not against insulin). These people are also likely to develop thyroid autoimmune disease.

(2) Diabetics who inherit only DR4 tend to develop T1DM earlier in life and have immune reaction against pancreatic insulin.

(3) Diabetics who inherit both DR3 and DR4 develop the disease at a very young age and have the highest level of antibodies against insulin.

Apart from DR3 and DR4 which are associated with significant risk, DR1 and DR5 also carry some amount of risk. On the other hand DR2, DR6 and DR7 are said to be protective against T1 DM.

Similarly HLAs involved like HLA DQA1 and HLA DQB1 loci are more strongly associated with T1DM in 40% of juvenile diabetics as reported in the USA. Again some alleles of HLA DQA1 and HLA DQB2 are found to be protective against Type 1 DM. Likewise HLA DPB1 allele is also seen to be associated with the same disease.

It has also been seen that HLA DR4 is associated with Type-2 DM and may become a marker for type II DM susceptibility in near future.

Among the HLA associated autoimmune diseases Type-1 DM remains the most intensely studied and the best example of MHC associated disease. Clearly the identification of all the genes involved in Type1 DM and their pathological roles have the highest potential for future research. As many authors have shown that in addition to DR molecule, there is a significant association of DQ molecules (and DP molecule to some extent) in the context of the genetic make up of T1DM, it is necessary that further study be taken up in this field. The future work will require new approach and more advanced techniques for these purposes.

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For details contact:
Dr. P.N. Govindaraju
Organising Secretary, IMACON-2011
No.17, 3rd Temple Street, B / W 15th & 16th Cross,
Malleswaram, Bangalore 560003
Cell : 94480-80460, Ph. : 080-23363038 [R]
Diabetes and CAD: Siamese Twin

T.K. Mishra¹, Biswajit Das², Chhabi Satapathy², S.N. Routray¹, H.N. Mishra³

Introduction:

Globally, diabetes mellitus is a major threat to human health. The number of people with diabetes has increased alarmingly since 1985 and the rate of new cases is escalating. In 1985, an estimated 30 million people worldwide had diabetes; by 2003, it was estimated that approximately 194 million people had diabetes, and this figure is expected to rise to almost 350 million by 2025.(1)

Diabetes mellitus, whether type 1 or type 2, is a very strong risk factor for the development of coronary artery disease (CHD)(2). People with diabetes have an increased prevalence of atherosclerosis and coronary heart disease (CHD) and experience higher morbidity and mortality after acute coronary syndrome and myocardial infarction (MI) than people without diabetes.

Analysis of data collected for the Organization to Assess Strategies for Ischemic Syndromes (OASIS) Registry, showed that diabetes significantly increased all-cause death and the incidence of new MI, stroke, and heart failure during a 2-year mean follow-up in patients who were hospitalized for unstable angina or non-Q-wave MI.

Patients with diabetes have a two- to fourfold increase in the risk of coronary artery disease (CAD).(3) In the Multiple Risk Factor Intervention (MRFIT) study, for every age stratum, ethnic background, and risk factor level, men with diabetes had an absolute risk of CAD death more than three times higher than that in the nondiabetic cohort, even after adjustment for established risk factors.

In the general population, women experience relative protection from myocardial infarction and usually develop CAD approximately 10 years later than men. However, diabetes blunts the cardiovascular benefit of female gender. Diabetes increases the risk of death after myocardial infarction in women more than men.

In Finnish epidemiological survey patients with diabetes but without prior myocardial infarction had the same level of risk for subsequent acute coronary events as nondiabetics with a history of previous myocardial infarction. In GISSI-2 study of thrombolytic therapy in patients with myocardial infarction, diabetes increased the rate of death in men by 40 percent and women by 90 percent. The results of the Chennai Urban Population Study (CUPS) revealed that overall 11% of the total population studied had CAD. This is 10 times higher compared to that reported 40 years ago. 21.4% of the diabetic subjects and 14.9% of the subjects with impaired glucose tolerance had CAD compared to 9.1% among subjects with normal glucose tolerance.(4) The reason for the enhanced susceptibility for CAD among diabetic subjects is still not clear. However, cardiovascular risk factors have been shown to be more pronounced among diabetic subjects. Further, the diabetes-specific factors like hyperglycaemia, advanced glycation products, altered lipoproteins and hypercoagulation tends to partly explain the high risk for CAD.

In the past, at least part of the increased cardiovascular risk associated with diabetes resulted from a failure to apply standard clinical measures known to improve outcome following cardiovascular events in patients without diabetes. For example, patients with diabetes were frequently denied beta blockers post-MI because of concern that use of these drugs could mask hypoglycemia and compromise glycemic control. Recent evidence suggests that MI patients with diabetes may actually have a better
response to standard treatments than patients without diabetes.(5)

Traditional CHD risk factors such as hypertension, dyslipidemia, and excess weight and obesity cluster in patients with impaired glucose tolerance or diabetes. In addition to the traditional risk factors, a number of diabetes-specific risk factors contribute to the increased morbidity and mortality of CAD. For example, patients with diabetes have lipid-rich atherosclerotic plaque that is more vulnerable to rupture than plaque found in patients without diabetes.

**Pathophysiology**:

The spectrum of metabolic disturbances associated with diabetes and insulin resistance extends beyond hyperglycemia and includes dyslipidemia, hypercoagulability, and inflammation.

**Diabetic Metabolic and Vascular Dysfunction**

Diabetes causes metabolic abnormalities, including hyperglycemia, dyslipidemia, and insulin resistance, that disrupt normal arterial function and render arteries susceptible to atherosclerosis. It specifically alters the function of vascular endothelium and smooth muscle cells, as well as platelets, in ways that promote atherogenesis.

**Endothelial Dysfunction**

Diabetes impairs the vasodilator function of endothelial cells and decreases the bioavailability of nitric oxide (NO). Moreover, characteristic metabolic disturbances in diabetes, including hyperglycemia, increased free fatty acid concentrations, and insulin resistance, can individually decrease nitric oxide bioavailability and attenuate endothelial function. Endothelial dysfunction also occurs in healthy adult offspring of type 2 diabetic parents, suggesting an inheritable abnormality as well. Hyperglycemia decreases NO production from endothelial nitric oxide synthase (eNOS) and increases its degradation via generation of reactive oxygen species (ROS). Hyperglycemia triggers the production of ROS in vascular cells through enzymatic (protein kinase C and the [NADPH] oxidases) and nonenzymatic sources of oxidant stress (e.g., the formation of advanced glycation end products, AGEs). As oxidative stress increases, the eNOS cofactor tetrahydrobiopterin becomes oxidized and uncouples eNOS, which cause the enzyme to produce superoxide anion instead of NO. Superoxide anion quenches NO in a diffusion-limited reaction to produce peroxynitrite. Peroxynitrite inhibits prostacyclin synthase and endothelium-dependent hyperpolarizing factor activity. Similar to the effects of hyperglycemia, free fatty acids activate intracellular enzymatic oxidant sources, including protein kinase C, NADPH oxidases, and eNOS, yielding analogous increases in superoxide anion.

The excess adipose tissue that usually accompanies type 2 diabetes mellitus releases excess fatty acids. Reduced skeletal muscle uptake of free fatty acids further augments their plasma levels. Increased concentrations of free fatty acids exert deleterious actions in several areas. In healthy humans, free fatty acid infusion impairs endothelial function and the co-infusion of an antioxidant restores it. Free fatty acids also attenuate prostacyclin bioavailability by inhibiting prostacyclin synthase. Moreover, free fatty acids interfere with intracellular signaling pathways to cause not only muscle and visceral insulin resistance but also vascular insulin resistance.

In diabetes, hyperglycemia and increased free fatty acids increase the concentration in the cell of the metabolite diacylglycerol. Diacylglycerol, in turn, activates a family of enzymes known as protein kinase C (PKC), that perform key regulatory functions by phosphorylating proteins important in metabolic control. Recent work has implicated activation of the PKC family in cardiovascular complications of diabetes. Activation of PKC can inhibit the expression of eNOS, augment cytokine-induced tissue factor gene expression and procoagulant activity in human endothelial cells, and increase the production of proinflammatory cytokines, proliferation of vascular wall cells, and production of extracellular matrix macromolecules that accumulate during atherosclerotic lesion formation.

Studies have identified a novel potential mechanism for mediating impaired endothelial-dependent vasodilator function. An endogenous competitive
inhibitor of nitric oxide synthase, known as asymmetric dimethylarginine (ADMA), increases directly with insulin resistance in nondiabetic subjects and glycemic control in diabetes.(6)

Diabetes also disturbs vascular function through nonenzymatic glycation of macromolecules. Glycated proteins can form structures known as AGEs that cause the macromolecule to take on a brown hue, similar to burnt sugar. Numerous chemical studies have characterized the structure of AGEs. AGEs accumulate in the vessel wall and appear to contribute to the pathobiology of complications of diabetes, notably the accelerated vascular disease characteristic of this condition. The hypothesis is that AGE triggers atherosclerotic process by glycosylation of low density lipoproteins, which in turn undergo oxidation to form OX-LDL. The OX-LDL could trigger the expression of adhesion molecules for monocytes and thus lead to formation of foam cells, plaque progression and ultimately to clinical events like myocardial infarction. Cells have several surface receptors for AGE that mediate their biological effects. Exposure to AGE-modified proteins can elicit the production of inflammatory cytokines from vascular cells, cause impaired endothelium-dependent vasodilator function, and augment endothelial expression of various leukocyte adhesion molecules implicated in atherogenesis in vivo. One extensively characterized receptor for AGE is known as the receptor for advanced glycation end products, RAGE.[50] Studies have supported a functional role for RAGE in the development of experimental atherosclerosis.

Smooth Muscle Cell Migration and Proliferation:

Diabetes impairs vascular smooth muscle function and augments the production of vasoconstrictor mediators, including endothelin-1, which causes vascular smooth muscle growth and inflammation. Patients with type 2 diabetes have impaired vasodilation, possibly reflecting an abnormality in NO signal transduction. Moreover, diabetic patients have attenuated vasoconstriction to endothelin-1 and angiotensin. Diabetes may alter subcellular calcium distribution in smooth muscle cells, resulting in augmented vasoconstriction in response to norepinephrine and phenylephrine. Similar to endothelial cells, diabetes activates atherogenic mechanisms within vascular smooth muscle cells, including protein kinase C, RAGE, NF-kB and the production of oxidative stress. Diabetes heightens vascular smooth muscle cell migration in atherosclerotic lesions. Advanced atherosclerotic lesions have fewer vascular smooth muscle cells in diabetic patients than nondiabetic patients, possibly resulting in decreased resiliency of the fibrous cap and thereby increasing the risk of rupture and luminal thrombosis.

Platelet Dysfunction:

Platelet abnormalities occur in diabetes that parallel those found in endothelial cells, including activation of protein kinase C, decreased production of platelet-derived nitric oxide, and increased oxidative stress. Diabetes impairs platelet calcium homeostasis, which may contribute importantly to abnormal platelet activity, because calcium regulates platelet shape change, secretion, aggregation, and thromboxane formation. Moreover, platelets from patients with diabetes have increased expression of the adhesive glycoproteins (GP) Ib and GP IIb/IIIa.

Coagulation And Fibrinolysis:

Type 2 diabetes and its associated metabolic abnormalities favor an imbalance in the coagulation and fibrinolytic systems that support clot formation and stability. Type 2 diabetes increases plasminogen activator inhibitor type 1 (PAI-1) levels, impairing fibrinolytic capacity in atherosclerotic lesions. Moreover, diabetes increases the expression of tissue factor and levels of plasma coagulation factors, and decreases levels of endogenous anticoagulants. These various abnormalities may contribute to heightened susceptibility to the thrombotic complications of atherosclerosis.

Insulin Resistance:

Insulin resistance, and the compensatory increase in insulin secretion bring about a state of chronically increased insulin and glucose levels in the blood (hyperinsulinemia and hyperglycemia) and thus is a predecessor for diabetes.(7)
Although typically associated with impairments in skeletal muscle glucose uptake, many tissues in the diabetic patient demonstrate insulin resistance, including adipose, liver, and endothelial cells. Normal vascular function requires intact endothelial insulin signaling. Endothelial insulin resistance alters the pattern of activation of intracellular signaling pathways, favoring stimulation of mitogen-activated protein (MAP) kinases over phosphatidylinositol 3 (PI-3) kinase. Preferential activation of the MAP kinase pathway decreases nitric oxide production, increases endothelin production, stimulates the transcription of inflammatory genes, and increases the tendency to coagulation. Drug-induced improvement in insulin sensitivity reduces cytokine production and inflammatory transcription factor activation and increases nitric oxide bioavailability.

Although the euglycemic-insulin clamp remains the gold standard for the measurement of IR, simpler formulae are employed clinically to quantify IR using the Homeostasis Model Assessment (HOMA IR = Serum Insulin x Serum Glucose / 22.5).

In long-term followup of type 2 diabetic patients, insulin resistance was independently predictive of cardiovascular disease, with a 1-unit increase in HOMA-IR associated with a 5.4 percent increased risk of cardiovascular disease. The Insulin Resistance and Atherosclerosis Study (IRAS) also demonstrated the relationship between insulin resistance and atherosclerosis in the carotid artery.

**Adipocyte Biology and Inflammation:**

The adipocyte, long regarded as a storage depot for triglycerides, actually can generate substantial quantities of proinflammatory mediators, such as tumor necrosis factor-alpha (TNF-α). TNF-α can cause insulin resistance and can thus causally link adiposity to type 1 diabetes.

TNF-α and allied proinflammatory cytokines derived from the adipocyte can activate vascular endothelial and smooth muscle cells to provoke aspects of vascular dysfunction, discussed earlier. In this manner, adipocyte products can directly promote vascular dysfunction and hasten atherogenesis.

Adipocytes can also elaborate chemoattractant molecules, such as monocyte chemoattractant protein, which can recruit inflammatory leukocytes to enter adipose tissue. Once present, these “professional” phagocytes can amplify the production of proinflammatory mediators and perpetuate the inflammatory cycle related to insulin resistance and the vascular complications of diabetes mellitus. Some evidence has suggested that visceral adipose tissue plays a particularly pernicious role in perpetuating proinflammatory pathways by producing proportionately more of these mediators than subcutaneous adipose tissue. Waist circumference and visceral adiposity, as determined by imaging, correlate with C-reactive protein levels, indicating a relationship between inflammatory burden and central obesity.

**Inflammation:**

Through decreases in NO, increases in oxidative stress, AGE production, and activation of its receptor, and insulin resistance, diabetes increases vascular inflammation via the activation and nuclear translocation of intracellular transcription factors, NF-kB and activator protein-1 (AP-1). These factors cause the expression of genes responsible for producing chemokines, cytokines, leukocyte adhesion molecules, and proinflammatory mediators, such as TNF-α. Diabetes further aggravates plaque progression by causing endothelial cells to produce cytokines, which decrease collagen production by vascular smooth muscle cells, and to enhance endothelial cell production of matrix metalloproteinases and tissue factor. These changes may decrease the stability of the atherosclerotic plaque’s fibrous cap, increasing the likelihood and severity of plaque rupture.

**Therapeutic Options:**

Treatment of diabetes has evolved from a focus on hyperglycemia to a broader view encompassing all the metabolic disturbances associated with diabetes, including insulin resistance, dyslipidemia, hypertension, and platelet activation.

STENO-2 demonstrated that a comprehensive multifactorial strategy (including lifestyle and
pharmacologic interventions) to reduce cardiovascular risk in type 2 diabetic patients with microalbuminuria was highly effective (hazard ratio: 0.47; 95 percent confidence interval: 0.24 to 0.73) when compared to usual care after a mean time of 7.8 years. The approach included targets of HbA1c less than 6.5 percent, blood pressure less than 130/80 mmHg, total cholesterol less than 175 mg/dL, and triglycerides below 150 mg/dL. Patients were prescribed aspirin and an ACE inhibitor or ARB. This study validates the multidisciplinary approach to the cardiovascular care of the diabetic patient.(9)

**Life Style Modification**:

Improvements in each dysmetabolic component of diabetes may be acquired through healthy modifications in life style. In the Diabetes Prevention Program, 3324 subjects with impaired glucose tolerance were randomized to intensive life style adjustments or standard life style and placebo or metformin. Both intensive life style changes and metformin significantly reduced the rate of diabetes development by 31 and 58 percent, respectively, in comparison with placebo.(10)

Weight loss is an important therapeutic strategy in all overweight or obese individuals who have type 2 diabetes or are at risk for developing diabetes. The primary approach for achieving weight loss, in the vast majority of cases, is therapeutic lifestyle change, which includes a reduction in energy intake and an increase in physical activity. Physical activity is an important component of a comprehensive weight management program. Regular moderate-intensity physical activity enhances long-term weight maintenance. Regular activity also improves insulin sensitivity, glycemic control, and selected risk factors for cardiovascular disease (i.e., hypertension and dyslipidemia), and increased aerobic fitness decreases the risk of CAD.

Initial physical activity recommendations should be modest, based on the patient’s willingness and ability, gradually increasing the duration and frequency to 30 to 45 minutes of moderate aerobic activity, 3 to 5 days per week, when possible. Greater activity levels of at least 1 hour per day of moderate (walking) or 30 minutes per day of vigorous (jogging) activity may be needed to achieve successful long-term weight loss. The American College of Sports Medicine now recommends resistance training be included in fitness programs for adults with type 2 diabetes.

**Pharmacological Therapy**

**Prevention of Diabetes**:

Recent clinical trials have demonstrated the potential of pharmacological therapy to decrease the frequency of progression to type 2 diabetes in patients with insulin resistance. The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study showed reduced rate of diabetes or death by 60 percent from 26 to 11.6 percent with rosiglitazone compared to placebo.(11)

**Dysglycemia Management**:

Hyperglycemia, a fundamental component of diabetes, adversely affects vascular function and directly correlates with cardiovascular events. In the United Kingdom Prospective Diabetes Study (UKPDS), hemoglobin A1c levels above 6.2 % indicated an increased risk of macrovascular disease. For each 1 percent elevation in hemoglobin A1c, CAD risk increased by 11%. A meta-analysis of almost 100,000 diabetic patients found that increases in plasma glucose concentration correlated with augmented cardiovascular risk, beginning with glucose concentrations below the diabetic threshold.

Several clinical trials have sought to determine whether intensive treatment of blood glucose levels can reduce the risk of CHD associated with diabetes. Large, adequately powered studies, such as UKPDS, have shown a nonsignificant trend in favor of intensive blood glucose control in terms of reduction of MI. Patients entered into the study had a low background prevalence of CAD and a low rate of CAD risk factors. In the Diabetes Control and Complications Trial (DCCT), microvascular endpoints were improved in the intensive therapy arm. There was also a trend for a reduced rate of myocardial infarction in the group receiving intensive blood glucose control.
data have supported the notion that tight glycemic control may decrease the rate of cardiovascular morbidity and mortality.

The American Heart Association and the American Diabetes Association have come to consensus for goals of targets. The HbA1c goal for patients in general is an A1c goal of <7 percent. The American College of Clinical Endocrinology goal is an A1c of <6.5 percent. However, the ideal A1c goal for the individual patient is an A1c as close to normal (<6 percent) as possible without significant hypoglycemia.

**Dyslipidemia:**

Even though patients with diabetes typically have LDL cholesterol levels in the average range, they often have elevated triglyceride and decreased HDL cholesterol levels and small dense LDL particles. Increased delivery of free fatty acids to the liver caused by adipose efflux and impaired skeletal muscle uptake increases hepatic production of very low-density lipoprotein (VLDL) and cholesteryl ester synthesis. Overproduction of triglyceride-rich lipoproteins and impaired clearance by lipoprotein lipase lead to hypertriglyceridemia in diabetics.

Life style modification should be the first step in management of dyslipidemia in those with diabetes and the metabolic syndrome, as in other populations. Each component of diabetic dysmetabolism improves with weight loss, exercise, and dietary modification. Large clinical trials have demonstrated the benefits of pharmacological intervention. Lipid-lowering therapy, particularly with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins, reduces cardiovascular risk more in diabetic than nondiabetic subjects. Fibric acid derivatives address particularly the increased triglyceride and decreased HDL concentrations characteristic of diabetic dyslipidemia. These agents may have value as second-lipid agents in diabetic patients with persistently elevated triglyceride levels and low HDL. Combinations of statins and fibrates, particularly gemfibrozil, warrant careful monitoring for muscle injury. Despite concern over worsening glycemic control, nicotinic acid therapy in diabetic persons can increase HDL levels.

**Hypertension:**

Hypertension and insulin resistance frequently occur together as part of the dysmetabolic syndrome. The addition of hypertension to the clinical picture of diabetes amplifies the already high cardiovascular disease risk in these patients. Aggressive blood pressure control prevents more cardiovascular events in diabetics than nondiabetics. Patients with diabetes should be treated to a systolic blood pressure of 130 mmHg and a diastolic blood pressure of 80 mmHg. Patients with a blood pressure 140/90 mmHg should receive drug therapy in addition to lifestyle and behavioral therapy. Multiple drug therapy (two or more agents at proper doses) is generally required to achieve blood pressure targets. All patients with diabetes and hypertension should be treated with a regimen that includes either an ACE inhibitor or an ARB. If one class is not tolerated, the other should be substituted. If needed to achieve blood pressure targets, a thiazide diuretic should be added as second line therapy based upon the ALLHAT (Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial) results. Achieving American Diabetes Association target blood pressure (130/80 mm Hg) almost always requires more than one agent.

**Medical Therapy Of Coronary Artery Disease:**

**Antiplatelet Drugs:** Studies have consistently shown that patients with either type 1 or type 2 diabetes have enhanced platelet aggregation in response to a variety of agonists. Thus, agents directed at inhibiting platelet aggregation in vivo consistently reduce the incidence of thrombotic events in nondiabetic and diabetic individuals.

**Aspirin:** In the Early Treatment of Diabetic Retinopathy Study (ETDRS), patients with type 1 or type 2 diabetes randomly assigned to aspirin, 650 mg/day, had a significantly lowered risk of MI without incurring an increase in the risk of vitreous or retinal bleeding, even in patients with retinopathy. The Hypertension Optimal Treatment (HOT) trial confirmed this benefit in 1501 diabetic subjects who experienced a significant 15 percent reduction in cardiovascular...
events and a 36 percent reduction in MI while being treated with aspirin, 75 mg/day. The American Diabetes Association currently recommends enteric-coated aspirin (81 to 325 mg/day) for (1) secondary prevention in men and women with diabetes and evidence of macrovascular disease and (2) primary prevention in persons with type 1 or type 2 diabetes and additional coronary risk factors. Recently the issue of aspirin resistance has been addressed in the diabetic patient. A study that compared platelet response to aspirin in patients with type 2 diabetes and nondiabetics demonstrated that aspirin, 150 mg, taken for 1 week reduced platelet adhesiveness in 69 percent of the nondiabetic patients but in only 29 percent of the patients with type 2 diabetes. Aspirin resistance has also been found in 19 to 22 percent of type 2 diabetic patients, and an additional 16.9 percent were found to be semiresponders in one study. Aspirin resistance occurred with similar frequency in both type 1 and type 2 diabetic patients.

**Adenosine Diphosphate Receptor Antagonists:**

The CAPRIE trial, which compared outcomes in patients with non-ST-segment elevation MI (NSTEMI), ischemic stroke, or established peripheral artery disease treated with aspirin or clopidogrel, enrolled 3866 patients with diabetes. Although the event rate was higher in the diabetic patients than in the overall study population, the response to treatment was also better.

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study tested clopidogrel plus aspirin against aspirin alone in patients with unstable angina or non-Q-wave MI. After 9 months the incidence of the primary composite endpoint (cardiovascular death, nonfatal MI, or stroke) was reduced in the clopidogrel plus aspirin group by 20%. Subgroup analysis showed that this effect extended to the patients with diabetes.

**Glycoprotein IIb/IIIa Blockers:**

These potent antiplatelet agents have improved outcomes in patients with unstable angina and non-Q-wave infarction and have reduced the incidence of acute ischemic events by 35% to 50 % in patients undergoing PCI. At least one of the GP IIb/IIIa inhibitors, abciximab, reduced longterm mortality.In general, these agents appear to have equal or better efficacy in diabetic than nondiabetic patients, although most studies lack sufficient power to evaluate this interaction fully. The survival benefit of GP IIb/IIIa blockade may be greater in diabetic patients treated with stents.

**Direct Thrombin Inhibitors:**

In the Randomized Evaluation in PCI Linking Angiomax to reduced Clinical Events (REPLACE-2) trial, there was no difference in the incidence of short-term or long-term ischemic events among the diabetic patients in the two treatment arms, suggesting that bivalirudin is equally effective in diabetic and nondiabetic patients. Patients treated with bivalirudin and provisional GP IIb/IIIa inhibitors experienced a significant reduction in minor bleeding events.

**Beta-Adrenergic Blocking Agents**

Beta-adrenergic blocking agents (beta blockers) reduce mortality and reinfarction in patients with MI and have recently become a routinely accepted treatment in the diabetic subgroup of this population. In the past, the use of beta blockers was sometimes avoided in diabetic patients because of the potential of these drugs to mask hypoglycemic symptoms, precipitate glucose intolerance, inhibit the release of insulin, adversely affect the plasma lipid profile, and precipitate development of diabetes in patients with CAD who were not previously diabetic. However, several studies of diabetic patients treated with beta blockers following MI indicate that use of these drugs reduces mortality and may provide benefit that exceeds that seen in nondiabetic patients. The greater relative benefit of beta blockers in diabetic patients may derive from several factors. Beta blockers can help restore sympathovagal balance in diabetic patients with autonomic neuropathy and may decrease fatty acid utilization within the myocardium, thus reducing oxygen demand. However, despite the continuing growth of evidence regarding their efficacy and safety in the
diabetic patient, beta blockers continue to be underprescribed in this group.

**Angiotensin-Converting Enzyme Inhibitors**

ACE inhibitors reduce infarct size, limit ventricular remodeling, improve survival after myocardial infarction, and may be of particular benefit in patients with diabetes. A post hoc analysis of one thrombolytic trial (Grupo Italiano per lo Studio della Sopravivenza nell’Infarto Miocardico-3 [GISSI-3]) revealed that early administration of lisinopril in the setting of acute MI reduced 6-week and 6-month mortality comparatively more in diabetic versus nondiabetic patients. Patients with diabetes experienced a greater relative improvement in survival over 5 years of follow-up than the nondiabetic cohort in (TRACE) study. Furthermore, ACE inhibition reduced the risk of sudden death, reinfarction, and progression of CHF by nearly 50% in patients with diabetes. These agents can prevent or limit remodeling of the ventricle, particularly when administered early in the course of acute MI, reduce recurrent ischemic events, and restore sympathovagal imbalance. ACE inhibitors and ARBs may also improve endothelial function in diabetes, promote fibrinolysis by suppression of PAI-1 expression, and decrease insulin resistance. In the Heart Outcomes Prevention Evaluation (HOPE) study, ramipril significantly reduced the rates of MI, stroke, and cardiovascular death in diabetic subjects with or without a prior history of CAD or CHF over a 5-year period when compared with placebo.(12)

**Insulin**

Aggressive control of plasma glucose levels during the treatment of myocardial ischemia in diabetic patients can improve outcomes. In the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study those receiving the intensive insulin regimen had a lower blood glucose level during the first hour and at discharge than the control group. During the first year of follow-up, a significant reduction in mortality was seen in the intensive insulin group compared with the conventionally treated group. Mortality remained lower in the intensive control group through 3.4 years than in the conventional care group. Predictors of mortality were age, history of CHF, diabetes duration, admission glucose, and admission HbA1C level. The subgroup whose diabetes had been managed with diet or oral hypoglycemic drugs before infarction enjoyed the greatest survival benefit.(13)

The value of intensive metabolic control for improving outcomes has recently been examined in two settings. In a study comparing perioperative outcomes of diabetic patients undergoing coronary artery bypass grafting (CABG) who were treated with continuous insulin infusion or intermittent subcutaneous insulin, insulin infusion significantly reduced mortality compared with subcutaneous insulin treatment.

Infusion of glucose-insulin-potassium (GIK) solution, originally used in the 1960s and 1970s as a polarizing agent to maintain electrical stability, is regaining favor as a method to influence myocardial metabolism positively during treatment of MI, coronary revascularization procedures, and CABG. In a prospective, randomized, open-label study of GIK infusion in 940 patients undergoing percutaneous transluminal coronary angioplasty (PTCA) for an acute MI, no mortality benefit was seen in the GIK group compared with the placebo group, although there seemed to be a benefit in the diabetic subgroup. A comparison of CABG outcomes in diabetic patients prospectively randomized to receive GIK solution to maintain tight glycemic control during surgery or receiving standard therapy has also been reported. GIK patients had lower serum glucose levels during the immediate postoperative period, a lower incidence of atrial fibrillation, and a shorter postoperative length of hospitalization. Although there was no difference in the two treatment arms in 30-day mortality, patients treated with GIK had a significant survival advantage over a 2-year period following surgery.(14)

**Coronary Revascularization**

Coronary revascularization procedures have become a mainstay of therapy for CHD patients, providing both symptomatic relief and mortality reduction in certain anatomic subsets. Several studies
have attempted to rationalize the use of different revascularization techniques by comparing them to medical therapy and to each other in various clinical settings. Although none of the preceding studies was specifically conducted in diabetic patients, subgroup analyses of these studies indicated that diabetic patients (1) are at greater risk for cardiac death and ischemic complications than nondiabetic patients and (2) despite a greater surgical risk, diabetic patients indeed may derive a greater long-term benefit from revascularization than do nondiabetic patients.(15)

**Options for Revascularization in Diabetic Patients: Coronary Artery Bypass Graft Surgery versus Balloon Angioplasty:**

For the past two decades, the question of preferred revascularization strategies—surgery versus percutaneous intervention (PCI), mostly as balloon angioplasty—in patients with obstructive coronary artery disease has led to 13 important randomized clinical trials. There is general consensus that both surgery and percutaneous interventional therapies result in similar death and MI frequency for the overall patient populations evaluated in these studies. The major departure from this observation was highlighted in the BARI trial substudy(16), wherein there was a clinically meaningful and statistically significant survival benefit favoring coronary artery bypass grafting (CABG) in diabetic patients. In the Northern New England Cardiovascular Disease Study, diabetic patients demonstrated a significant mortality benefit in favor of CABG.

**Modern Percutaneous Coronary Intervention Techniques:**

**Bare Metal Stents:**

Many of the technical limitations of balloon angioplasty have been overcome by coronary stent implantation during PCI. Stenting is more predictable, giving a more reliable angiographic result in a wide variety of lesion types and is associated with lower restenosis in many lesion subsets. The advantage of stent implantation versus percutaneous transluminal coronary angioplasty alone with respect to angiographic restenosis and the need for repeat revascularization procedures has also been applicable to diabetic patients. This was evident from subgroup analyses from the stent versus angioplasty trials, as none of the studies was specifically conducted exclusively in diabetic patients. What is clear is that diabetic patients are at significantly higher risk for restenosis after either balloon angioplasty or stent implantation compared to nondiabetic patients, as shown in all previous clinical studies on restenosis.

The Arterial Revascularization Trial Study (ARTS) randomized trial compared the clinical outcomes of aggressive stenting versus CABG surgery in 1205 patients with multivessel coronary disease and demonstrated no important differences in death, myocardial infarction, or stroke at 1 year. However, there was still a 14 percent difference, favoring CABG, in 1-year repeat revascularization rates. The diabetes subset from the ARTS revealed that multivessel stenting had a poorer 1-year major adverse cardiac event rate than did CABG; the results were mainly driven by the higher incidence of repeat revascularization after stenting than after CABG.

**Drug-Eluting Stents:**

The advent of drug-eluting stents (DESs) has revolutionized the field of percutaneous interventions, especially in the diabetic patient. While DESs have not had a major impact on hard cardiovascular end points such as death and MI, they have been successful in reducing angiographic restenosis and the rates of target-vessel revascularizations. A recent meta-analysis of DES studies showed that for patients with diabetes the number needed to treat to reduce major adverse cardiac events were four patients for the SES and six patients for the PES.

**Bypass Outcomes:**

Bypass conduits attrition rates are higher in diabetic patients than they are in nondiabetic patients. Bilateral IMA grafting provides even further survival advantage than left IMA plus saphenous vein grafts; these data have led to an increased application of CABG with total arterial revascularization. Nonetheless,
the use of bilateral IMA grafting in diabetic patients remains controversial because of the potentially increased risk for sternal wound infection. Neurologic dysfunction remains a devastating complication of CABG, especially in diabetics. Diabetes is the single greatest predictor of mortality during ischemic stroke and diabetes is an important risk factor for stroke during coronary artery bypass surgery. Therefore, if drug-eluting stenting for diabetic patients with multivessel coronary artery disease proves to be equivalent to coronary bypass surgery in achieving successful revascularization of the coronary arteries, a significant advantage for stenting may be a reduction in stroke morbidity.

Conclusion:
CAD is a multifactorial condition for which diabetes is an important risk factor. Tremendous progress has been made in the understanding of CAD in diabetic patients. However, it is now well recognized that as diabetes itself involves interplay of several risk factors, mere control of hyperglycemia may not be sufficient to prevent CAD in diabetic patients. A multi-pronged approach with reduction in serum lipids, better control of blood pressure, weight reduction, cessation of smoking and probably using aspirin or other antiplatelet therapies would probably be needed to prevent CAD in diabetic subjects.

References:
Gestational Diabetes Mellitus – Where we are?
Gayatri Kar¹, Saubhagya Kumar Jena², Basanta Kumar Behera³

Introduction:
Sometimes during pregnancy some new diseases are developed and Gestational diabetes mellitus (GDM) is one of those diseases. The detection of GDM is important because of its associated maternal and fetal complications. Treatment with medical nutrition therapy, close monitoring of glucose levels, and insulin therapy if glucose levels are above goal can help to reduce these complications.

Definition:
Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance (hyperglycemia) of varied severity with onset or first recognition during the present pregnancy. The definition applies irrespective of whether or not insulin is used for treatment or the condition persists after pregnancy. It does not exclude the possibility that glucose intolerance may have antedated the present pregnancy.

Prevalence:
GDM affects 7% of all pregnancies, the prevalence ranges from 1 to 14%.¹,² According to the WHO estimates by the year 2050 India will be the diabetes capital of the world. The recognition of glucose intolerance during pregnancy is more relevant in the Indian context as; Indian women have 11 fold increased risk of developing GDM compared to white women. In India the prevalence of GDM ranges between 16 to 19% and it is increasing.³ Up to now which was a disease of urban people, it is steadily increasing in rural population.

Pathogenesis:
Pregnancy is a diabetogenic condition characterized by insulin resistance with a compensatory increase in β-cell response and hyperinsulinemia. Insulin resistance usually begins in the second trimester and progresses throughout the remainder of the pregnancy. Women with GDM have a greater severity of insulin resistance compared to the insulin resistance seen in normal pregnancies. They also have an impairment of the compensatory increase in insulin secretion, particularly first-phase insulin secretion.

There is also a subset of women with GDM who have evidence of islet cell autoimmunity. The reported prevalence of islet cell antibodies in women with GDM ranges from 1.6 to 38%. The prevalence of other islet autoantibodies, including insulin autoantibodies and glutamic acid decarboxylase antibodies, has also been variable. These women may be at risk for developing an autoimmune form of diabetes later in life.⁸ Finally, in 5% of all cases of GDM, the β-cell’s inability to compensate for the insulin resistance is the result of a defect in the β-cell, such as a mutation in glucokinase.⁷

Diagnosis:
The oral glucose tolerance test (OGTT) is most commonly used to diagnose GDM. There is no international agreement as to the optimal glucose tolerance test for the definitive diagnosis of gestational diabetes. The World Health Organization (WHO) diagnostic criterion, which is used in many countries, is based on a 2-hour 75-g OGTT (Table -1).

<table>
<thead>
<tr>
<th>Plasma Glucose</th>
<th>ADA 100 gm OGTT</th>
<th>ADA 75 gm OGTT</th>
<th>WHO 75 gm OGTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting (mg/dl)</td>
<td>95</td>
<td>95</td>
<td>126</td>
</tr>
<tr>
<td>1-hour (mg/dl)</td>
<td>180</td>
<td>180</td>
<td>—</td>
</tr>
<tr>
<td>2-hour (mg/dl)</td>
<td>155</td>
<td>155</td>
<td>140</td>
</tr>
<tr>
<td>3-hour (mg/dl)</td>
<td>140</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

(Summarizes ADA and WHO criteria for the diagnosis of GDM)
For the ADA criteria, two or more of the values from either the 100 or 75 gm OGTT must be met or exceeded to make the diagnosis of GDM. For the WHO criteria, one of the two values from the 75 gm OGTT must be met or exceeded to make the diagnosis of GDM.

According to diagnostic criteria recommended by the American Diabetes Association (ADA), GDM is diagnosed either by 3 hour 100 gm OGTT or 2 hour 75 gm OGTT (Table - 1). These values are lower than the thresholds recommended by the National Diabetes Data Group and are based on the Carpenter and Coustan modification (Table -2). The ADA recommendations also include the use of a 2-hour 75-g OGTT with the same glucose thresholds listed for fasting, 1-hour, and 2-hour values.1, 2

The American College of Obstetricians and Gynaecologists (ACOG), 2001 recommends the same criteria used by ADA using 100 gm 3 hour oral glucose tolerance test (Table - 2).

### Table – 2

(ACOG, 2001 Criteria for Diagnosis of GDM using 100 gm OGTT)

<table>
<thead>
<tr>
<th>Status</th>
<th>Carpenter and Coustan</th>
<th>National Diabetes Data Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting (mg/dl)</td>
<td>95</td>
<td>105</td>
</tr>
<tr>
<td>1-hour (mg/dl)</td>
<td>180</td>
<td>190</td>
</tr>
<tr>
<td>2-hour (mg/dl)</td>
<td>155</td>
<td>165</td>
</tr>
<tr>
<td>3-hour (mg/dl)</td>
<td>140</td>
<td>145</td>
</tr>
</tbody>
</table>

According to the Diabetes In Pregnancy Study Group India (DIPSI) criteria 75 gm of oral glucose given without regard to the time of last meal. GDM is diagnosed if 2 hours plasma glucose is >140 mg/dl. This single step procedure serves both as screening and diagnostic test for GDM, is simple, economical, feasible and more realistic in Indian context.

The term Gestational Glucose Intolerance (GGI) is used when the 2 hour post glucose is more than 120 mg/dl but less than 140 mg/dl (Table - 3). Women with GGI and without overt gestational diabetes were associated with a significantly increased incidence of cesarean section, pre eclampsia and macrosomia.

### Table – 3

(With 75 gm OGTT, WHO criteria)

<table>
<thead>
<tr>
<th>Plasma Glucose</th>
<th>In Pregnancy</th>
<th>Outside Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 hr &gt; 200 mg/dl</td>
<td>Diabetes</td>
<td>Diabetes</td>
</tr>
<tr>
<td>2 hr &gt; 140 mg/dl &lt; 199 mg/dl</td>
<td>GDM</td>
<td>IGT</td>
</tr>
<tr>
<td>2 hr &gt; 120 mg/dl &lt; 139 mg/dl</td>
<td>GGI</td>
<td>Normal</td>
</tr>
</tbody>
</table>

### Screening

There is no worldwide agreement on the best way to screen for GDM. Previously, universal screening at 24-28 weeks of gestation with a 50-g oral glucose challenge test was recommended. Women with a 1-hour glucose level > 140 mg/dl were referred for a diagnostic OGTT. However, Naylor et al. developed a selective screening approach with data collected from 3,131 pregnant women. Screening, whether it is universal or selective, remains a controversial subject. The ADA now recommends selective screening for GDM.

Ethnically Indian women are more prone to develop glucose intolerance during pregnancy and have increased risk compared to white Caucasians. The specificity of ADA screening with 50 gm 1 hour GCT without regard of the last meal is low. A pregnant woman visiting the ante-natal clinic for the first time usually does not come in the fasting state. Hence, instead of performing screening test using 50 gm 1 hour test and then 100 gm OGTT, a single step procedure of OGTT using 75 gm glucose should be done. Plasma glucose value of >140 mg/dl after 2 hours is abnormal and it serves both as screening and diagnostic test for GDM. It should be universal at least in India.

### Complications

There are both fetal and maternal complications associated with GDM. Fetal complications include macrosomia, neonatal hypoglycemia, perinatal mortality, congenital malformations, hyperbilirubinemia, polycythemia, hypocalcemia, and respiratory distress syndrome.1-3, 9 Maternal complications associated with GDM include hypertension, preeclampsia, and an increased risk of cesarean delivery.6, 10
TREATMENT

Glucose Monitoring:

Self-monitoring of blood glucose is recommended for women with GDM. The goal of monitoring is to detect glucose concentrations elevated enough to increase perinatal mortality. The Fourth International Workshop-Conference on Gestational Diabetes Mellitus recommends maintaining the following capillary blood glucose values: preprandial glucose < 95 mg/dl, 1-hour postprandial glucose < 140 mg/dl, and 2-hour postprandial glucose < 120 mg/dl. ACOG guidelines are the same except that the 1-hour postprandial glucose value is considered acceptable at either 130 or 140 mg/dl.

However, women who had mean blood glucose values < 87 mg/dl had a higher incidence of infants with IUGR, whereas women who had mean blood glucose values > 104 mg/dl had a higher incidence of LGA infants. This study suggests that although it is important to treat hyperglycemia in GDM, it is also important not to over treat because this can increase the risk of IUGR.

It is important for women to check postprandial glucose levels because these have been shown to correlate more with macrosomia than fasting levels. The Diabetes in Early Pregnancy Study found that third-trimester postprandial glucose levels were the strongest predictor of percentile birth weight. In women with GDM who require insulin therapy, adjustments of their insulin regimens based on postprandial, rather than preprandial, glucose levels decreased the incidence of neonatal hypoglycemia, macrosomia, and cesarean delivery for cephalopelvic disproportion.

Medical Nutrition Therapy (MNT):

Nutritional counseling is required for all women with GDM. The goals of MNT are to provide adequate nutrition for the mother and fetus, provide sufficient calories for appropriate maternal weight gain, maintain normoglycemia, and avoid ketosis. In general, there is not an increased energy requirement during the first trimester of pregnancy. However, most normal-weight women require an additional 300 kcal/day in the second and third trimester.

In normal-weight women with GDM, the recommended daily caloric intake is 30 kcal/kg/day based on their present pregnant weight. In women with GDM who are overweight (BMI > 30 kg/m²), a 33% calorie restriction of their estimated energy needs is recommended (25 kcal/kg/day based on their present pregnant weight).

Ketonemia in mothers with diabetes during pregnancy has been associated with lower IQ levels and impaired psychomotor development in their children. Monitoring with pre breakfast ketone measurements is recommended for patients who are on a hypocaloric or carbohydrate-restricted diet.

Carbohydrates should be distributed throughout the day. Eating three small- to moderate-sized meals and three snacks per day is recommended. Limiting carbohydrates to 40% of the total daily caloric intake has been shown to decrease postprandial glucose levels. Further limitation of carbohydrates at breakfast to 33% may be required to meet the desired postprandial glucose goals because insulin resistance is greatest in the morning. In addition, carbohydrate restriction to < 42% in patients with GDM resulted in a decreased incidence of LGA infants, a decrease in cesarean deliveries for macrosomia and cephalopelvic disproportion, and a decreased need for insulin therapy compared to patients on a diet with a higher carbohydrate content (45-50%). Consuming carbohydrates with a low glycemic index also results in lower postprandial glucose levels, especially late in gestation.

Exercise:

A potential benefit of exercise in women with GDM is improved glycemic control. Based on the potential benefits of exercise in women with GDM, the ADA recommends starting or continuing a program of moderate exercise in women without medical or obstetrical contraindications.

Insulin:

Insulin therapy is the most commonly used treatment when MNT fails to maintain blood glucose levels at the desired ranges or when there is evidence of excessive fetal growth. Because there are no data demonstrating an optimal insulin regimen, the type and dose of insulin must be tailored to meet each patient’s requirements. Human insulin is currently
recommended by the ADA. Although insulin lispro appears to be safe in pregnancy if started after 14 weeks of gestation, it is considered to be in Pregnancy Category B by the Food and Drug Administration (FDA), and the official recommendation of the ADA is to use human insulin until further studies verify the safety of insulin lispro.

The short-term efficacy of insulin aspart was evaluated in a small study of 15 women with GDM during standardized meal tests. Although this study found that insulin aspart was effective in decreasing postprandial glucose concentration, further studies need to be done to ensure the safety of this medication in pregnant women. Insulin aspart is considered to be in Pregnancy Category C by the FDA.

The use of insulin glargine in humans has only been reported in case reports. There have been no clinical trials evaluating the use of insulin glargine in pregnancy. It is currently considered to be in Pregnancy Category C by the FDA.

**Oral Agents:**

Currently, oral hypoglycemic agents are not recommended by the ADA or ACOG. The older sulfonylureas chlorpropamide and tolbutamide could cross the placenta, stimulate the fetal pancreas, and cause fetal hyperinsulinemia. However, the transfer of glyburide, a second-generation sulfonylurea, across the human placenta was insignificant in experimental models.

Metformin has also been used to treat pregnant women with GDM. A retrospective cohort study found an increased prevalence of preeclampsia and perinatal mortality in women treated with metformin. However, the women in the metformin group were more obese and older, and their treatment was begun later in gestation. Recent studies involving women with polycystic ovary syndrome or women with type 2 diabetes who continue metformin in pregnancy have found no adverse pregnancy outcomes.

**Antepartum Fetal Assessment:**

ACOG recommends antepartum fetal assessment in women whose blood glucose is poorly controlled, who require insulin therapy, who have a history of an adverse obstetrical event, or who have a history of a hypertensive disorder. Providers can determine which type of antepartum test to use (biophysical profile, nonstress test, or contraction stress test). The recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus are to consider nonstress testing starting at 32 weeks of gestation in patients on insulin and at or near term in patients managed by diet alone. Antepartum fetal assessment with ultrasound may play a role in the future management of patients with GDM.

**Peripartum Considerations:**

When glycemic control is acceptable and there are no other known complications, routine delivery before 40 weeks of gestation is not recommended. If a delivery is indicated before 39 weeks, pulmonary maturity should be assessed by amniocentesis before induction if possible. The rate of cesarean deliveries is much higher in women with GDM compared to women without GDM. The increase in rate is higher than would be expected based solely on the associated obstetric complications. Therefore, part of this increase is likely influenced by physician knowledge of a history of GDM. ACOG recommends counseling women about the possibility of cesarean section without labor when the estimated fetal weight is > 4,500 g. If the estimated fetal weight is 4,000-4,500 g, additional risk factors for shoulder dystocia, such as clinical pelvimetry, progression of labor, and patient’s past delivery history, should be considered.

**Postpartum Considerations:**

Women with GDM have an increased risk of developing diabetes, most commonly type-2 diabetes, after pregnancy. A recent systematic literature review of 28 studies found that the cumulative incidence of type 2 diabetes ranged from 2.6 to > 70% in studies with postpartum follow-up ranging from 6 weeks to 28 years. A meta-analysis calculated the relative risk for developing diabetes after GDM to be 6.0 (95% CI 4.1-8.8). Maternal glycemic status should be reclassified 6 weeks or more after pregnancy ends and every 3 years thereafter as either diabetes mellitus, impaired fasting glucose, impaired glucose tolerance, or normoglycemia. All patients with a history of GDM should be educated about MNT, exercise, maintenance of normal body weight, the need for family planning, and symptoms suggestive of hyperglycemia.
Conclusion:

GDM is a common medical problem that results from an increased severity of insulin resistance as well as an impairment of the compensatory increase in insulin secretion. Controversy surrounds the ideal approach for detecting GDM, and the approaches recommended for screening and diagnosis are largely based on expert opinion. Controlling maternal glycemia with MNT, close monitoring of blood glucose levels and treatment with insulin if blood glucose levels are not at goal has been shown to decrease fetal and maternal morbidities. In addition, certain types of exercise appear to have potential benefits in women without any contraindications. Other treatment modalities, such as oral agents, need further study to validate their safety and efficacy. Additionally, more research on the use of antepartum fetal assessment to help guide treatment in women with GDM is needed. Finally, postpartum management of women with GDM is critical because of their markedly increased risk of type 2 diabetes in the future. As the offspring is also prone for obesity, IGT and diabetes as short intensive care to the mother gives a long term pay off for both the women and her offspring.

References:

Anaesthesia in Diabetes Mellitus

Sidhartha Mohanty1, Ranjit Kishore Mohanty2, Dipankar Padhihari3

Introduction:
The diabetic patient provides many challenges to the anaesthetist, most of which can be anticipated with good preoperative assessment, careful monitoring and an understanding of the relevant pathophysiology. It is the most commonly encountered peri-operative endocrinopathy.

CONSEQUENCES OF HYPERGLYCEMIA: Of concern to the anesthesiologist because of its impact on the peri-operative course.

1) Nervous System:

Peripheral neuropathy (glove and stocking) →50% incidence in chronic disease

Implications: Increased susceptibility to nerve injuries. Hence utmost care has to be taken during shifting & positioning of the patient. Adrenaline containing local anaesthetic solutions for giving peripheral nerve blocks should be avoided.

Autonomic neuropathy → postural dizziness, post gustatory sweating, nocturnal diarrhoea and impotence

Implications: Gastroparesis; Advice to prolong the fasting period prior to surgery (more than the usual 6hrs.). Otherwise, we can go for cricoid pressure during intubation. There will be blunted heart rate response to anti-cholinergic / beta blocker

At Pre Anaesthesia Clinic (PAC): Look for autonomic neuropathy – More than 30mmHg fall of systolic BP (from supine to standing) & Less than 10 beats /mt increase of HR in response to deep breathing. Make a clear note of peripheral neuropathy. Look for H/O heartburn on lying flat, abdominal distension (Gastroparesis)

Anticipated intra-operative problems: Unstable BP, Myocardial ischemia, Arrhythmias, Gastric reflux and Aspiration; Inability to maintain body temperature under anaesthesia. Poor patient positioning is likely to result in pressure sores that are often slow to heal (poor peripheral blood flow).

2) Cardiovascular:

Coronary artery disease (increased risk : 2 times in males, 3 times in females) Silent ischemia; Hypertension (29 – 54% of all diabetics); Reduced threshold for dysrhythmias

Implications: Cardiac Dys-autonomia – Sudden hypotension at induction. Absence of hypertensive response or tachycardia with intubation

PAC : Palpate all Peripheral pulses; Loss of sinus arrhythmia (reflex bradycardia on expiration); ECG changes in 15 – 60% without any symptoms of Coronary artery disease; H/O shortness of breath, palpitations, ankle swelling, tiredness (but no chest pain – in many); Look for - distended neck veins, ankle swelling, tender swollen liver, crackles in the chest; Note down Drugs (anti-hypertensive & lipid lowering) & their timings

3) Opthalmic:

Patients having diabetic retinopathy, posted to undergo any prolonged surgery in prone position (spine surgery), need to have a pre-operative fundoscopic examination. This will provide an insight into the patient’s risk of developing postoperative blindness.

4) Renal:

Intrinsic renal disease (glomerulosclerosis and renal papillary necrosis) will enhance the risk of ARF peri-operatively. Dialysis if necessary should optimally be done on the day before surgery. Patients are more susceptible for Urinary infection. Hence there should be maintenance of strict aseptic measures & unnecessary catheterisation should be avoided for simpler procedures.
PAC: Micro-albuminuria is an early indicator of renal complication. Electrolytes (specifically K+ level) as we may possibly need suxamethonium (due to gastro paresis).

5) **Immune System:**

Hyperglycaemia facilitates proliferation of bacteria and fungi thereby depressing the immune system. There occurs proteolysis and decreased amino acid transport causing delay in wound healing. Loss of phagocytic function increases risks of post-operative infection.

Implication: Strict sterile techniques for regional anaesthesia, endo-tracheal intubation, LMA insertion, drug loading & central line placements.

PAC: Look for any infected focus (abscess / non-healing ulcer)

6) **Skeletal System:**

There occurs non-enzymatic glycosylation, which causes abnormal cross-linking of collagen that leads to joint rigidity. Rigidity occurs at atlanto-occipital joint and temporo-mandibular joints. The small joints of the fingers and hands are affected causing failure to approximate the palmar surfaces of the interphalangeal joints (“POSITIVE PRAYER SIGN”). This might indicate towards cervical spine immobility and a potential for a difficult endo-tracheal intubation.

PAC: Proper airway assessment, cervical spine X-ray

**Drugs:**

1) **ORAL HYPOGLYCAEMIC AGENTS:**

Duration of action of commonly used agents is < 24hrs, hence we need to be unduly worried about stopping OHA > 24 hrs prior to surgery

2) **INSULIN:** The morning dose of insulin has to be omitted.

3) **DRUGS FOR OTHER COEXISTING ILLNESS:** Hypertension, IHD

**Pre-operative Investigations:**

Blood glucose – fasting and postprandial; Urinalysis (albumin, ketones); Serum urea, creatinine and electrolytes; ECG (ask for old ECG strips, if possible)

All NIDDM patients, undergoing major surgeries & in all IDDM patients, a blood sample for fasting glucose & serum Potassium should be drawn in the morning of surgery.

Glycosylated Haemoglobin (HbA1c or A1C): reflects the average blood sugar levels over the preceding 2-3 months. \( \leq 6 \) indicates good control of blood glucose.

**BLOOD GLUCOSE FOR ACCEPTANCE AT PAC**

General surgical - Fasting: 90-126 mg/dl Random: <200 mg/dl

Cardiac surgery & Critically ill - Random <150 mg/dl

Neurosurgery - 80-140 mg/dl

**PRE ANAESTHESIA PREPARATION** –

Insist upon posting diabetics as first operative case in the list to minimize the starvation period. Provide adequate insulin to the patient to counteract the catabolic processes that develop in response to surgery (Stress imposed by the anaesthetic is usually minor compared to the stress of the surgery). Provide Glucose to meet the increased metabolic needs (caused by surgical stress) as well as basal metabolic requirements.

**GLUCOSE:** Prevents hypoglycemia & provides basal energy requirements

Dose: 0.1g/kg/hour of 5D (100ml/hr in a 50kg individual). Children: 0.3 g/kg/hr.

**INSULIN:** Continuous I.V. infusion of regular Insulin.

**Requirement** = patient’s daily insulin requirement (hourly) / 24 hours

Eg: patient receives 12 U before breakfast, 12 U before lunch & 8 U before dinner. Total insulin = 32 U in 24 hrs

Hence hourly requirement to maintain a tight control over blood glucose will be approximately 32/24 = 1.3U per hr

**POTASSIUM:** serum levels can fluctuate. Insulin stimulates the uptake of potassium into cells causing hypokalemia. Dehydration / Hyperglycemia / Acidosis can cause hyperkalemia

**FLUIDS:** As long as the patient is receiving enough glucose, insulin (and potassium), normal saline (NS) is the ideal intra-operative fluid. Avoid RL - lactate is a gluconeogenic precursor (especially in a
Control of BG gets complicated. Surgeries where the patient can be expected to eat and drink within 4 hours of, is classified as MINOR. All other surgeries other than minor is classified as MAJOR.

1) NIDDM for Minor Surgery: Omit OHA
   RBS < 180mg% - no insulin ; RBS > 180mg% -
   500ml D5 + 5 U Regular insulin
   Repeat RBS- 1 hour preoperatively and at least once
during surgery
   Postoperative - 2 hourly until pt starts eating. Next
day - Restart OHA with first meal

2) IDDM for Minor Surgery: Place first on list & omit
   morning dose of insulin
   6AM BG & K+ & start 500ml D5 + 5 U Regular insulin
   Repeat RBS-1 hr preoperatively and during surgery;
   Postoperatively - 2 hourly until eating then 4 hourly

3) NIDDM / IDDM for Major surgery: Place first on
   list & omit OHA or subcutaneous (S/C) insulin; 6AM
   BG & K+ & start 500ml D5 + 5 U Regular insulin
   Repeat RBS- 1 hour preoperatively then hourly from
   start of infusion
   Recovery area - 2 hourly post operatively

INSULIN REGIMENS

1) Alberti’s Regimen (GIK)
   Relatively safe as they provide insulin and
   dextrose together, preventing potential disasters.
   Advantage: Need to change the GIK bag every
time the blood glucose is outside the acceptable range.

   **Blood sugar** Insulin infusion (in 500 ml 10D)
   <90mg% 5U + 10mmol KCl
   90-180 mg% 10U + 10mmol KCl
   180-360mg% 15U + 10mmol KCl
   >360mg% 20U + 10mmol KCl

2) Tight Control (target BG 99 to 110mg%)
   Hyperglycaemia at the time of cerebral ischemic
   insults ( Eg. Hypotensive Anaesthesia / Neurosurgery /
   During Cardiopulmonary Bypass / Carotid
   endartrectomy) is associated with a poor outcome.
   The extra glucose allows greater intracellular lactate
   accumulation and a more severe acidosis.

Separate infusion of D5 @ 50ml/ hr & Insulin
(50U in 250 ml NS) at the Rate \( \rightarrow \) blood glucose / 150 ( U/hr)

   Advantage: Inadvertent discontinuation of one
   infusion increases the chances of Hyper / hypo
   glycaemia / hypokalemia (Meticulous monitoring
   needed)

3) Vellore Regimen
   – 6AM blood glucose if >100mg% \( \rightarrow \) Add 5 U
   regular insulin to 5 D (500ml) \( \rightarrow \) 100ml
   withdrawn into the measured volume set (burette)
   \& started at 100 mL/hr until the start of surgery
   – Blood glucose at start of induction \( \rightarrow \) 1 U
   increment added for every 50 mg%
   measurements more than 150 mg/dl (solution
   already had 1 U/100 mL).
   – Blood glucose measured when the burette was
   empty (ie. end of each hour and the burette is
   refilled to 100 mL).
   – Blood glucose determined hourly until the
   patients left the recovery room

   **Blood Glucose** Insulin added to 100ml 5D
   101 -150 0 (+ 1 already in 100ml)
   151-200 1 ( \( \ldots \) )
   201-250 2 ( \( \ldots \) )
   251-300 3 ( \( \ldots \) )

CHOICE OF ANAESTHESIA

A) Regional
   **Pro**: Regional anaesthesia blunts the increases
   in cortisol, glucagon, and glucose.

   Spinal / epidural modulate catecholamine
   secretion, preventing high glucose and ketosis. This
   effect could continue in the post operative period
   (continuous epidural / intra-thecal opioid)

   **Con**: Autonomic neuropathy \( \rightarrow \) profound
   hypotension may occur (disastrous in compromised
   cardiac status). Infections and vascular complications
   \( \rightarrow \) (epidural abscesses are more common in diabetics).
   It is a wise precaution to chart any pre-existing nerve
damage before the block is performed. Any Neuropathy
presenting post-op may be attributed to the regional
blockade.
B) General

Pro: High dose opiate technique may be useful to block the entire sympathetic nervous system and the hypothalamic pituitary axis. Better control of blood pressure in patients with autonomic neuropathy

Con: May have difficult airway (“Stiff-joint syndrome”). Risk of aspiration due to Gastro-paresis. Aggravated hemodynamic response to intubation may rupture of the new retinal vessels (diabetic retinopathy). Anaesthesia masks the symptoms of hypoglycemia. Positioning related N injuries

Emergency Surgery

We are likely to encounter, uncontrolled blood glucose levels, in a patient who is infected, dehydrated and has metabolic de-compensation. Rapid assessment of Airway, Breathing and Circulation and obtaining good intravenous access. Quick estimation of blood glucose & ABG (with Electrolytes). Patient can be taken up for surgery with the correction process continuing (fluids; insulin ; potassium)

POST OPERATIVE: After surgery, intravenous insulin (if used) should be continued for at least 2 h after the first oral intake. Nausea and vomiting should be prevented / treated vigorously to re-establish early normal dietary intake. Good analgesia is important, as adequate pain relief decreases catabolic hormone secretion. Non-steroidal anti-inflammatory drugs used with caution (pre-existing renal dysfunction). Surgical removal of infected tissue (ie amputation of gangrenous limb, incision of abscess, etc) may result in dramatic reductions in Insulin requirement (and the danger of hypoglycaemia) postoperatively.

Summary:

As the incidence of diabetes mellitus continues to increase in India more diabetic patients will present for both elective and emergency surgery. Understanding the anaesthetic implications & careful control of blood glucose is the key to successful peri-operative management.

References:

Oral Manifestation in Patients with Diabetes Mellitus

Indu Bhusan Kar¹, Pravas Kumar Mohanty², Niranjan Mishra³, Alok Kumar Sethy⁴

Introduction:
The rising burden of Diabetes mellitus in the world population is a great concern to all the medical specialties involved, policy makers and public. It has been a concern to all specialties to get involved to reduce the complications associated with this state of life. Oral cavity being known to be an incubator for micro-organisms, shows manifestations in diabetic patients, where the immunity is compromised. Approximately one-third of population are in an undiagnosed state and the preventive care is not well accounted for with diabetes. In Indian scenario a significant percentage of population with diabetes have oral manifestations. Thus, the role of dental professional in diagnosis of the patients in diabetes during oral health care surveys would help in reducing the morbidity and mortality of the disease by referring the patients to appropriate physicians.

Oral Complications:
The varied oral findings in uncontrolled diabetes patients may be, involvement of gingival & periodontal diseases but may range from xerostomia to salivary gland dysfunction, increased susceptibility to bacterial, viral and fungal (oral candidiasis), caries, periapical abscess, loss of teeth, impaired ability to wear dental prosthesis, taste impairment, OLP and burning mouth syndrome¹. The oral complication are most likely due to altered response to infection, microvascular changes and possibly increased glucose concentration in the saliva (salivary hyperglycaemia) and gingival crevicular fluid².

Gingivitis & Periodontal Diseases:
Susceptibility to periodontal disease is often known as the 6th common complications of diabetes³. The oral complications with uncontrolled diabetes are most likely due to altered response to infections, microvascular changes and possibly increased glucose concentration in saliva (salivary hyperglycaemia) and gingival crevicular fluid².

Increased tissue destruction in diabetes with altered pathogens is due to difference in host response in the dental plaque³,⁴. It starts with gingivitis and gradually in poor glycemic control leads to periodontal diseases in a prevalence of 9.8% in type – I diabetes⁵. The patient with diabetic retinopathy in type – I diabetes have more loss of periodontal attachment by 4th & 5th decades of life⁶. Thus a frequent checkup and good oral hygiene maintenance by a dentist is extremely important for type – I diabetic patients. There is evidence that periodontal disease can disrupt control of diabetes status, suggesting that periodontal infections may have systemic repercussions⁷.

Though fewer studies are available showing periodontal involvement in type – II diabetes, some studies have shown that the type – II diabetes have 3 times more involvement of periodontal diseases and tooth loss⁸,⁹.

Diabetes with smoking habits likely to have 20 times more risk to have periodontal disease with loss of supporting bone than normal population¹⁰.

Dental infections in patients in diabetic may exuberate problems with metabolic control and also evidences are there that the management of periodontal infection in poorly controlled diabetes may help in glycaemic control¹¹,¹².

Salivary gland dysfunction & Xerostomia:
Dry mouth (xerostomia) is often a complaint of patient with diabetes¹³,¹⁴, which may be due to polyurea or an underlying metabolic or endocrine problem. This leads to dry, atrophic & crackling oral mucosa with mucocits, ulcers and disquamated, deppapillated and inflamed tongue. A consequence to this may be difficulty in deglutition & change in taste.

Dental Caries:
Salivary dysfunction also leads to increase of dental caries index¹⁵.
Candidiasis:
Marginally controlled or uncontrolled diabetes can have opportunistic infection by the candida albicans\textsuperscript{16,17}, in the oral cavity as an opportunistic infection resulting in atrophic glossitis, angular cheilosis, more so in immunocompromised patients like AIDS.

Burning Mouth Syndrome:
Though causes of burning mouth syndrome are varied, still uncontrolled diabetes can have the symptom as a neurological complication, or as a combination with other conditions like depression\textsuperscript{18,19,20}, which is more marked in type – II diabetes patients\textsuperscript{20}.

Oral Lichen Planus:
It is a mucocutaneous lesion of unknown origin and considered to have been immunologically mediated involving hypersensitivity reaction at microscopic level\textsuperscript{18}, characterised by increased CD\textsubscript{3} & CD\textsubscript{8} cells located at epithelial-connective tissue interface. Previously proposed Grinspan’s Syndrome (hypertension, OLP & diabetes mellitus) have not been well correlated. However, studies have shown that OLP is related to diabetes than non-diabetics\textsuperscript{21}.

Acute Oral Infections:
In uncontrolled or marginally controlled diabetes, a recurrent bout of Herpes Simplex infections, periodontal abscess, Palatal ulcers may be of frequent occurrence\textsuperscript{22,23}. These infections may be due to impaired wound healing, diminished chemotactic & PMN function.

Management:
In an crowded care of angina for diabetes the guidelines of oral health care is often considered too much. However International Diabetic Federation and World Dental Federation came together to formulate an evidenced based guideline for maintenance of oral health in diabetics.

The recommendations are:
1. Normal oral care procedures to be taken routinely in patient with diabetes like proper cleaning of mouth, use of cleaning aids like dental flush, inter-dentition brush, home care methods.
2. Symptoms like gum bleeding, swollen gum, bad breath, painful gum, loosening of teeth are to be taken care by the dental professionals.
3. Educating diabetics that, the oral care & mouth wash is a self management protocol.
4. Dental professionals to be made aware about the symptoms of diabetes and the proper referral protocols to be followed.

Implementations:
1. Professional education and awareness within diabetes community with easy acess
2. Healthcare personnel should be empowered to explain the need of oral hygiene maintenance and its background for gum diseases.
3. Awareness that certain drugs like calcium channel blockers, TCA may result in dry mouth, thus increasing the chance of getting bacterial plaque and more dental diseases.
4. Training to health care personnel to educate people with diabetes about the symptoms of gum diseases and liasoning with community preventive measures.
5. Oral health to be introduced in the curriculum of Diabetic management.
6. Assessment of periodontal disease status with questionnaires and more research on evidence based for understanding interrelationship between diabetes and oral health both basic and clinical.

Conclusion:
Oral disease shares the same burden of preventing chronic diseases in Diabetes and thus to reduce the risk factors and complications ,they should be well accounted for in the global health programme as proposed by the WHO.

References:
5. Robertson C, Drexler AJ, Vernillo AT. Update on diabetes diagnosis and management. JADA 2003;134(supplement):16S-23S.
19. Levin RP. How treating the patient with diabetes can enhance your practice: recommendations for practice management. JADA 2003;134 (supplement) : 49S-53S.

Members of IMA, Odisha are requested to correct their contact details at State HQ Office, Cuttack
Introduction:

In a normal 120 days ife span of the red blood cell, glucose molecules react with haemoglobin to form glycosylated haemoglobin. It is formed in a non-enzymatic glycosylation pathway by haemoglobin’s exposure to plasma glucose. It is also termed as glycated haemoglobin, HbA1 or A1C or Hb1c. It is a process by which glucose chemically attaches to the amino group of proteins without the aid of enzymes. Glucose forms chemically reversible glycosylation products with protein that may rearrange to form more stable Amadori-type glycosylation products1. The degree of enzymatic glycosylation is directly related to the level of blood glucose.

Once a haemoglobin molecule is glycated, it remains that way. Normal levels of glucose produces a normal amount of HbA1c. As the average amount of plasma glucose increase, the fraction of glycated haemoglobin increases in a predictable way. This serves as a marker for average blood glucose levels over the previous months prior to the measurement. It reflects the average level of glucose to which the cell has been exposed during its life cycle.

Importance:

Measuring HbA1c assess the effectiveness of therapy by monitoring long-term plasma glucose regulation. The HbA1c level is proportional to average blood glucose concentration over the previous four weeks to three months.

In 2010 American Diabetes Association Standards of Medical Care in Diabetes added the A1c ≥ 6.5 % as another criterion for the diagnosis of diabetes2, but this is controversial and has not been universally adopted. In Diabetes higher amounts of glycosylated haemoglobin, indicating poorer control of blood glucose levels, have been associated with cardiovascular disease, nephropathy and retinopathy. Monitoring the HbA1c in type-I diabetic patients may improve treatment3.

Measuring A1c:

A number of techniques are used to measure A1c. Most laboratories adopt the following measures

- HPLC (high performance liquid chromatography)
- Immunoassay
- Boronate affinity chromatography.

A1c lists are certified by the national glycohemoglobin standardisation program (NASP) to standardize them against the results of the 1993 Diabetes control and complications trial (DCCT). However, the American Diabetes Association (ADA), European Association for the study of Diabetes (EASD) and International Diabetes Federation (IDF) have agreed that, in the future, HbA1c is to be reported in the international Federation of Clinical Chemistry (IFCC) units. IFCC reporting was introduced in Europe except for the UK in 2003, and the UK has of June 2009 introduced dual reporting unit dt. June 2011.

Conversion between the units is by the following equation IFCC-HbA1c (mmol/Mol) = [DCCT – HbA1c(%) – 2.15] X 10.929.

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1 Assistant Professor, Department of Pathology
2 Professor & HOD, Department of Pathology
SCB Medical College, Cuttack
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Interpretation of results:

Laboratory results may differ depending on the analytical technique, the age of the subject, and biological variation among individuals. Two individuals with same average blood sugar can have A1c values that differ by as much as 3%. Results can be unreliable in many circumstances, such as after blood loss like surgery, blood transfusions, anemia or high erythrocyte turnover, in the presence of chronic renal or liver disease, after administration of high dose vit C or erythropoietin treatment. In general, the reference range is about 4% - 5.9%.

Higher levels of HbA1c are found in people with persistently elevated blood sugar, as in Diabetes mellitus. A diabetic person with good glucose control has a HbA1c level that is close to or within the reference range. American Diabetes Association recommends that the HbA1c be below 7.0% for most patients. Recent results from large trials suggests that a target below 7% may be excessive. Below 7% the health benefits of reduced A1c becomes smaller, and the intensive glycemic control required to reach this level leads to an increased rate of dangerous hypoglycemic episodes4. A retrospective study of 47,970 diabetes patients found that patients with an A1c greater than 6.5% had an increased mortality rate.

Patients at high risk of microvascular complications may gain further benefits from reducing A1c below 7%. A high HbA1c represents poor glucose control. However, a ‘good’ HbA1c in a patient with diabetes can still be riddled with a history of recent hypoglycemia or even spikes of hypoglycemia. So, regular blood glucose monitoring is still the best method for the analysis of overall vascular health with respect to blood sugar control.

Persistent elevations in blood sugar and HbA1c increases the risk for the long-term vascular complications of diabetes such as coronary disease, heart attack, stroke, heart failure, kidney failure, blindness, erectile dysfunction, neuropathy, gangrene, gastro paresis, and short-term complications of surgery such as poor wound healing.

Reduced, level of HbA1c is seen in shortened red blood cell life span like sickle cell disease or G6PD deficiency and hemolytic Anemia.

Indications & use:

a) Checking blood sugar control in people who might be pre-diabetic.
b) Monitoring blood sugar control in patients in the more elevated levels, termed diabetes mellitus.

For a single blood sample it provides for more revealing informations on glycemic behavior then a fasting blood sugar value. The American Diabetes Associations guidelines are similar to others in advising that the glycosycated haemoglobin test be performed at least 2 times a year in patients with diabetes that are meeting treatment goals (that have stable glycemic control) and quarterly in patients with diabetes whose therapy has changed on that are not meeting glycemic goals.

Reference:

Current Perioperative Treatment of Patients with Diabetes

Nibedita Pani¹, Sidharth Routray²

Introduction:

Diabetes mellitus is the most common metabolic disease, and its incidence is rapidly increasing in epidemic proportions all over the world owing to the aging of the general population, reduced physical activity, and an excess of caloric intake[1,2]. A team approach is highly desirable in the evaluation of the diabetic patient undergoing surgical intervention because of the complexity and severity of this disease. A perioperative management plan should be agreed on by the diabetologist, the surgeon, and the anesthesiologist and should take into account parameters such as the type of diabetes, the quality of previous and current metabolic control, the current pharmacologic treatment, the type of intervention, and the postoperative course foreseen. Perioperative management protocols have been developed and implemented, leading to a better outcome. This article reviews the following issues: the classification of diabetes, the pathophysiology of glucose metabolism during surgical stress, the evaluation of operative risk, and the perioperative management of blood glucose and metabolic control.

Diabetes classification and pathophysiology:

Most diabetic patients are classified into two main categories [3]: (1) those with type 1 diabetes, which is caused by an absolute lack of insulin secretion [4], and (2) those with type 2 diabetes, which is characterized by the presence of insulin resistance and inadequate insulin secretion [3]. Type 1 diabetes is caused by autoimmune destruction of insulin-secreting pancreatic β cells and requires intensive insulin treatment, usually administered through a multiple-injection regimen or, in selected patients, delivered by an insulin pump. Blood glucose must be strictly monitored in type 1 diabetic patients because they tend to be metabolically unstable and to have broad glycemic fluctuations that can easily lead to a catabolic state with enhanced lipolysis and proteolysis resulting in ketoacidosis. Insulin resistance, which is a feature of type 2 diabetes, often characterizes other clinical conditions of enhanced cardiovascular risk. Many type 2 diabetic patients also have intra-abdominal (visceral) obesity, hypertension, atherogenic dyslipidemia. [6]. The clustering of these abnormalities, which is referred to as the “metabolic syndrome,” explains why patients with type 2 diabetes are at increased risk for macrovacular complications such as myocardial infarction, peripheral arterial disease, and stroke. In many patients, diabetes remains undiagnosed for a long period of time; therefore, they show significant target organ damage when the disease is recognized. Different regimens may be used in the treatment of type 2 diabetes combining diet, several classes of oral hypoglycemic agents, and insulin.

The metabolic response to surgical stress and anesthesia:

Anxiety over the forthcoming intervention, a fasting state, anesthesia, surgical maneuvers, and any other stress elicit a complex neuroendocrine response leading to inhibition of insulin action and secretion [7] and to stimulation of counter regulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone. Although this hormonal imbalance is overcome in normal subjects by increased insulin secretion, in diabetic patients it results in enhanced insulin resistance that induces a reduction in peripheral glucose uptake, an increase in hepatic glucose production, and fat and protein breakdown. As a consequence, there is a risk for diabetic ketoacidosis in type 1 diabetes and for hyperglycemic hyperosmolar states in type 2 diabetes. These complications are also promoted by surgery-induced fluid losses, dehydration, fluid under replacement, prolonged bed rest, and hypothermia that are common in the perioperative
period. Spinal, epidural, and other regional anesthesia techniques block most stress-induced metabolic and hormonal responses \[8\]. High doses of opioids may also inhibit this response, and a clear-cut advantage among these techniques is not yet evident. Patients treated with neural blockade resume oral feeding earlier than after general anesthesia and have a lesser disruption of their usual life; conversely, the risk of local infections and vascular damage is more likely with regional techniques. General anesthesia is associated with more hemodynamic stability in patients with autonomic neuropathy and prepares them better for possible complications \[9\].

**Preoperative evaluation:**

The mainstay of preoperative assessment is a thorough medical history and physical examination. It is necessary to ascertain the type of diabetes, the details of the pharmacologic regimen, the timing of meals and medications, and the ability of the patient to deal with the disease and to manage potential problems such as hypoglycemia. A specific assessment of the symptoms related to chronic microvascular, macrovascular, and neurologic complications must be performed. All chronic complications correlate with the duration of the disease; therefore, evidence of one complication must prompt the physician to search for the others. All of these findings have important implications for anesthesia. The aim of these inquiries is the formulation of a thorough intraoperative and postoperative management plan.

**Cardiovascular system:**

The excess mortality of diabetic patients is almost entirely due to cardiovascular diseases. Global cardiovascular risk in diabetic men is four times greater than in their non-diabetic counterparts, and in diabetic women the difference is even more pronounced \[10\]. Diabetic patients without a history of coronary heart disease have the same cardiovascular mortality as non-diabetic patients who sustain a cardiac attack; therefore, diabetes is considered an equivalent of coronary heart disease. Coronary atherosclerosis is more precocious, more extensive, and more severe in diabetic patients, although typical symptoms may be absent, particularly in women. Silent ischemia is common in diabetes and is related to autonomic neuropathy and sympathetic and vagal cardiac denervation. These patients often have tachycardia at rest, orthostatic hypotension, and a decrease of R-R variations during the Valsalva maneuver and must be regarded to be at high risk for silent ischemia and cardiorespiratory complications during anesthesia. The threshold for suspicion of coronary heart disease must be lower in patients aged more than 60 years, in those with a duration of diabetes longer than 15 years, and in those with a diabetic foot, macroalbuminuria or impaired renal function, or peripheral or autonomic neuropathy. In these patients, an exercise electrocardiographic test should be performed. Pharmacologic stress testing with imaging techniques (echocardiography, radionuclide study) should be performed in patients who are unable to exercise, as is common in patients with a diabetic foot. A specific cardiomyopathy may occur in diabetic patients without evidence of coronary artery disease.

**Kidney and urinary tract:**

In Western countries, diabetes is the leading cause of end-stage renal disease, and type 1 diabetic patients are one of the major cohorts of candidates for kidney transplantation. Diabetic nephropathy is common after 10 years of type 1 disease and may be present at diagnosis in type 2 diabetes. Microalbuminuria is an early marker of nephropathy in type 1 patients, whereas in type 2 patients it is a predictive factor of cardiovascular mortality. Urinary tract infections are also common in diabetes owing to the well-known susceptibility to infections and the impairment in bladder emptying in the presence of autonomic neuropathy. Renal failure is the most frequent major complication in diabetic patients undergoing general and cardiac surgery, affects about 7% of patients, and causes longer hospital stays with increased morbidity and mortality. Proteinuria, an increased serum creatinine level, advanced age, anemia, and a positive cardiovascular history are risk factors for perioperative renal dysfunction. A complete urinalysis to rule out infections and to assess proteinuria, serum creatinine, and electrolyte levels is mandatory before surgery. Renal hypoperfusion must be avoided through appropriate volume replacement, always watching for latent heart failure.

**Respiratory system:**

Lung function is impaired in diabetes, and clinical
infections are more frequent in diabetic patients, although a direct correlation with metabolic control is not clearly demonstrated. In type 1 diabetes, respiratory function tests may show a progressive impairment that correlates with autonomic neuropathy, but the clinical relevance of this finding needs to be ascertained.

**Diabetic joint stiffness:**

Diabetes mellitus is associated with abnormalities in the skin and periarticular tissues, resulting in affections that limit joint movement. Typical diabetes-associated conditions include palmar flexor tenosynovitis, Dupuytren disease, carpal tunnel syndrome, Charcot arthropathy, and shoulder-hand reflex dystrophy. In all of these conditions, advanced glycation end products are thought to form from nonenzymatic glycation of collagen proteins, resulting in the presence of pathologic connective tissue that, together neuropathy and microangiopathy, leads to the limitation of joint mobility. When the atlanto-occipital joint is involved and the extension of the occiput on the cervical spine is impaired, endotracheal intubation may be difficult or even impossible. A positive prayer sign (the patient’s inability to press the hands together to achieve a complete overlapping of palms and fingers) is highly correlated to the cervical spine involvement and may be a marker of difficult intubation. Difficulties in performing laryngoscopy and intubation are reported to be tenfold more common in diabetic patients when compared with non-diabetic patients. In patients with diabetic neuroarthropathy such as Charcot’s foot, stiffness of joints is frequent, and the patient during surgery must be carefully positioned in the operatory bed to avoid musculoskeletal or neurovascular injuries.

**Gastrointestinal system:**

Visceral neuropathy leads to vagal denervation with delayed gastric emptying, reduced peristalsis, and antroduodenal incoordination up to gastric paresis, and esophageal reflux with an increased risk of vomiting and aspiration of gastric contents. Considerations in such patients should include a prolonged presurgery fasting time, the use of an aspiration tube, and the inhibition of acid secretion. Optimal fluid and electrolyte balance is mandatory to favor the gastrointestinal motility. Prokinetic drugs are widely used, but their efficacy is not yet fully ascertained.

**Infectious risk:**

Diabetes increases the risk of morbidity and mortality from infectious diseases, and infections account for most diabetes-related hospital admissions. Hyperglycemia impairs polymorphonuclear and macrophage functions such as chemotaxis, phagocytosis, and bactericidal activity. The presence of micro- and macroangiopathy and the delayed wound healing further promote infections in diabetic patients. Pressure wound develops quickly, and during bed stays bony prominence must be carefully protected. During hospital admission, patients with an ischemic foot may quickly experience calcaneal wound pressure that may lead to infection and worsen the outcome. Ancillary surgical procedures must be performed with strict aseptic techniques, and antibiotic therapy must be performed using a full dosage regimen with bactericidal agents.

**Perioperative treatment of diabetes mellitus:**

The preparatory plan must consider the type and duration of diabetes, the potential complications, the actual treatment, the surgical procedure scheduled, the type of anesthesia chosen, and the time necessary before the patient to resume diabetes regimen. Patients must be hospitalized in good metabolic control and with their nutritional status optimized. Hyperglycemia is detrimental for diabetic and non-diabetic patients, whereas tight glycemic control improves clinical outcomes. Continuous intravenous insulin infusion is considered the best way to control blood glucose during surgery because it ensures an effective tissue delivery of the hormone and a simple and rapid titration owing to the short half-life of the intravenous insulin. Although many protocols have been advocated for the management of diabetic patients during surgery and in critical care units, there is no consensus on the best way to achieve optimal results in terms of glycemic control without important side effects.

Although there is no general agreement about the glycemic goals during surgery, the American Association of Clinical Endocrinologists and the American Diabetes Association have recently recommended in a hospital setting a range between 80 and 110 mg/dL for patients admitted in intensive care units and a random blood glucose level less than 180 mg/dL with a mean glycemia around 110 mg/dL in...
non–critically ill patients. Some concerns have been raised about these recommendations. They are not evidence based because the data are derived mainly from the study of patients in a single intensive care unit and not from controlled protocols. Moreover, a recent article has been published that questions such tight control. Very tight blood glucose control is associated with an increased risk of hypoglycemia, the symptoms of which are often masked in patients hospitalized for different illnesses or even anesthetized. Although surgical patients are not prone to hypoglycemia due to increased insulin resistance during a hospital stay, the harmful effects of hypoglycemia, especially in cardiac patients, cannot be underestimated. It is difficult to overcome all of the problems connected to the achievement of an optimal glycemic target without increasing the risk of hypoglycemia. Currently, a mean blood glucose level of 130 mg/dL with daily fluctuations in the range of 100 to 160 mg/dL is a good target for all hospitalized patients. In patients undergoing cardiac surgery, a more strict control of glycemia is strongly advised.

Patients with non-optimal metabolic control should be admitted almost the day before surgery and treated with insulin to normalize blood glucose. In general, surgery must be scheduled early in the morning to avoid a protracted fasting and to allow a longer surveillance period. A surgical intervention is defined as minor if the patient can resume oral food intake about 6 hours after operation. Surgery is defined as a major intervention when oral food intake cannot be resumed until 6 hours after operation or when protracted general anesthesia (ie, longer than 1 hour) is required.

Minor surgery

**Type 2 diabetic patients treated with diet or oral hypoglycemic agents:**

Metformin should be discontinued 48 hours before surgery and resumed after the assessment of renal function. Oral hypoglycemic agents should not be administered on the morning of intervention, and blood glucose should be checked before intervention and then every 1 to 2 hours until the patient resumes oral food intake and their usual drug regimen; as a rule, no additional treatment is necessary. If unexpected hyperglycemia occurs, single doses of regular insulin or a short-acting analogue should be administered.

**Type 2 diabetic patients treated with insulin or type 1 diabetic patients**

Long-acting insulin should be discontinued. On the evening before intervention, intermediate insulin can be administered although in reduced doses because the patient is in a semifasting state in view of the forthcoming operation. The experience with the new peakless insulin glargine as basal insulin is favorable; the day before the intervention, it can be injected at usual doses in patients undergoing minor surgery. Blood glucose should be checked at the beginning and then every hour throughout the intervention. Usual treatment should be restarted when oral food intake is resumed. Marked glycemic fluctuations should be avoided in these patients. If they occur, the following measures can be taken: either single doses of regular insulin or a short-acting analogue injected subcutaneously, or a short-lasting intravenous insulin infusion

**Major surgery:**

Patients undergoing major surgery must be treated with an intensive regimen of intravenous infusion of insulin, glucose, and potassium. Many protocols of insulin infusion have been published in recent years. These protocols use infusion algorithms that can be tailored to individual patients considering their clinical state and response to insulin infusion. A simple protocol is the GIK regimen (insulin, glucose, potassium), in which insulin may be infused in the same bag with glucose and potassium or given separately by an infusion pump. The GIK regimen starts with an intravenous infusion of 500 mL of 5% glucose added with 8 units of regular insulin and 20 mEq of KCl at a rate of about 100 mL/h. If a reduction in the total amount of administered fluids is desirable, 10% glucose solutions with 16 units of insulin can be used. Adjustments of insulin concentration are made according to the values of blood glucose obtained hourly by portable devices. If the blood glucose is higher than desired, 5 units of insulin are added; if hypoglycemia occurs, it is enough to stop the infusion (Table 2). A bolus of 5 units of regular insulin may be injected at the beginning of infusion if the blood glucose is more than 200 mg/dL. This regimen is safe, simple, and effective, but it is necessary to change the whole
infusion set if the patient experiences hyperglycemia and needs higher dosages of insulin. This change be prevented by administering glucose and potassium separately through one intravenous line and insulin, preferably with a pump, through another. An infusion rate of 1 U/h is appropriate for the great majority of patients. The starting solution is prepared by adding regular insulin to normal saline (eg, 25 units of regular insulin in 250 mL of normal saline) at an infusion rate of 10 mL/h; glucose infusion is kept constant at 5 to 10 g/h. If blood glucose levels rise, the rate of insulin infusion can be increased by 0.5 U/h. A close watch on the two infusion lines is recommended so that they will not clog and their flow will not be altered by other infusion lines. The infusion of glucose and insulin must be continued to prevent an excessive catabolism until normal food intake is resumed. The mean amount of glucose required is about 120 g/day at a rate of 5 to 10 g/h. This amount is best achieved giving a 10% dextrose solution at 100 mL/h. This dosage of insulin applies to patients with normal insulin sensitivity, which varies considerably from one patient to another.

**Table-1**

<table>
<thead>
<tr>
<th>Plasma Glucose (mg/dl)</th>
<th>Type-2 Diab</th>
<th>Type-1 Diab</th>
</tr>
</thead>
<tbody>
<tr>
<td>120-180</td>
<td>500 ml of 5% dextrose with 8 U insulin, 20mEq KCL infusion rate 100 ml/hr</td>
<td>500 ml of 5% dextrose with 16 U insulin, 20mEq KCL infusion rate 50 ml/hr</td>
</tr>
<tr>
<td>181-280</td>
<td>Add insulin 4 U</td>
<td>Add insulin 8 U</td>
</tr>
<tr>
<td>&gt;280</td>
<td>Add insulin 8 U</td>
<td>Add insulin 16 U</td>
</tr>
</tbody>
</table>

Higher dosages are necessary in conditions such as infections, hepatic disorders, obesity, neoplasms, and systemic illnesses. Preoperative insulin requirements can be indicative of the amount of insulin needed during intraoperative infusion. Insulin requirements are ten times higher during extracorporeal circulation because of hypothermia and the aspecific binding of insulin to the surface and tubing of the apparatus used for extracorporeal circulation. Neurosurgery also markedly increases insulin requirements.

**Emergency surgery:**

The goal is to maintain blood glucose levels within a target range (e.g., 120 to 180 mg per dL [6.67 to 10 mmol per L]) during the perioperative period. In a patient with type 1 diabetes, the insulin infusion is started at a rate of 0.5 to 1 U per hour. In a patient with poor control or in one with type 2 diabetes, the starting dose is usually higher, about 2 to 3 U per hour or more. The rate of insulin is adjusted according to a glucose feedback algorithm based on hourly glucose readings. An example of variable rate IV insulin infusion is shown in Table 2.

**Table 2**

Variable rate iv insulin infusion

Mix 100 U short acting insulin in 100 ml normal saline(1U=1ml)

Start insulin infusion at 0.5-1 U per hr.(0.5-1 ml/hr)

Start a separate infusion of 5 % dextrose in water at 100-125 ml per hr.

Monitor blood glucose level every hourly(2 hourly when stable) and adjust insulin infusion rate according to the following algorithm

**Target blood glucose range** is 120 t0 180mg/dl.

<table>
<thead>
<tr>
<th>Blood glucose (mg/dl)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 70</td>
<td>Turn off insulin infusion for 30 min. recheck blood glucose level, if blood glucose level is still below 70, give 10g glucose ,recheck blood glucose every 30 min. until the level is above 100,then restart insulin infusion and decrease rate at 1 U per hr</td>
</tr>
<tr>
<td>71-120</td>
<td>Decrease insulin infusion at the rate 1 U /hr</td>
</tr>
<tr>
<td>121-180</td>
<td>Continue insulin as it is</td>
</tr>
<tr>
<td>181-250</td>
<td>Increase insulin at 2 U / hr</td>
</tr>
<tr>
<td>251-300</td>
<td>Increase insulin at 3 U /hr</td>
</tr>
<tr>
<td>301-350</td>
<td>Increase insulin at 4 U/hr</td>
</tr>
<tr>
<td>351-400</td>
<td>Increase insulin at 5 U /hr</td>
</tr>
<tr>
<td>&gt;400</td>
<td>Increase insulin at 6 U/ hr</td>
</tr>
</tbody>
</table>

**Postoperative/intensive care management:**

Several studies have evaluated the effects of
hyperglycemia in the postoperative period. Glycemic control is known to decrease the risk of wound infection in diabetics after cardiac surgery. Analysis of 1585 diabetic patients undergoing cardiac surgery before and after the implementation of an insulin protocol (target BG < 200 mg/dL) revealed a significant decrease in the incidence of deep wound infection (2.4 to 1.5%). Furnary et al. had similar results in a prospective study of 2467 patients with the same BG goal; IIT was associated with a 66% decrease in deep sternal wound infection. In a retrospective analysis by Golden et al., postoperative hyperglycemia was an independent predictor of infectious complications in diabetic patients undergoing coronary artery bypass surgery. A more recent retrospective review also showed mortality benefit in this population; however, diabetic patients were the only subgroup in the Leuven studies to show no mortality benefit from IIT.

Studies on the effects of postoperative hyperglycemia outside of the diabetic cardiac surgery population and the critical care population are lacking. One retrospective cohort study by Vriesendorp et al. found elevated postoperative glucose levels to be an independent risk factor for infection in patients undergoing infra inguinal vascular surgery. In addition, in a prospective randomized pilot trial comparing IIT (target BG 80–120 mg/dL) to conventional treatment (target BG 80–220 mg/dL) in patients with aneurysmal subarachnoid hemorrhage status after surgical clipping, IIT was associated with decreased infection rate (42 to 27%) but no difference in the incidence of vasospasm, neurologic outcome, or mortality. The frequent use of intraoperative dexamethasone, which is known to further increase glucose levels, could make postoperative glycemic control harder to achieve in this patient population.

**Summary and Conclusion:**

In summary, due to the rising prevalence of diabetes, the provision of safe anaesthesia for these patients will become increasingly important. Type 1 diabetes always requires the administration of insulin and type 2 patients undergoing moderate or major surgery will require conversion to an insulin regimen during the peri-operative period. Although it is clear that hyperglycemia is harmful, there is currently insufficient evidence to support the routine use of tight glycemic control (target BG 80–110 mg/dL) in the operating room or the ICU. With careful, stepwise implementation of IIT protocols, maintaining BG less than 150 mg/dL and reducing BG variability may be both safe and effective.

**References:**


An Overview of Diabetic Foot

K.C. Mohapatra

“We are troubled not by the things of the world but, rather, by our perception of those things. Changing the interior states of our minds, we can change the exterior dimensions of our lives.”

This review article is intended for those people who valiantly care for patients with diabetic foot.

In this small article it is not possible to describe every aspect of diabetic foot but at least a conscious attempt has been made to give an insight to this mammoth and complex problem.

Despite advancements in the management of diabetes and its other complications, the outcome of diabetic foot has not changed. Lower extremity amputations continue to occur or even more than before. Every 30 seconds a part or whole of the foot is amputated due to diabetes. Even more distressing and frightening to know that more than 50% of lower extremity amputations world over are due to diabetes. Is it not a big challenge for the medical professionals involved in the management of diabetes and its complications to think and find out ways to tackle this ever increasing public health problem.

Diabetic foot is one of the most fascinating and challenging of all diabetic complications. It is the commonest cause of hospitalisation in a diabetic. They require long hospital stay, mounting cost and a huge burden on the health care system. In many countries, a large chunk of money from the health budget is spent in managing diabetic foot. In a poor country like India it is high time that the health care providers-government and non-governmental agencies should make an effective approach towards bringing down the rate of diabetic foot amputations. There is an ever increasing demand for research, information and education in this exciting field.

Human foot is a great architectural masterpiece and engineering work. 26 bones, 29 joints, many ligaments, tendons, muscles and neurovascular structures together form a unique structure for stability and mobility. Each and every structure of the foot is a highly specialised part to subserve diverse functions. Foot is a rigid compartment having many spaces within, so pathological changes leading to oedema and swelling will cause compartmental syndrome jeopardising the viability of the foot.

NEW APPROACH TO THE DIABETIC FOOT

Three great pathologies come together in the diabetic foot: neuropathy, ischaemia and infection. Their combined impact is so great that it causes more amputations than any other lower limb disease. Although there have been many advances in the management of the diabetic foot, it nevertheless remains a major global public health problem. All over the world health-care systems have failed the diabetic foot patient; however, amputations are not inevitable. As diabetic foot problems quickly reach the point of no return, it is vital to diagnose them early and provide rapid and intensive treatment. Furthermore, it is important to achieve early recognition of the at-risk foot so as to institute prompt preventive measures. The multidisciplinary foot clinic can reduce the number of amputations and has been developed as a successful model of care through the world.

It is necessary to understand the natural history of the diabetic foot to improve outcomes. The simple staging system developed in the King's Diabetic Foot Clinic, London by Edmunds and Foster is very helpful and provides an informative framework for early diagnosis and management. It also provides knowledge about the degree of involvement of foot.

RAPID ASSESSMENT OF THE FOOT

A simple and quick examination of the foot is necessary. It includes inspection, palpation and sensory testing. Shoe inspection should be included in the foot assessment. The diabetic patient should be examined from toe to head (Apada-Mastak) and both the feet should be examined together and the comparison is made. During this examination, 8 clinical features are
very important to elicit. They are – Neuropathy, Ischaemia, Deformity, Callus, swelling, Skin breakdown, Infection, Necrosis and Gangrene. Foot is classified into either neuropathic or neuro-ischaemic foot. A simple staging is evolved describing six stages. A simple management plan is outlined for each stage incorporating six aspects or controls.

**Six Stages of the Diabetic Foot**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Normal</td>
</tr>
<tr>
<td>Stage 2</td>
<td>High risk</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Ulcerated</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Infected</td>
</tr>
<tr>
<td>Stage 5</td>
<td>Necrotic</td>
</tr>
<tr>
<td>Stage 6</td>
<td>Unsalvageable</td>
</tr>
</tbody>
</table>

Three exceptions to this simple staging system are Charcot foot, neuropathic fracture and painful neuropathy.

**Six Aspects Of Patient Treatment (Controls), within a multi-disciplinary framework**

- Wound Control
- Microbiological Control
- Mechanical Control
- Vascular Control
- Metabolic Control
- Educational Control

The aim of managing diabetic foot is always to keep the patient as low a stage as possible. At each stage of the diabetic foot, it is necessary to intervene early and take control of the foot to prevent further progression.

**Multi-Disciplinary Diabetic foot Team & Diabetic Foot Clinics**

No one person can handle every aspect of preventing and treating diabetic foot problems and that it takes a multi-disciplinary team to reduce amputation. This comprises of several members within one roof who will be visiting regularly for ward rounds, X-ray conferences to tailor treatment plan for each patient. Each team member should be available quickly in an emergency. The diabetic foot clinic should provide access, early diagnosis and prompt treatment for patients with foot problems.

**Classification & Grading of Diabetic Foot**

In order to know the exact extent and degree of foot problem, several grading and classification systems are in vogue. They are helpful for prognosticating the foot problem such as Wagner’s, Modified Texas and PEDIS systems.

**Management**

The mainstay of diabetic foot management is prevention. Diabetic foot clinics should organise patient educational programmes about foot care, identification of risk features and seek medical attention at an early stage of a lesion. Diabetic foot care nurses, health workers and educators should be available at primary care levels and also reach to the people in rural areas for surveillance.

In stage 1 and stage 2, i.e., pre-ulcerative stage, we have to protect the foot by using proper footwear. Regular foot inspection and examination at intervals (neuropathy and vasculopathy) is mandatory. When neuropathy (loss of protective sensation) is present, utmost care is exercised to safeguard the foot from injury and infection.

When an ulcer has developed (stage 3), in area of high Plantar pressure, the aim of treatment is to achieve healing of the ulcer by using advanced wound care products and reducing pressure by orthotic devices (off-loading).

The 4th stage or the stage of infection which may be either minimal, moderate or severe. The foot has to be rested and proper antibiotic should be given. In minimal infection antibiotic treatment is sufficient but moderate and severe infections would need hospitalization, surgical debridement followed by culture specific antibiotic for a period of 2-3 weeks. Following debridement newer and effective wound care products with optimal triple layer dressing is required. If osteomyelitis is present the management is either medical or surgical. The medical management of osteomyelitis comprises of off-loading plus antibiotic for a prolonged period of 4-6 weeks. Alternatively the necrotic bone of osteomyelitis can be resected and sent for culture and sensitivity. The culture-specific antibiotic so obtained will be administered for a period of 6-12 weeks.
The 5th stage is the stage of necrosis, marked by extensive loss of tissue which may affect a part of or whole of the foot. Aggressive and radical debridement of all necrotic tissue is recommended. The aim of such surgical approach is to remove all possible non-viable tissues and leave behind apparently healthy tissues, the remaining part can perform the functions of the foot. In the 6th stage, foot is extensively gangrenous. Such a foot cannot be salvaged and amputation is inevitable. In all these stages, management of diabetes and its other associated complications are simultaneously taken care of under an integrated multi-disciplinary foot care team.

During the management of the diabetic foot in any of these stages, the six aspects of control mentioned earlier are followed.

**Newer Technology, Tools, Products & The Future in Diabetic Foot Management**

Though lots of advancements have been made in the diagnosis and treatment of diabetic foot, the most important parameter is the clinical judgement and the experience of the treating surgeon or physician. In the basket of modern investigations for diabetic foot, like MRI, CT, Isotope scans, CT angio, MR angio, PET Scan, TcPO₂, the plain radiography of the foot continues to be the most informative, simple and easy-to-read test.

The dys-vascular foot management has been very rewarding today with many diagnostic and therapeutic tools in our hand. The procedures like distal angioplasty, stenting, atherectomy and bypass surgery of the pedal vessels have been met with satisfactory outcomes in preventing amputations.

The medical as well as surgical management of osteomyelitis and charcot’s foot is also revolutionised. MRI can predictably distinguish between acute osteomyelitis and acute charcot’s foot, thus enabling proper treatment. Chronic, unstable charcot feet are now amenable to internal fixation and external Ilizarov fixators. Many reconstructive procedures, flaps, orthopaedic procedures such as Bunionectomy, Keller’s arthroplasty, metatarsal head excision, Flexer Tenotomy for correction of foot deformities for effective surgical offloading are also valuable adjunct to the treatment.

The microbiology of diabetic foot infections have been well studied. A generation of new antibiotics effective against MRSA and VRE is very much used with successful control of infection.

Besides surgical debridement by conventional scalpel, burr and saw, we know see new technology in the form of VERSAJET, ULTRASONIC and LASER debriders which function with precision, not hurting the normal tissues.

A full basket of wound care materials are available today in the market based on scientific research for various types of wounds. Hydrocolloids, hydrogels, algenates, ceramic granules collagens, growth factors like PDGF and EGF, bio-engineered skin substitutes and maggots are few of them.

Addressing psychosocial aspects of care for diabetic patients undergoing limb surgery is of immense help. An integrated multi-disciplinary approach is essential to improve the emotional well being of these patients to avoid potential complications that may prolong their convalescence and further degrade psychosocial welfare.

The future of diabetic foot management appears to be blissful. More numbers of surgeons and physicians should develop interest in this field of medicine so that we can play the number game to curb this menace and assure a healthy foot to the diabetic patient.

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Original articles, Reviews, Case Reports, Pictorial CMEs are invited for next issue of OMJ on theme “ANEMIA” to reach Editor / State HQ Office Before end of August, 2011
Skin Lesions Associated with Diabetes Mellitus

C S Sirka

Introduction:

Diabetes mellitus is known to induce different dermatological diseases depending on its effect on the different organs. The well understood mechanisms are through: insulin resistance, microangiopathy, biochemical alterations, slowing the activity of killer cells and inhibiting chemotaxis of polymorphous cells.

Biochemical Alterations:

The process of non-enzymatic glycosylation occurs in diabetics with increased blood sugar. This glycosylation of proteins are believed to be responsible for some of the skin changes associated with aging, and this process is accelerated in persons with elevated blood sugars. Glucosylation of the red cell membrane is apparently responsible for the stiffness of diabetic erythrocytes. Glucosylation of collagen results in increased stiffness and become resistance to enzymatic degradation. Protein glycosylation with changes in tertiary structure and solubility of proteins could conceivably be responsible for many of the complications of this disease.

Problems associated with insulin resistance

Acanthosis nigricans:

It results in the darkening and thickening of certain areas of the skin especially in the skin folds. The skin becomes tan or brown and is sometimes slightly raised and described as velvety. Most often the condition, typically looks like a small wart, appears on the sides or back of the neck, the armpits, under the breast, and groin. Occasionally it occurs on the dorsal aspects of knuckles. Acanthosis nigricans usually occurs on people who are overweight. Acanthosis nigricans usually precedes diabetes. There are other conditions that also are known to cause acanthosis nigricans, that includes including Acromegaly and Cushing’s syndrome. This condition is often a skin manifestation of insulin resistance in most people. Diagnosis is mostly clinical. There is no cure for acanthosis nigricans, but losing weight may improve the condition.

Problems associated with reduced blood supply to the skin

Skin problems linked to atherosclerosis:

Atherosclerosis is most often occurs in the major blood vessels but it can affect blood vessels throughout the body, including those supplying the skin. The narrowing bloodvessels due to atherosclerosis and stiffness of diabetic erythrocytes hinders the blood supply to the skin there by bring about decrease oxygen supply. This decrease blood supply leads to hair loss, thinning and shiny skin on the shins, thickened and discolored toenails, and cold skin. At the same time following trauma it takes long time to heal because of the decrease blood supply. The limited reach of white blood cells to the infected site and diabetis having inhibitory affect on the killer cells and polymorphs the body also fails fight infection effective when the infection is at distant site.

Necrobiosis lipoidica diabeticorum:

Necrobiosis lipoidica diabeticorum (NLD) is caused due to changes in the collagen and fat content of the skin. The lesion is characterized by localized area of thin skin with redness. The commonest site of occurrence is on the lower legs and it may ulcerate if subjected to trauma. Lesions usually have well defined border and sometimes the lesions could be itchy and painful. As long as the plaque do not break open, treatment is not necessary.

Diabetic dermopathy:

It is also known as shin spots, it develops as a result of microangiopathy of vessels that supply the skin. It appears as a shiny round and atrophic area of...
skin over the front lower parts of the lower legs (shin). The patches are mostly asymptomatic, although rarely they can be itchy or causes burning sensation. Treatment generally is not necessary.

**Digital sclerosis:**

Digital sclerosis (binding down of skin to underlying structure of fingers and toes) is a condition in which the skin of toes, fingers, and hands becomes thick, waxy, and tight. Stiffness of the finger joints also may get affected. Patient find difficult to oppose his/her fingers. The treatment is to bring the blood glucose level to normal. Lotions and moisturizers may help to soften the skin.

**Eruptive xanthomatosis:**

This occurs when triglycerides level is very high and blood glucose levels are not well controlled. Eruptive xanthomas appear as a firm, yellow, waxy pale papule on the skin. The papules are surrounded by red halos and are usually asymptomatic are found on the face and buttocks. They can also be seen on the back side of the arms, legs and extends on to the distal part of extremities. Treatment for eruptive xanthomatosis consists of controlling the level of Triglyceride and blood glucose in the blood. The skin eruptions resolve over several weeks on controlling blood glucose level and taking lipid-lowering drugs.

**Diabetic blisters (bullous diabeticorum):**

It occurs in long standing diabetes with high blood sugar, where peripheral neuritis has set in causing decrease perception to temperature, pain, trauma and decreased sweating due to involvement of the autonomic nervous system. The blisters occur on the fingers, hands, toes, feet, legs, or forearms due to trauma or exposure to extreme temperature, which remains un-noticed by the patient because of peripheral neuropathy. These blisters are usually painless and heal on their own. Bringing your blood glucose level under control often reverts the neuropathy and avoiding extreme temperature can minimize diabetic bulla.

**Disseminated granuloma annulare:**

This condition is characterized by sharply defined ring or arc-shaped skin coloured to slightly erythematous plaque with beaded border. The centre of the lesion is depressed. Cause is not known but it is seen mostly in diabetics. Treatment usually is not encouraging, but sometimes drugs like topical steroid, and normal saline intra-lesional injection gives variable results.

**Scleroderma diabeticorum:**

It is a condition characterized by localized thickening of the skin; affecting the skin of back of the neck and upper back. This condition is rare but often affects people with diabetes who are overweight. The treatment is controlling blood glucose level.

**Bacterial and fungus infections:**

When the bacteria makes an entry through the unhealthy skin it may causes wide spread infection and may take long time to heal as there is decrease in the chemotaxis in the diabetic patients. Similar is the case with fungus, the normal commensals may grow more as the increase blood sugar is a good medium for the fungus to grow and the chemotaxis is abnormal. Fungal infection of nails is more than the normal individual as the nails become brittle due to neuropathy and decrease flow of blood due to atherosclerotic changes and this facilitate the fungal infection.

**Suggested readings:**

1. Rook’s textbook of Dermatology 8th ed.
2. Fitzpatrick’s Dermatology in Internal Medicine 7th ed.
3. Andrew’s diseases of the skin: Clinical Dermatology 10th ed.
Anesthetic Implications of Diabetes – Recent Evidence

Bhavna Sriramka¹, Narayan. Sahoo², Sanjukta Panigrahi¹

Introduction:

The world has been experiencing a great and progressive growth in the number of people who are known to be diabetic. The risks involved in caring for someone with diabetes are similar to the risks for someone much older, i.e., someone who has a much higher physiologic age ("RealAge")¹, ². Patients undergoing surgery move through a continuum of medical care to which a primary care physician, an anesthesiologist, and a surgeon or obstetrician-gynecologist contributes to ensure the best outcome possible. The importance of this integrating expertise is even greater within the context of the increasing life span of our population³. At a time when medical information is encyclopedic, it is difficult if not impossible for even the most conscientious anesthesiologist to keep abreast of the medical issues relevant to every aspect of perioperative or periprocedure patient management. Patients with diabetes undergo surgical procedures at a higher rate than do nondiabetic people and have increased postoperative morbidity and mortality⁴, ⁵.

The stress of surgery itself results in metabolic perturbations that alter glucose homeostasis, and persistent hyperglycemia⁶. Hyperglycemia impairs leukocyte function⁷, causes endothelial dysfunction, impairs wound healing⁸ and increases postoperative sepsis⁹. The stress response itself may precipitate diabetic crises (diabetic ketoacidosis [DKA], hyperglycemic hyperosmolar syndrome [HHS]) during surgery or postoperatively, with negative prognostic consequences¹⁰, ¹¹. HHS is a well known postoperative complication following certain procedures, including cardiac bypass surgery, where it is associated with 42% mortality¹¹, ¹². Furthermore, gastrointestinal instability provoked by anesthesia, medications, and stress-related vagal overlay can lead to nausea, vomiting, and dehydration. This compounds the volume contraction that may already be present from the osmotic diuresis induced by hyperglycemia, thereby increasing the risk for ischemic events and acute renal failure. Subtle to gross deficits in key electrolytes (principally potassium, but also magnesium) may pose an arrhythmogenic risk, which often is superimposed on a milieu of endemic coronary artery disease in middle-aged or older people with diabetes. It is therefore imperative that careful attention be paid to the metabolic status of people with diabetes undergoing surgical procedures. Elective surgery in people with uncontrolled diabetes should preferably be scheduled after acceptable glycemic control has been achieved. Admission to the hospital 1–2 days before a scheduled surgery is advisable for such patients. Even emergency surgery should be delayed, whenever feasible, to allow stabilization of patients in diabetic crises.

Preoperative and Preprocedure Diabetes Mellitus:

The Diabetes Control and Complication Trial for Type I diabetics¹³ (DCCT) and the UKPDS for Type II diabetics confirm that tight control of blood glucose does benefit the pregnant diabetic (and her future offspring), those undergoing cardiopulmonary bypass, for those undergoing (global) CNS ischemia, and for those requiring postoperative or postprocedure care in an intensive care unit. The major risk factors for diabetics undergoing surgery are the end-organ diseases associated with diabetes: cardiovascular dysfunction, renal insufficiency, joint collagen tissue abnormalities¹⁷ (limitations of neck extension and “stiff joint syndrome”), poor wound healing, inadequate granulocyte production, and neuropathies.

Thus a major focus of the anesthesiologist should be the preoperative and preprocedure evaluation and treatment of these diseases to ensure optimal
preoperative and preprocedure conditions. Regional anesthesia may be indicated to facilitate some procedures. The following considerations should be kept in mind regarding the use of regional anesthesia for diabetic patients. Local anesthetic requirements are lower and the risk of nerve injury is higher in diabetic patients. Also, combining local anesthetics with epinephrine may pose even greater risk of ischemic and/or edematous nerve injury in the diabetic. Nosocomial infection rates are probably decreased with outpatient surgery; complications may be decreased in those diabetics most at risk by either tight control of blood glucose or intense postoperative care, or both.

**Goals Of Perioperative Glycemic Control:**

The goals for glycemic control are tailored to each patient based on a number of factors, such as the nature of the surgery, severity of the underlying illness, modality used to achieve glycemic control, patient age, and sensitivity to insulin. Numerous clinical trials have involved various patient populations and examined the implications of perioperative hyperglycemia. Based on data derived from these studies, the American Diabetes Association made recommendations for managing blood glucose levels in hospitalized patients with diabetes mellitus (Table 1).

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Blood Glucose Target</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>General medical/surgical*</td>
<td>Fasting: 90-126 mg/dL Random: &lt;200 mg/dL</td>
<td>Decreased mortality, shorter length of stay, lower infection rates</td>
</tr>
<tr>
<td>Cardiac surgery†</td>
<td>&lt;150 mg/dL</td>
<td>Reduced mortality, reduced risk of sternal wound infections</td>
</tr>
<tr>
<td>Critically ill†</td>
<td>&lt;150 mg/dL</td>
<td>Beneficial effect on short-term mortality, morbidity; length of stay</td>
</tr>
<tr>
<td>Acute neurologic disorders ‡</td>
<td>80-140 mg/dL</td>
<td>Lack of data, consensus on specific target; consensus for controlling hyperglycemia</td>
</tr>
</tbody>
</table>

* American Diabetes Association
† Society Critical Care Medicine.
‡ American Heart Association/American Stroke Association

The best marker for recent control is the percentage of glycosylated haemoglobin (HbA1C). If available, levels less than 7% indicate good control whilst levels over 9% and particularly 12%, indicate poor control and likely associated electrolyte and water loss. These patients should be admitted preoperatively for correction of these abnormalities and stabilisation of blood sugar levels before the addition of surgical stressors. If this is unavailable, try to assess control by looking at the patient’s own log of urine or blood glucose. The length of surgery, the type of surgery, and the degree of glycemic dysregulation dictate the amount of supplemental insulin. It is recommended for patients with type 1 diabetes to schedule elective surgeries as the first case of the day to minimally disrupt their diabetes mellitus (DM) regimen.
General Principles Of Anesthetic Management:

- Avoid hypoglycaemia (under 4mmol/l) as this can cause irreversible cerebral damage.
- Avoid severe hyperglycaemia (over 14mmol/l) to minimise dehydration and metabolic upset.
- Diabetic patients should be placed first on the operating list to shorten the preoperative fast and potentially allow normal oral intake later that same day.
- Tight metabolic control is important for both type 1 and type 2 patients. If control has been tight in the preceding weeks then fluid and electrolyte balance will be essentially normal.
- Continue all diabetic medication until the day of surgery except: Chlorpropamide which can be stopped 3 days prior and substituted with a shorter acting sulphonylurea; and Metformin/ Glitazones if there is risk of lactic acidosis. In major surgery or those on long acting insulin should be substituted with short/intermediate acting.
- If the patient is expected to eat within 4 hours of the operation or is a type 2 diabetes NOT on insulin (diet/tablet controlled), then treat this group as having "Minor" Surgery. Otherwise surgery is "Major."
- Establish separate intravenous access for a "piggyback" infusion of regular insulin and intra-arterial catheter placement for checking blood glucose concentrations every 1-2 hours intraoperatively and postoperatively. A second intravenous catheter may be used for intravascular volume replacement with a normal saline solution.

Numerous insulin protocols are available, with varying reliability and validation. In addition, computer-based systems are available that calculate the continued dosing based on glucose concentration and rate of change. An example of such a system is the Glucommander. The programme recommends the amount of insulin based on glucose parameters using a simple equation:

Insulin per hour = multiplier x (blood glucose – 60):

The two commonly used regimens used are the classic and the tight control regimen. Type 1 diabetic patients definitely need insulin and might be considered candidates for tight control of blood glucose levels. In regards to type II diabetic patients there is a debate on whether to switch over to insulin or continue oral hypoglycemic. Although Type 2 diabetics not receiving insulin and undergoing minor surgery usually can be managed satisfactorily without insulin. However in our institution we do prefer to have insulin, and current data indicate they do not benefit from tight perioperative control, unless they need intensive care. In any case if local guidelines exist, those can be followed for continuity of practice.

Protocol: **Classic “Nontight Control” Regimen**

1. Day before surgery: Patient should be given nothing by mouth after midnight
2. At 6 AM on day of surgery, institute intravenous fluids using plastic cannula and a solution containing 5 percent dextrose, infused at the rate of 125 ml/h/70 kg body weight.
3. After institution of intravenous infusion, give one-half the usual morning insulin dose (and usual type of insulin) subcutaneously.
4. Continue 5 percent dextrose solutions through operative period, giving at least 125 ml/h/70 kg body weight.
5. In recovery room monitor blood glucose concentrations and treat on a sliding scale.

Protocol: **“Tight Control” Regimen**

1. Evening before operation, determine pre-prandial blood glucose level.
2. Through a plastic cannula, begin intravenous infusion of 5 percent dextrose in water at the rate of 50 ml/h/70 kg body weight.
3. “Piggyback” to the dextrose infusion an infusion of regular insulin (50 units in 250 ml 0.9 percent sodium chloride) and an infusion pump. Before attaching this piggyback line to the dextrose infusion, flush the line with 60 ml of infusion mixture and discard the flushing solution. This approach saturates insulin-binding sites of the tubing.
4. Set the infusion rate, using the following equation: 
\[ \text{Insulin (U/h) = plasma glucose (mg/dl)/150.} \] 
(Note: This denominator should be 100 if patient is taking corticosteroids, e.g., 100 mg of prednisolone a day or its equivalent, not to include inhaled steroids.)

5. Repeat measurements of blood glucose levels every 4 hours as needed, and adjust insulin appropriately to obtain blood glucose levels of 100 to 200 mg/dl.

6. The day of surgery, intraoperative fluids and electrolytes are managed by continuing to administer non-dextrose containing solutions, as described in steps 3 and 4.

7. Determine plasma glucose level at the start of operation and every 1 to 2 hours for the rest of the 24-hour period. Adjust insulin dosage appropriately.

The rate of infusion is adjusted according to a glucose feedback algorithm based on hourly glucose readings. An example of variable rate IV insulin infusion is shown in Table 2.

Table 2: Variable Rate Infusion Regimen:

<table>
<thead>
<tr>
<th>Blood glucose level, mg per dl (mmol per L)†</th>
<th>Action</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 70 (3.89)</td>
<td></td>
<td>Stop insulin if on infusion. Rapid infusion of 100 ml of D5W</td>
</tr>
<tr>
<td>71 to 120 (3.94 to 6.67)</td>
<td>Turn off insulin for 30 minutes, recheck blood glucose level. If blood glucose level is still below 70, give 10 g glucose and recheck blood glucose level every 30 minutes until the level is above 100 (5.56), then restart infusion and decrease rate by 1 U per hour.</td>
<td>Decrease insulin infusion rate by 1 U per hour</td>
</tr>
<tr>
<td>121 to 180 (6.72 to 10.0)</td>
<td>Continue insulin infusion as is</td>
<td></td>
</tr>
<tr>
<td>181 to 250 (10.1 to 13.89)</td>
<td>Increase insulin infusion rate by 1 U per hour</td>
<td></td>
</tr>
<tr>
<td>251 to 300 (13.94 to 16.67)</td>
<td>Increase insulin infusion rate by 2 U per hour</td>
<td></td>
</tr>
<tr>
<td>301 to 350 (16.72 to 19.4)</td>
<td>Increase insulin infusion rate by 3 U per hour</td>
<td></td>
</tr>
<tr>
<td>351 to 400 (19.5 to 22.2)</td>
<td>Increase insulin infusion rate by 4 U per hour</td>
<td></td>
</tr>
<tr>
<td>Above 400 (22.2)</td>
<td>Increase insulin infusion rate by 5 U per hour</td>
<td></td>
</tr>
</tbody>
</table>

*—Glucose infusion rate can also be increased if tendency toward hypoglycemia persists.
†—Target blood glucose range is 120 to 180 mg per dL (6.67 to 10.0 mmol per L).

This regimen has been associated with some insulin resistance in patients undergoing cardiopulmonary bypass, hypothermia, catecholamine supplementation, low flow rates, sepsis and severe surgical stress. Insulin requirements may exceed 10U/hr and frequent blood sugar determination becomes critical.

Mariam A et al have devised a simple glucose-insulin-potassium infusion regimen popularly known as the Vellore regimen. In this regimen; neutral insulin 5U in 500 ml of D5W is started in morning 8 am using a measured volume burette set at rate of 100ml/hr until the time of operation. At zero hour, the blood glucose is checked and burette filled to 100 ml, insulin is added as per blood glucose shown in Table 3.

Table 3: Vellore Regimen:

<table>
<thead>
<tr>
<th>Blood glucose level, mg per dl</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 70</td>
<td>Stop insulin if on infusion. Rapid infusion of 100 ml of D5W</td>
</tr>
<tr>
<td>71 – 100</td>
<td>Stop insulin, infuse D5W at 100 ml/hr</td>
</tr>
<tr>
<td>101 – 150</td>
<td>1 U of insulin 100 ml of D5W/hr</td>
</tr>
<tr>
<td>151 – 200</td>
<td>2 U of insulin 100 ml of D5W/hr</td>
</tr>
<tr>
<td>201 – 250</td>
<td>3 U of insulin 100 ml of D5W/hr</td>
</tr>
<tr>
<td>251 – 300</td>
<td>4 U of insulin 100 ml of D5W/hr</td>
</tr>
<tr>
<td>&gt;300</td>
<td>1 U of insulin for every 1-50 mg more than 100 mg/dl in 100 ml of normal saline/hr</td>
</tr>
</tbody>
</table>

Adsorption of insulin on to the surface of syringes, IV fluid bags and IV sets is an unavoidable problem. In solutions with a concentration of insulin of >400 ng/ml (<“10 U/L) the effect is minimal. However, significant amounts of insulin may be adsorbed on to giving sets, particularly if they have a relatively high surface area, thereby reducing initial rates of insulin delivery if a highvolume, lowinsulin concentration regimen is used. More consistent delivery can be achieved with more concentrated solutions of lower volume administered from a syringe.

Postoperative diabetic patients present unique challenges. Initiating nutrition is often delayed and frequently interrupted for diagnostic studies or procedures. To reduce the likelihood of adverse effects, the regimen selected should include nutritional feeding (continuous vs. intermittent). Perioperative beta-blocker therapy should be considered for all diabetic patients undergoing intermediate or major risk noncardiac surgery as a means to decrease the incidence of postoperative myocardial ischemia and infarction. It is prudent to also assess all patients for orthostatic hypotension. This is easily diagnosed by performing a “tilt test” in the operating room, with patients receiving appropriate intravascular volume resuscitation before initiating any form of regional or general anesthesia. Patients suspected of gastroparesis should receive a prokinetic drug before the administration of general anesthesia to decrease the incidence of gastric acid
aspiration. Aseptic technique is particularly critical for patients with diabetes mellitus (DM) to decrease the incidence of postoperative infection. In addition, temperature control is also essential, as hypothermia can lead to peripheral insulin resistance, hyperglycemia, deceased wound healing, and infection. Hypothermia has been associated with an increase in wound infection following colon resection, craniotomy for cerebral aneurysm clipping, and open heart surgery with cardiopulmonary bypass.

Intraoperative management of intravascular volume may require the use of a central venous pressure catheter, a pulmonary artery catheter, or transesophageal echocardiography (TEE) to optimally guide therapy and to prevent end-organ hypoperfusion. Arterial blood gas (ABG) analysis should include assessment of blood glucose levels, in addition to sodium, potassium, and pH. Patients with type 1 diabetes are predisposed to developing ketoacidosis during periods of major stress; therefore, they should be monitored by arterial blood.

**Emergency Surgery:**

Approximately 5% of people with diabetes will require emergency surgery over their lifetime. The commonly performed surgeries include general procedures (laparotomy, appendectomy, cholecystectomy, and so forth) and diabetes-related procedures, such as abscess drainage, ulcer care, and lower-extremity amputation.

By definition, the time of occurrence of these emergencies cannot be predicted, and appropriate surgical care must not be unduly delayed. Nonetheless, particular care must be taken to exclude DKA and other conditions that are likely to be mistaken for surgical emergencies. Many patients with DKA and prominent abdominal symptoms have undergone needless surgical exploration for a nonexistent acute abdominal emergency. Functional syndromes due to diabetic autonomic neuropathy of the gastrointestinal tract (gastroparesis, gastroenteropathy, intractable or cyclical vomiting) may mimic anatomical surgical emergencies. Similarly, the rare diabetic pseudotabes syndrome, characterized by sharp neuropathic pain along thoracolumbar dermatomes, can be confused with visceral disorders. Patients with pseudotabes typically have pupillary and gait abnormalities from associated cranial and peripheral neuropathy. The initial evaluation of a diabetic patient with a suspected surgical emergency must, therefore, include a thorough medical history and physical examination directed at excluding the aforementioned diagnostic pitfalls. Unfortunately, many patients who require emergency surgery will have suboptimal glycemic control. However, this is not necessarily a contraindication to the timely performance of potentially life-saving surgery. An intravenous access should be secured and immediate blood specimens should be sent for glucose, electrolyte, and acid-base assessment. Gross derangements of volume and electrolytes (e.g. hypokalemia, hypernatremia) should be corrected. Surgery should be delayed, whenever feasible, in patients with DKA, so that the underlying acid-base disorder can be corrected or, at least, ameliorated. Patients with HHS are markedly dehydrated and should be restored quickly to good volume and improved metabolic status before surgery. Blood glucose should be monitored hourly at the bedside, and insulin, glucose, and potassium infusion should be administered, as appropriate, to maintain blood glucose in the 120–180 mg/dl range. Serum potassium should be checked frequently (every 2–4 h), and potassium supplementation should be adjusted to ensure that the patient remains euclidean throughout surgery and postoperatively.

**Summary:**

The increasing prevalence of diabetic patients undergoing surgery and the increased risk of complications associated with diabetes mellitus (DM) require optimal perioperative assessment and management. Diabetes management and its associated morbidities present a number of challenges, which are becoming an increasingly common medical issue. Although the benefits of tight glycemic control have been well documented in specific patient populations, the optimal range has yet to be well defined. Intensive glycemic control necessitates close monitoring to reduce the incidence of hypoglycemia, which may negate the benefits of tight control. Computerized methods, such as the Glucommander, appear to provide a more responsive alternative to insulin protocols. Recent outcomes data are lacking, but it is likely that advances in surgical science, anesthesiology, and intensive care medicine, together with increased awareness and
appropriate metabolic intervention, may have improved the perioperative fate of diabetic patients in recent times. However, future research is still needed to help optimize the perioperative management of the diabetic patient.

References:
Rheumatological Manifestations in Diabetes Mellitus

Prasanna Kumar Rathor

Introduction:
Diabetes mellitus affects every system of the body including musculoskeletal system. The first description of neuropathic joint in diabetes was made in 1936. But in the last 3 decades the articular features of diabetes have been clearly defined. Many rheumatic syndromes occur more frequently in diabetic patients than in general population.

The rheumatological manifestations of diabetes are enumerated in the tabular form as follows:

Table: 1

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Typical joint involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diabetic stiff hand syndrome (Diabetic cheiroarthropathy)</td>
<td>Metacarpophalangeal, proximal inter phalangeal Joint</td>
</tr>
<tr>
<td>2. Dupuytren’s contracture</td>
<td>Fourth &amp; other flexor tendons</td>
</tr>
<tr>
<td>3. Trigger finger</td>
<td>Flexor tendons</td>
</tr>
<tr>
<td>4. Adhesive capsulitis</td>
<td>Shoulders</td>
</tr>
<tr>
<td>5. Reflex sympathetic dystrophy</td>
<td>Shoulders, hands</td>
</tr>
<tr>
<td>6. Carpal Tunnel Syndrome (CTS)</td>
<td>First 4 fingers</td>
</tr>
<tr>
<td>7. Charcot’s arthropathy</td>
<td>Foot, ankle</td>
</tr>
<tr>
<td>8. Diffuse idiopathic skeletal Hyperostosis (DISH)</td>
<td>Spine</td>
</tr>
<tr>
<td>9. Osteomyelitis</td>
<td>Foot</td>
</tr>
<tr>
<td>10. Diabetic angiopathy</td>
<td>Shoulder, back, Thigh</td>
</tr>
</tbody>
</table>

Diabetic Cheiroarthropathy:
This condition is also known as diabetic hand syndrome (DHS), limited joint mobility syndrome (LJM). It is a common complication of Type-1 and Type-2 DM. It may be due to excessive glycosylation of collagen in skin, blood vessels and periarticular sites and due to decreased collagen degeneration and removal resulting in thick inelastic tissues. This complication of LJM occurs in 30% patient with long term complications.

In 1957 Lundback Published a description of hand stiffness as a complication of diabetes mellitus. This was the first widely published description of the condition. This LJM occasionally may extend to the proximal upper extremities and spine.

Clinical Features:
In diabetic cheiroarthropathy there is extension of MP, PIP and DIP joints. It generally begins in ulnar digits and spreads radially.

Simple Physical examination signs used to screen for diabetic cheiroarthropathy

i. Preacher’s sign or Prayer’s sign

ii. Table Top sign

The preacher’s sign involves the patient holding palms apposed to one another vertically with elbows flexed and wrists extended. A positive sign is indicated by an inability of the patient to completely approximate the palmar surface of digits. The table top sign is a similar test in which the patient places the palms flat on a hard surface with the digits spread. Normally the entire palmar surface of the digits should contact the
If the test is positive, the digits and palm will not lie flat.

Both these tests can be positive with other clinical conditions such as dupuytren’s contracture or previous trauma. So a careful history taking and physical examination helps to rule out these conditions.

Almost universally, studies show a positive relationship of LJM with age and duration of diabetic diseases. Notably a study which investigated 78 cases with a relatively short duration of Type-2 DM (<10 yrs) found no evidence of the condition. Lowson et al indicated that in Type-1 DM, LJM was related to retinopathy independent of age and duration of disease. In Type-2 DM, LJM (Diabetic Cheiroarthropathy) was linked to age and duration but not independently to retinopathy.

**Dupuytren’s Disease (DD):**

Dupuytren’s disease (DD) is more common among those with diabetes than in general population. The pathophysiology of DD differs in people with or without diabetes. Further more, although LJM (diabetic cheiroarthropathy) and DD may coexist in people with diabetes, the two are distinct clinical entities. The prevalence of Dupuytren’s contracture is about 30%.

**Clinical Features:**

Dupuytren’s disease consists of palmar and digital nodules and cords, palmar skin tethering and digital contractures. In the setting of DM, involvement is predominantly of the ring and middle digits as opposed to DD which more commonly involves the small and ring digits.

As with LJM (Diabetic cheiroarthropathy), DD has been found to have an increased incidence among diabetic patients and age and duration are likewise associated with an increased incidence of DD. DD is also associated with neuropathy and diabetic cheiroarthropathy independent of age and duration. In contrast to most cases of LJM, Dupuytren’s contracture may be seen early in the course of the diabetes.

**Frozen Shoulder (Adhesive Capsulitis of shoulder)**

It is a well established complications of diabetes. It presents with pain and restriction of shoulder joint movement. The glenohumeral joint is normal. It may occur with or without calcific tendinitis and may be associated with reflex sympathetic dystrophy.

A recent series from India has reported an incidence of 17.9% in diabetic persons. The patients are managed with physiotherapy NSAID therapy, local stenting & surgery.

**Carpal tunnel Syndrome (CTS):**

Carpal Tunnel Syndrome has well documented correlation with diabetes. Besides, carpal tunnel syndrome seems to provide less reliable symptoms relief in the diabetic population. CTS occurs in about 25% of individuals with diabetes mellitus.

**Clinical features:**

CTS present with similar clinical findings in both diabetic and non-diabetic patients. The incidence of carpal tunnel syndrome in the diabetic population has consistently been reported as between 11 and 21% in numerous studies. The exact mechanism of CTS in the setting of DM is not known. Two theories are there. One is that glycosylation of connective tissue increases collagen cross linking, leading to increased stiffness and thickening of the transverse carpal ligament or peritendinous tissue. A second view is that polyneuropathy caused by diabetic microvascular leads to increased susceptibility of the median nerve to a compressive injury. In the diabetic population, carpal tunnel syndrome has been connected independently to retinopathy, general peripheral neuropathy, stenosing tenosynovitis and Dupuytren’s disease.

**Trigger finger (Stenosing tenosynovitis):**

A catching and snapping of the finger is less well documented among diabetics than are diabetic cheiroarthropathy Dupuytren’s disease and carpal tunnel syndrome.

**Clinical features:**

Patients present with complaints of stiffness pain or locking in the digit with tenderness and often a palpable nodule. Trigger finger is more common in female patients more often bilateral, more often multidigit and relatively sparing of the index and small fingers. Trigger finger in diabetic patients respond less well to corticosteroid injection, a common initial treatment and more often requires surgery.

Trigger finger has been shown to have a prevalence of approximately 20% in diabetic population compared with 2% in general population.
Charcot’s arthropathy:

In diabetes this condition involves the feet (ankle or midfoot) and invariable occurs in individuals with sensory neuropathy. The onset is abrupt with swelling often with minor trauma. Radiograph shows the bone fragments, and disorganization. Physicians may mistake it for infection. Splinting and bracing is the fruitful treatment available for this condition.

Diffuse idiopathic skeletal hyperostosis (DISH)

Hyperostosis is more common in diabetics than in the general population. It is a systemic condition and the enthesal regions are predominantly affected. Hyperostosis may present as calcification of ligaments (hyperostotic spondylosis), abnormal deposition of bone on inner aspects of frontal bone (hyperostosis frontalis interna) or at any site of the body. Calcification of the spinal ligament is the commonest and is known as diffuse idiopathic skeletal hyperostosis (DISH). Clinically new bone deposition is mostly asymptomatic apart from increasing stiffness in the neck, back or peripheral joints. The radiological diagnostic criteria includes bridging of four contiguous vertebral bodies by new bone formation in the absence of degenerative disc disease and the absence of inflammatory sacroiliitis or facet changes. The suggested pathogenesis of DISH is hyperinsulinemia over a prolonged period which has contributory role towards new bone formation at enthesal sites.

Osteomyelitis:

Osteomyelitis in the foot is a major problem & diabetes. Because of diabetic peripheral sensory neuropathy, patient is unaware of foot ulcer and pressure ulcers. Patients may not realize the situation until advanced osteomyelitis develop. Also subcutaneous foreign bodies e.g. needles and splinter can be present for weeks or even months before the patient is aware of these. By meticulous footcare infection and other complications can be minimized to a great extent.

Diabetic amyotrophy:

Diabetic amyotrophy also known as diabetic muscle infarction is a rare and associated with abrupt onset of pain and rapid atrophy in large muscle groups of thighs, the perispinous muscles and the shoulder griddle. Severe pain and profound weakness is the preserving clinical feature. This problem usually resolves largely in majority of cases.

Other rheumatological disease are prevalent more in diabetic compared to common population such as osteoarthritis (OA) of knee, hip and spine, osteoporosis, osteolysis of foot (forefoot area), migratory osteolysis of hip and knee etc. All the above diseases have severe & prolonged course of illness and have a bad prognosis in diabetics.

References:

A single step procedure to diagnose Gestational Diabetes Mellitus and its effects on feto-maternal outcome

Subhalaxmi Dash1, Sujata Misra2, Sudhanshu Sekhara Nanda3, Sidhartha Das4,

Abstract:

Objectives: Our study was designed to find out the incidence of Gestational Diabetes Mellitus by using 75 gm oral glucose tolerance test as a single step procedure to both screen and diagnose and to know the effects of gestational diabetes towards maternal and fetal outcome.

Methods: 500 pregnant women with singleton pregnancy were screened with 75 gm oral glucose tolerance test. Those with 2 hour venous plasma glucose of ≥ 140mg/dl were diagnosed as gestational diabetes and were put under medical nutrition therapy or insulin. All the cases were followed up till delivery for fetal and maternal outcome.

Results: The overall incidence of gestational diabetes mellitus was 5.2%. It was more common in obese patients, with family history of diabetes and in multigravidas. Maternal complications like vaginal candidiasis, hypertension, polyhydramnios, and preterm labour were more common in diabetic group. Fetal outcomes like macrosomia, shoulder dystocia, still birth, hypoglycemia, congenital anomalies, trauma during delivery were all found to be more in patients with gestational diabetes.

Conclusion: The rise in prevalence of Gestational Diabetes in our community and its associated increased risk of pregnancy and delivery complications justifies a need to screen pregnant mothers who attend the antenatal clinic. This single step procedure (75gm OGTT) is a simple economic and feasible method. It serves both for the purpose of screening and diagnosis at the same time.

Key words: OGTT-Oral glucose tolerance test, GDM-Gestational diabetes mellitus, ADA-American Diabetes Association.

Introduction:

Gestational diabetes mellitus is defined as carbohydrate intolerance of variable severity with onset or first recognition during the present pregnancy. The definition applies whether or not insulin is used for treatment or the condition persists after pregnancy. It does not exclude the possibility that the glucose intolerance may have antedated the pregnancy1,2. Although the prevalence of GDM is usually reported as 2 to 5 % in pregnant women, it can be as high as 14% depending on the population described and the criteria used for diagnosis3. The prevalence in women with defined high risk factors such as being older than 25 years, being obese or having a family history of diabetes ranges from 3.3% to 6.1%4. They are at risk of development of type-2 diabetes in approximately 50% of cases in later life5. Studies have shown that there is a much higher rate of maternal and fetal compromise in diabetic pregnancies as compared with normal pregnancies6. Diabetic mothers are exposed to an increased risk of hypertension in late pregnancy7. Other obstetric complications such as polyhydramnios, preterm labour and abortions are also commonly encountered in pregnant diabetics. Infants of diabetic mothers are exposed to variety of problems such as, sudden intrauterine death, respiratory distress syndrome, hypoglycemia, cardiomyopathy, neonatal jaundice, impaired calcium and magnesium homeostasis and many more.

Rationale of GDM screening include-

- It allows identification GDM and hence treatment disposition thereby reducing the associated maternal and neonatal risk.
It also allows identification of a group of women who have an increased risk of developing diabetes mellitus later in life.

The screening procedure should be simple, safe, precise and validated. It should also be acceptable to the population with well defined cut off levels.

DIPSI (Diabetes In Pregnancy Study Group India) recommends “A one step procedure with a single glycemic value”, to diagnose GDM in the community: It recommends 75g OGTT irrespective of fasting status and GDM is diagnosed if 2-hour plasma glucose is > 140 mg/dl. This test correctly identifies subjects with GDM, as well as woman with normal glucose tolerance8.

Categorizing abnormal glucose tolerance in pregnancy (75gm OGTT):

<table>
<thead>
<tr>
<th>2 hr plasma Glucose</th>
<th>In Pregnancy</th>
<th>Outside Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 200 mg/dl</td>
<td>Diabetes</td>
<td>Diabetes</td>
</tr>
<tr>
<td>140 - 199 mg/dl</td>
<td>Gestational Impaired Diabetes Mellitus (GDM)</td>
<td>Glucose Tolerance (IGT)</td>
</tr>
<tr>
<td>120- 139 mg/dl*</td>
<td>Gestational Glucose Intolerance (GGI)</td>
<td>- -</td>
</tr>
<tr>
<td>&lt; 120 mg/dl</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

* Needs follow up

Our study was designed to find out the incidence of carbohydrate intolerance in the form of GDM by using 75 g oral glucose tolerance test as a single step procedure to both screen and diagnose gestational diabetes mellitus and to know the effects of hyperglycemia (GDM) towards maternal and fetal outcome.

Materials and Methods:

This was a prospective cohort study conducted from September 2008 to October 2010 in the Dept. of Obstetrics & Gynecology, SCB Medical College, Cuttack. 500 pregnant women with singleton pregnancy who had come for antenatal check up were interviewed using partially coded questionnaires with both open and close ended questions regarding their family history, previous health status & obstetric outcome. Each mother at 24-28 weeks of gestation was given 75 gm glucose dissolved in a glass of 200 ml water to drink and after two hours venous blood was collected. This was analysed in auto analyser in our central laboratory using GOD-POD method. The WHO criteria for diagnosis of gestational diabetes using two hour plasma glucose value of 140mg/dl or more was used as the cut off value to diagnose GDM. Those mothers having blood glucose values more than 140 mg/dl were marked as having GDM and the rest with blood glucose values less than 140mg/dl were marked as non diabetic controls. The mothers having GDM were offered treatment. GDM patients with 2 hr blood glucose less than 200mg/dl were given dietary advice in the form of medical nutrition therapy(MNT) initially for two weeks. The cases in which MNT fails to achieve control i.e. to maintain FPG =90mg/dl and/or 1 ½ hr PPG =120 mg/dl, insulin was initiated . Those with a 2- hr blood glucose >200mg/dl were started on insulin after confirmation of the results with diabetic physicians. The mothers who had some high risk factors in their history were called for rescreening between 34-36 weeks of gestation. The same protocol was followed as during the initial screening procedure. All screen positive mothers were followed up and encouraged to deliver in our hospital. Sociodemographic characteristics, pregnancy complications like hypertension, candidiasis, fever, polyhydramnios, intrauterine fetal death, modes and complications of delivery, birth weight, Apgar score, still birth, or preterm labour, antepartum hemorrhage and congenital abnormality in the babies were recorded. They were asked to come back to postnatal clinic where they were reviewed and those who had gestational diabetes were again required to undergo a 75 g oral glucose tolerance test.

Observation:

Out of 500 patients at 24-28 weeks of gestation screened with 75 g oral glucose tolerance test, 20 patients exhibited plasma glucose level > 140 mg/dl and were diagnosed to have Gestational Diabetes Mellitus (GDM). Total number of patients who presented for re-screening at 32-36weeks were 300 out of whom 6 patients were again screen positive after undergoing a 2-hr 75 g OGTT. The overall
incidence of GDM was 26 per 500 cases (5.2%) (Table-1).

<table>
<thead>
<tr>
<th>Table-1: Incidence of GDM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Cases picked up after initial screening</td>
</tr>
<tr>
<td>Cases picked up after re-screening</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Highest number of GDM were observed in the 26 to 30 year age group i.e. 10 cases out of 26 diagnosed cases of GDM (Table-2). Incidence of GDM is high among multigravid women (G3+G4+G5 =69.23%) as compared to primigravida/G2 which is 30.79% (Table-3). 26.9% of GDM cases had BMI<30 kg/m² as compared to 70.05% controls and 73.08% GDM cases had a BMI >30kg/ m² as compared to 29.95% of controls which was significant(Table-4). This indicates that BMI>30 kg/m² is a significant risk factor in the occurrence of GDM. GDM is more common among uneducated and patients with primary education as compared to women having higher education which was statistically not significant (Table-5). Positive family history of Diabetes in GDM is 61.53% as compared to 9.91% in controls. Thus family history is a major factor in the occurrence of GDM and is statistically significant (Table-6).

<table>
<thead>
<tr>
<th>Table -2: Patients Characteristics (Age)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
</tr>
<tr>
<td>&lt; 20</td>
</tr>
<tr>
<td>20-25</td>
</tr>
<tr>
<td>26-30</td>
</tr>
<tr>
<td>31-35</td>
</tr>
<tr>
<td>&gt;35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table-3: Patients Characteristics (Parity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parity</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>Grandmultipara</td>
</tr>
</tbody>
</table>

Table-4: Patients Characteristics (Obesity)

<table>
<thead>
<tr>
<th>BMI(kg/m²)</th>
<th>GDM</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>7(26.92%)</td>
<td>332(70.05%)</td>
</tr>
<tr>
<td>≥30</td>
<td>19(73.08%)</td>
<td>142(29.95%)</td>
</tr>
</tbody>
</table>

Table-5: Patients Characteristics (Education)

<table>
<thead>
<tr>
<th>Education</th>
<th>GDM</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uneducated</td>
<td>11(42.30%)</td>
<td>147(31.01%)</td>
</tr>
<tr>
<td>Primary</td>
<td>8(30.76%)</td>
<td>138(29.11%)</td>
</tr>
<tr>
<td>Higher</td>
<td>7(26.92%)</td>
<td>189(39.87%)</td>
</tr>
</tbody>
</table>

Table-6 : Family History

<table>
<thead>
<tr>
<th>Family history of Diabetes</th>
<th>GDM</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>16(61.53%)</td>
<td>47(9.91%)</td>
</tr>
<tr>
<td>No</td>
<td>10(38.47%)</td>
<td>427(90.09%)</td>
</tr>
</tbody>
</table>

Various complications encountered during pregnancy in patients diagnosed to have GDM. Vaginal candidiasis was found to be 18 times more likely & hypertension 11 times more likely in women with GDM. Polyhydramnios was 20 times more likely in GDM patients and preterm labour was 6 times more likely in GDM. There were no documented cases of abortion and APH in GDM cases (Table-7). There were increased incidence of operative vaginal delivery and caesarean section in patients with GDM, which were statistically significant(Table-8).

<table>
<thead>
<tr>
<th>Table -7 : Maternal Complications in GDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complications</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Vaginal candidiasis</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Polyhydramnios</td>
</tr>
<tr>
<td>Preterm labour</td>
</tr>
<tr>
<td>Abortions</td>
</tr>
<tr>
<td>APH</td>
</tr>
</tbody>
</table>
Table -8 : Modes of Delivery in GDM

<table>
<thead>
<tr>
<th>Modes of delivery</th>
<th>GDM</th>
<th>Controls</th>
<th>RR</th>
<th>95% C.I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal vaginal delivery</td>
<td>4 (15.38%)</td>
<td>314 (66.24%)</td>
<td>0.10</td>
<td>0.03-0.31</td>
</tr>
<tr>
<td>Operative vaginal Delivery</td>
<td>10 (38.46%)</td>
<td>40 (8.45%)</td>
<td>5.62</td>
<td>2.66-11.72</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>12 (46.16%)</td>
<td>120 (25.32%)</td>
<td>2.39</td>
<td>1.13-5.03</td>
</tr>
</tbody>
</table>

Table - 9 : Fetal Outcome in GDM

<table>
<thead>
<tr>
<th>Outcome</th>
<th>GDM</th>
<th>CONTROLS</th>
<th>RR</th>
<th>95% C.I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal babies</td>
<td>11 (42.30%)</td>
<td>458 (96.62%)</td>
<td>0.04</td>
<td>0.02-0.09</td>
</tr>
<tr>
<td>Macrosomia</td>
<td>5 (19.23%)</td>
<td>5 (1.05%)</td>
<td>11.67</td>
<td>5.52-24.60</td>
</tr>
<tr>
<td>Still birth</td>
<td>1 (3.84%)</td>
<td>1 (0.21%)</td>
<td>9.96</td>
<td>2.36-41.93</td>
</tr>
<tr>
<td>Shoulder Dystocia</td>
<td>2 (7.69%)</td>
<td>1 (0.21%)</td>
<td>13.80</td>
<td>5.66-33.62</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>1 (3.84%)</td>
<td>1 (0.21%)</td>
<td>9.96</td>
<td>2.36-41.93</td>
</tr>
<tr>
<td>Trauma</td>
<td>1 (3.84%)</td>
<td>1 (0.21%)</td>
<td>9.96</td>
<td>2.36-41.93</td>
</tr>
<tr>
<td>Cong.Anomaly</td>
<td>2 (7.69%)</td>
<td>1 (0.21%)</td>
<td>13.80</td>
<td>5.66-33.62</td>
</tr>
<tr>
<td>Hyaline membrane disease</td>
<td>1 (3.84%)</td>
<td>1 (0.21%)</td>
<td>9.96</td>
<td>2.36-41.93</td>
</tr>
<tr>
<td>Jaundice requiring phototherapy</td>
<td>2 (7.69%)</td>
<td>2 (0.42%)</td>
<td>10.33</td>
<td>3.59-29.67</td>
</tr>
<tr>
<td>Early neonatal death</td>
<td>0</td>
<td>1 (0.21%)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Fetal outcomes like macrosomia, shoulder dystocia, still birth, hypoglycemia, congenital anomalies and trauma during delivery were all found to be more in patients with GDM than in controls which were statistically significant (Table-9). All the GDM patients were followed up for postpartum (6 weeks) glucose tolerance test with 75 gm glucose. None of them came positive.

Discussion:

Pregnancy is a diabetogenic state manifested by insulin resistance and hyperglycemia and is implicated to be associated with significant obstetric complications. Diabetes complicates 3-4% pregnancies according to various researchers in America, Europe and Asia. Gestational diabetes has a rising trend in the recent times and depending on the type of population, it is said to complicate 1 – 16% of all pregnancies. In our study 26 out of 500 mothers were diagnosed as GDM the prevalence being 5.2% in our hospital.

A single test procedure by single step 75 gm OGTT was used in this study to screen and diagnose the cases of GDM. This test procedure is done in the non-fasting state which is justified as a patient of GDM has an underlying defect in secretion of insulin consequently her glycemic level increases with a meal and with glucose challenge this glycemic excursion exaggerates further. The second important reason for recommending this procedure is because the specificity of the ADA screening test with 50 g 1 – hr GTT without regard to time of last meal is low. It is thus preferable to perform this single step procedure as compared to 50gm-1 hr test and then 100 gm OGTT. This single step procedure serves both as screening and diagnostic test for GDM, is simple, economical and feasible.

In our study, 73% of patients of GDM had a BMI > 30kg/m², which is in accordance with the Fourth International Workshop expert Committee conclusion that BMI > 27 kg/m² is a high risk factor for occurrence of GDM. Family history was found to be a significant risk factor in causation of gestational diabetes as reported in many other studies.

There have been significant advances in the quality of care imparted to diabetic mothers which subsequently led to a dramatic fall in perinatal deaths attributed to diabetic problem. However adverse maternal and neonatal outcomes are still associated with the pregnant diabetic woman. Gestational diabetes still remains fraught with risks for the mother through the greater predisposition towards hypertensive disorders of pregnancy and preeclampsia, and is further more associated with a greater morbidity brought on by obstetric interventions.

Preterm labour as an outcome of diabetic pregnancies was significant i.e 6 times more common in GDM than non diabetic groups. Several studies have found out that the frequency of preterm labour is up to 20% higher in GDM pregnancies. Polyhydramnios and increased susceptibility to infection in poorly controlled diabetes may be the contributory factors.

Congenital anomalies in GDM was found to be 7.69% and in non GDM control subjects it’s incidence was around 0.21%. Different researchers have reported that approximately 3 to 8% of infants of diabetic mothers suffer from major congenital malformations. Macrosomia complicates 19.23%
of GDM pregnancies which was comparable with other studies (Can Fam Physician, 2005;51:688-95). Still birth was 9 times more common among GDM pregnancies as compared to non diabetic controls suggesting that factors other than placental insufficiency are involved in the etiopathogenesis.

**Conclusion :**

The rise in prevalence of Gestational Diabetes in our community and its associated increased risk of pregnancy and delivery complications justifies a need to screen pregnant mothers who attend the antenatal clinic. Our results suggest that a policy of universal screening for GDM should be adopted in all antenatal clinics and 75 gm OGTT has a high predictive value .This single step procedure is a simple economic and feasible method. It serves both for the purpose of screening and diagnosis at the same time. So looking towards the sociodemographic characteristics of our patients it should be followed in our region to achieve a better outcome .As in this study significant number of patients were detected in on repeat OGTT , it is emphasized that rescreening at a later gestation age of 32 weeks or later must form an essential component of screening. It will not only improve the perinatal outcome but also enable us to identify women at risk of developing diabetes in the future. The postpartum screening should be at regular interval to detect the recurrence of future diabetes. These potential diabetic women can be warned of the future happening and advised to adopt preventive measures to halt or delay that process. This will in turn shed load from health care resources responsible to take care of the diabetic patients in the long run.

Regarding management, it should be individualized and MNT should be the first line of choice over insulin initially. Considering sociodemographic differences and indoor treatment might be more beneficial.

**References :**

8. **V Seshiah DIPSI Guidelines - Kolkata Declaration, Fifth National Conference of Diabetes in Pregnancy Study Group, India, JAPI • may 2010 • VOL. 58,329-330**
15. **Sheffield et al Diabetes and malformations :Obst &Gynecol 2002 :100;925-30.**
Cardiovascular Risk in Cases of Non-alcoholic Fatty Liver Disease

P.Ch. Dash¹, S. Devi², A. Acharya³, S.N. Das⁴, S.K. Mohapatra⁴, G. Ray⁵

Abstract:

The present study was conducted in the Department of Medicine, S.C.B. Medical College and Hospital, Cuttack, 30 cases of NAFLD were taken into study and subjected to routine physical examination, biochemical, imaging and some special investigations like CIMT (by Carotid B-mode ultrasonography), liver biopsy, insulin resistance (by HOMA –IR), hs CRP etc. In this study out of 30 cases, 22 (73.36%) were male and 8 (6.64%) were female. Maximum 20 of male patient are over weight having BMI 25 – 29.9 Kg/m² where as more no. of females 5.26% were obese with BMI >30Kg/m². Insulin resistance was found to be high in 17 cases with a mean value 2.5 ÷ 1.84 (56.7%), hs CRP >3mg /L in 13 (43.29%) cases of male, 4 (13.42%) cases of female. The CIMT is high in 17(56.7%) males and 8(26.64%) females independent of age (with a p value of <0.05). NAFLD represents a high risk of CVD independent of other prognostic risk factors.

Introduction:

Nonalcoholic fatty liver disease is a spectrum of Liver disease that occurs in individuals who do not consume significant quantity of alcohol. NAFLD include hepatic steatosis (fatty liver), NASH (Non Alcoholic steatohepatitis) and cirrhoiss with eventual portal hypertension and other complications including hepatocellular carcinoma. In United States, the prevalences of NAFLD is 10-20%, out of which 3% is NASH. Out of NASH 10-20% progress to cirrhosis or end stage liver disease. Most patients of NAFLD are associated with type-2 DM, hyperlipidemia, obesity, hyperinsulinemia, insulin resistance, glucose intolerance and hypertension. This strongly supports the notion that NAFLD may be a hepatic manifestation of metabolic syndrome. Currently the importance of NAFLD and its relationship with metabolic syndrome is increasingly recognized and this has stimulated an interest in the possible role of NAFLD in the development of atherosclerosis. Several studies have shown that adult and children with NAFLD are enriched with risk factors that are generally accepted as surrogates for the risk of CVD. Various surrogates in clinical studies include Framingham risk score (consisting age, gender, hypertension, smoking and hyperlipidemia) carotid intima media thickness, hs CRP, atheroma formation and endothelial dysfunction.

Materials & Methods:

30 cases of NAFLD within the age group of 18 – 70 yrs both male and females were taken into study. Patients of type–2 DM, Hypertension, CKD, alcoholic liver disease were excluded from our study. After proper exclusion these cases were subjected to detail clinical examination and investigation. All the 30 cases were subjected to physical examination with Ht, weight, BMI, Waist hip ratio. Routine investigations like CBC, LFT, Lipid Profile FBS, 2 hr PGBS were done in each case and also special investigation like Plasma insulin, hs CRP (determined by Immune nephelometry, Normal Value < 0.3 mg/dl), carotid CIMT (B-mode ultrasonography), Apolipoprotein, B-100, (by turbidometry, reference range 0.53 to 1.73 gm/l) insulin resistance by HOMA –IR, (Glucose x insulin / 405, plasma glucose is given in mg/dl, plasma insulin in ml/minute, both are in fasting stage, HOMA – IR > 2 is abnormal) USG-Abdomen, Liver biopsy, Brachial artery flow mediated vasodilatation (FMVD) were done in all cases. The results were interpreted, analysed and conclusion was derived.

¹Asst. Prof., ²Senior Resident, ³Associate Professor, ⁴Professor Department of Medicine
S.C.B Medical College, Cuttack, Orissa.
²Asst. Prof., Medicine, Pratima Inst. of Med. Sc., Karim Nagar, AP
Submitted on : 20.04.2011 Accepted on : 30.04.2011
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Observation and Discussion:

Sex Distribution in Cases

Out of 30 cases, maximum 11 (36.75%) cases were between the age of 41-50 years, 22 (73.36%) cases were males and 8 (26.64%) were females. The male dominance was also found in a study by Bacon et al. NAFLD is a disease of females as suggested by Dichl et al. is not seen in our present study. Masalide Amaguchi et al. have documented more no. of males having NAFLD associated with CVD.

Body Mass Index of Cases

BMI 25-29.9 KG/m² was found in 13 (43.39%) cases of male and 5 (16.65%) cases of females, having BMI >30 kg/m². Ibrahim Halil Bucecioglu has found 85% patient of NAFLD were over weight and 37% were obese. In our study, 8 (26.64%) cases having waist hip ratio more than normal limit, out of which 3 (9.99%) were male and 5 (16.65%) were females. Out of 30 cases, 4 (13.32%) cases have shown impaired blood glucose level. A study conducted by Angel Brea et al. have shown out of 30 NAFLD cases, 7 (17.5%) were diabetic. Insulin Resistance calculated by HOMA-IR method was found to be high in 17 (56.7%) cases with a mean value 2.5 ± 1.84. Similar observation was found by Ajay Duseja et al. and Kitt Falk Peterson et al.

Insulin Resistance (IR) by HOMA-IR Method

Insulin resistance is very common in NAFLD leading to increased lipolysis and hepatic steatosis. Serum hs CRP level is generally low in general population <0.3mg/dl without acute disease. In our study out of 30 cases, 7 (23.31%) cases of male and 3 (9.99%) cases of female were having hs CRP <1mg/L. In 2 (6.66%) cases of male and 1 (3.33%) case of female hs CRP was <2 mg/L. In 13 (43.29%) cases of male and 4 (13.42%) cases of female hs CRP was >30mg/l. All cases having raised hs CRP level (<0.03mg/dl). Angel Brea et al. has found elevated hs CRP in 60% cases of NAFLD. Lizardi – Cervera J et al. had similar observation in cases of NAFLD suggesting that patients with hepatic steatosis had shown an increased concentration of hs CRP independently as other metabolic disturbances.

Noninvasive assessment of CIMT by high resolution carotid B-mode USG is widely used at Proxy end point for cardiovascular disease. Recent study have shown NAFLD patients have significantly greater carotid intima media thickness (CIMT). Out of 30 cases, 5 (16.65%) cases of male having CIMT within the normal value, 17 (56.7%) males and 8 (26.64%) females [total 25 (83.25%)] cases had CIMT more than normal value independent of age, gender and it is
significant, (p value <0.05). Silvia Sookoian et al\(^9\) had observation of 13% cases of NAFLD having raised CIMT. This observation suggest benefits of primary prevention and decision to treat existing cardiovascular disease in NAFLD. Volzke et al\(^7\) described an independent association of hepatic steatosis with carotid plaques but not with CIMT. Endothelial dysfunction is an important process accepted as a predictor of atherosclerosis. In the present study showing mean FMVD was 6.47 ± 3.78%. Nicola Vilonova\(^10\) has observed mean branchial artery FMVD as 5 ± 4%. Our observation has strong correlation by students t-test with that of value obtained by Nicola Villanova et al\(^10\). Aydin Yıldırım et al shown that decrease in brachial artery FMVD is more prominent in patients with elevated liver enzymes. This finding suggest that NAFLD patients with higher enzyme level may have developed more severe and active metabolic process causing worsening of endothelial function.

Mean of Brachial Artery Flow Mediated Vasodilatation (FMVD) compared with other Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean of Cases</th>
<th>Control</th>
<th>Student t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>6.47 ± 3.78</td>
<td>-</td>
<td>t-value N = 1.989</td>
</tr>
<tr>
<td>Nicola Vilonova et al</td>
<td>6.33 ± 5.93%</td>
<td>12.22 ± 5.05%</td>
<td>Obs. = 1.99</td>
</tr>
<tr>
<td>Aydin Yıldırım et al</td>
<td>5 ± 4%</td>
<td>9.7 ± 3.5%</td>
<td>P Value &lt; 0.05</td>
</tr>
</tbody>
</table>

Summary & Conclusion :

NAFLD encompass a broad clinicopathologic spectrum ranging from steatosis to NASH which may advance to cirrhosis and end stage liver disease. NAFLD can occur in all adult age group but more common in middle age group (41-50 yrs). Relationship of abdominal obesity and insulin resistance is well established. Incidence of CVD is very common in NAFLD. NAFLD itself represents a high risk of CVD independent of other prognostic risk factors suggesting more complex and interwined relationship between NAFLD, metabolic syndrome and atherosclerosis. The importance of evaluating the global CVD risk among patients diagnosed as NAFLD is strongly emphasized. CVD risk factors like obesity, dyslipidemia significantly associated with NAFLD. Markers of subclinical atherosclerosis like CIMT, Brachial artery FMVD has strong correlation with incidence of NAFLD. Our study showed that endothelium derived vasodilation and indicators of endothelial function was significantly reduced in patients of NAFLD. As CIMT is a marker of early arterial change including atherosclerosis and vascular hypertrophy and patient with NAFLD has increased risk of high CIMT, routine detection of CIMT may provide benefit on primary prevention and a decision to treat existing but not diagnosed CVD in patients with NAFLD.

Reference :

Perinatal outcome in various grades of anaemia

Mayoor Daigavane¹, Shyama Kanungo²

Abstract:

Objectives: To study maternal and fetal outcome in various grades of anaemia and its comparison with non anaemic in a cohort of 1000 pregnant women

Methods: All singleton pregnancies delivered in S.C.B. Medical college from June 2010 to Dec 2010.

Results: Out of 1000 patients delivered 333 were non anaemic and 666 were anaemic (HB < 11 gm/dl). Out of this 516 were with mild anaemia (HB > 9 to < 11), 114 were with moderate (HB > 7 to < 9), 36 with severe anaemia (HB < 7). Neonatal outcome observed were preterm delivery, intra uterine fetal death, average neonatal weight, neonatal admission on pediatric side, neonatal antibiotic requirement. Maternal outcome observed were antepartum haemorrhage, pregnancy induced hypertension, wound dehiscence in caesarean delivery, maternal mortality, heart failure, blood transfusion requirement, and hospital stay more than 10 days. ‘Z’ TEST was used to determine the level of significance.

Conclusion: Regular antenatal care from first trimester has a vital role in assessing and managing maternal anaemia timely and it directly affects perinatal outcome.

Introduction:

Maternal anaemia is the most common problem in pregnancy in developing countries like India. It is estimated that 1200 million are anaemic globally. According to WHO anaemia is defined as haemoglobin level less than ≤11 gm/dl. Mild anaemia is ≤ 11 to 9 gm/dl, moderate is ≤ 9 to 7 gm/dl, and severe is ≤ 7 gm/dl. Prevalence of anaemia depends upon socio-economic status, parity, associated medical problems, antenatal care and lifestyle. Maternal anaemia in pregnancy has a adverse perinatal outcome. However the extent to which maternal haemoglobin level affects perinatal outcome is still uncertain. So for better understanding of the effect of reduced Hb status anaemic patients have been divided into mild, moderate and severe category and compared with normal haemoglobin controls.

Thus the aim of our study was to find out the relationship between normal and subnormal HB levels and fetomaternal outcome.

Material And Methods:

A retrospective cohort study was conducted on pregnant women admitted and delivered in labour room in S.C.B. Medical College Cuttack from June 2010 to Nov 2010 having at least one antenatal haemoglobin estimation were included in the study. Total of 1000 patients were included in this trial.

Women with
1) multiple pregnancy,
2) age < 18 yrs,
3) coexisting medical condition,
were excluded from the study.

The data was analysed by ‘Z’ test to determine the level of significance. Results are expressed as percentage for better co relation.

Results:

Out of 1000 pregnant patients, 666 were anaemic and 334 were with normal haemoglobin. Out of 666, 516 were with mild anaemia, 114 were with moderate anaemia and 36 were with severe anaemia.

From table 1, average birth weight is 2.813 kg and average weight in mild, moderate and severe, is 150, 323 and 383 gram respectively less than non anaemic babies.

The preterm rate and perinatal mortality rate is not statistically significant between mild and non
anaemic patients. But the preterm rate is significantly higher i.e 15.7 % and 16.66 % in moderate and severe group respectively compared to normal . The neonatal admission on pediatric side in non anaemic group is 7.2% but in mild , moderate and severe group it is 11.4%, 12.2% and 16.6 % respectively. Antibiotic requirement to the baby in normal group is 4.5 %. And in mild, moderate and severe group it is 6.39 %, 8.7 % and 27.7 % respectively. Apgar score is no longer used as a guide for resustitation as the evaluation cannot be done rapidly, reliably and unobtrusively in emergency condition(1). So not included in study.

### TABLE NO. 1

**FETAL OUTCOME**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HB&lt;11</td>
<td>HB&lt;8</td>
<td>HB&lt;5</td>
<td>HB&lt;3</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>requirement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABO</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Rh</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average wt. of neonate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.833 Kg</td>
<td>2.607 Kg</td>
<td>2.49 Kg</td>
<td>2.44 Kg</td>
</tr>
<tr>
<td>Preterm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>69(11.9%)</td>
<td>56(9.3%)</td>
<td>59(5.7%)</td>
<td>6(0.666)</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18(5.4%)</td>
<td>18(3.4%)</td>
<td>11(9.6%)</td>
<td>7(10.4%)</td>
</tr>
<tr>
<td>Neonatal admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24(7.2%)</td>
<td>57(11.4%)</td>
<td>14(22.2%)</td>
<td>6(14.6%)</td>
</tr>
<tr>
<td>Antibiotic Requirement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15(4.5%)</td>
<td>33(6.3%)</td>
<td>20(8.5%)</td>
<td>10(27.7%)</td>
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</tbody>
</table>

APH is insignificant in mild anaemia but in moderate and severe anaemia it is 7 % and 16.6 % respectively. No statistically significant difference in PPH in anaemic and non anaemic group.

Wound dehiscence at CS was found to be 5.81%, 9.6%, 16.6% in mild, moderate and severe anaemia respectively as compared with 4.5 % in non anaemic group. The hospital stay is prolonged in the anaemic group i.e 5.2%, 10.5 % and 30.5% in mild, moderate and severe anaemia as compared with 2.5 % in non anaemic group .

Blood transfusion requirement is 7.89% in moderate and 52% in severe anaemia as compared to nil in mild and non anaemic patients .Maternal mortality is 0.8% in moderate and 5.5 % in severe anaemic patients and nil in mild and non anaemic patients. Heart failure rate is 0.8% in moderate & 5.5 % in severe anaemic patients and nil in mild and moderate anaemic patients.

**Discussion**:

Anaemia is a common problem in pregnant and accounts for 40 to 50 % of maternal deaths in developing countries (2). It is estimated that 73 million perinatal deaths occur annually due to anaemia.(6) As the study was done in tertiary hospital majority of women delivered, and it is expected that burden of anaemia and its effect on pregnancy outcome is much greater outside hospital settings.

Anaemia predisposes to preterm labour directly or indirectly due to increased risk of infection. The direct effect is increased synthesis of corticotrophin-releasing hormone[CRH] as a result of tissue hypoxia .These raised level induce maternal and fetal stress and thus produce risk factor for preterm labour , PROM, & PIH. CRH also increases fetal cortisol production which inhibit longitudinal growth of fetus . Iron deficiency also increases oxidative stress in fetoplacental unit which can stimulate production of CRH.(3)

Iron deficiency was associated with lower lymphocyte stimulation index and decreased iron dependent enzymatic activity in cells which leads to more chances of infection.(4)

Maternal mortality in anaemia is more due to poor ability to withstand excessive blood loss &

### TABLE NO. 2

**MATERNAL OUTCOME**

From table 2 , PIH and APH significantly increases as the severity of anaemia increases. PIH is 3 % in non anaemic group and in mild , moderate , and severe it is 9.8%, 18.4 % and 22.2% respectively.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital stay</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood transfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>requirement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABO</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rh</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average wt. of neonate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.833 Kg</td>
<td>2.607 Kg</td>
<td>2.49 Kg</td>
<td>2.44 Kg</td>
</tr>
<tr>
<td>Preterm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>69(11.9%)</td>
<td>56(9.3%)</td>
<td>59(5.7%)</td>
<td>6(0.666)</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18(5.4%)</td>
<td>18(3.4%)</td>
<td>11(9.6%)</td>
<td>7(10.4%)</td>
</tr>
<tr>
<td>Neonatal admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24(7.2%)</td>
<td>57(11.4%)</td>
<td>14(22.2%)</td>
<td>6(14.6%)</td>
</tr>
<tr>
<td>Antibiotic Requirement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15(4.5%)</td>
<td>33(6.3%)</td>
<td>20(8.5%)</td>
<td>10(27.7%)</td>
</tr>
</tbody>
</table>

ORISSA MEDICAL JOURNAL
increased risk of infection. Accidents of labour like haemorrhage and shock are rendered more serious in anaemia. Anaemia has case fatality rate ranging from 1% to 50% depending on available obstetric care. Preeclampsia and APH is aggravated by anaemia(5).

Active management of the third stage of labour significantly decreased the incidence of PPH.(6) Hb less than 10gm/dl is described as a risk factor for wound dehiscence.(7).

Daily iron requirement in pregnancy is 4 mg (2.5 mg in early pregnancy & 6-8 mg after 32 weeks of gestation). WHO recommendation for iron intake is 1) where prevalence <40% = 60 mg of elemental iron for six month in pregnancy & 2) where prevalence is more than 40% = continue iron supplementation for three months post partum. Cochrane database studies concluded that routine iron and folic acid supplementation has no detectable effect on substantive measures of fetal and maternal outcome but other studies have favourable outcome. Hermanski and Starfield concluded that routine iron did not improve preterm labour & birth weight. Stephansson et al found increased risk of still birth and growth restricted infants in women with Hb >14.6 gm/dl. (12)

References :

2) High risk pregnancy by D.K James, P.J. steer, C.P weiner , anaemia and white cell disorder, chapter 39 Jane Strong page 865-869.
3) Biological mechanisms that might underlie iron’s effects on fetal growth & preterm birth Lindsay H. Allen. Program of international nutrition.
A Comparative Study of Forced Expiratory Volume in 1 Sec (FEV 1) between Trumpet Blower Smokers and Healthy Smokers and Non-Smokers

Sanjeev Satpathy

In today’s world, people, in search of name, fame and wealth, try to take lots of unnecessary stress. Then they try to blow their stress out by the cigarette smoke.

1 cigarette can reduce the life span by 8 sec. Main cause for its addiction is Nicotine.

3 Accelerated decline in the volume of air exhaled within the first second of the Forced Expiratory Manoeuvre (FEV1) in a dose response relationship to the intensity of cigarette smoking. Smoking can lead to Obstructive Lung Disease (Emphysema and Chronic Bronchitis) where the Vital Capacity may be normal but FEV1 is reduced.

Pathophysiology - The main pathology of development of Obstructive Lung Disease (OLD) is that regular smoking lead to development of both acute and chronic inflammation which cause increase secretion of mucus. Nicotine in the smoke cause ciliary immotility, thus mucus is not able to be removed.

Added to it, free-radicals also develop due to smoking, which damages the anti protease called α-1antitrypsin (α-1AT), that protects the lung from the enzyme ELASTASE, released by neutrophil.

All this add together to produce OLD.

Keeping in the view that regular exercising the lung and chest wall may protect an addicted smoker from development of OLD, this study was done.

Material and Method -

MATERIAL - They included

• NORMAL HEALTHY NON-SMOKERS - 30
• NORMAL HEALTHY SMOKERS - 30
• TRUMPET BLOWER SMOKERS - 30

All subjects are within age group of 20-45 years.

Smokers taken have been smoking a minimum of 8 cigarettes/ day, for 7 years and more.

Trumpet blowers have been playing for 5 years and more, practicing for at least an hour a day.
Method:
FEV1 detected by SPIROMETER (studied in SLEEP LAB, CUTTACK AND DEPT OF PULMONARY MEDICINE, BURLA).
CHEST EXPANSION was also compared in the 3 groups. It was measured by MEASURING TAPE.
Each individual was described the procedure and then allowed to blow in the spirometer three times and the best of the three was taken.

Observation:
The FEV1 measured in litre of all the 90 subjects are shown here.

<table>
<thead>
<tr>
<th>HEALTHY NON-SMOKER</th>
<th>HEALTHY SMOKER</th>
<th>TRUMPET BLOWER</th>
</tr>
</thead>
<tbody>
<tr>
<td>(FEV1 in lfs)</td>
<td>(FEV1 in lfs)</td>
<td>(FEV1 in lfs)</td>
</tr>
<tr>
<td>1.3.566</td>
<td>3.123</td>
<td>3.81</td>
</tr>
<tr>
<td>2.2.944</td>
<td>3.59</td>
<td>3.18</td>
</tr>
<tr>
<td>3.2.703</td>
<td>1.84</td>
<td>2.78</td>
</tr>
<tr>
<td>4.2.721</td>
<td>3.171</td>
<td>2.29</td>
</tr>
<tr>
<td>5.3.122</td>
<td>1.942</td>
<td>3.37</td>
</tr>
<tr>
<td>6.3.096</td>
<td>1.536</td>
<td>3.37</td>
</tr>
<tr>
<td>7.2.919</td>
<td>1.739</td>
<td>3.17</td>
</tr>
<tr>
<td>8.2.929</td>
<td>2.731</td>
<td>3.83</td>
</tr>
<tr>
<td>9.3.57</td>
<td>2.449</td>
<td>3.17</td>
</tr>
<tr>
<td>10.2.93</td>
<td>2.81</td>
<td>3.31</td>
</tr>
<tr>
<td>11.2.83</td>
<td>1.341</td>
<td>2.032</td>
</tr>
<tr>
<td>12.2.701</td>
<td>1.793</td>
<td>2.438</td>
</tr>
<tr>
<td>13.2.32</td>
<td>1.601</td>
<td>3.511</td>
</tr>
<tr>
<td>14.2.101</td>
<td>2.317</td>
<td>2.367</td>
</tr>
<tr>
<td>15.2.907</td>
<td>2.013</td>
<td>2.83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.302</td>
</tr>
</tbody>
</table>

A graph is plotted taking the MEAN and STANDARD DEVIATION (SD) of the 3 groups.
It was found that the FEV1 of Trumpet Blower Smoker was nearly same or even better than normal Healthy Non-Smoker. FEV1 of Healthy Smokers was the worst.
To know the significance of the test, comparison were made b/n the 3 groups i.e. H N-Sm Vs H-SM, H-SM Vs T B SM, H N-SM Vs T B SM t-value were found by STUDENT’S t-test.

HEALTHY NON-SMOKERS vs HEALTHY SMOKERS
SD=0.57
t = 20.94 (by STUDENT’S t-TEST)
Degree of freedom=58
p < 0.01 (Significant)

HEALTHY SMOKERS vs TRUMPET BLOWER SMOKERS
SD=0.62
t = 1.79
Degree of freedom=58
P < 0.05 (Significant)

HEALTHY NON-SMOKERS vs TRUMPET BLOWER SMOKERS
SD=0.57
t = 25.24
Degree of freedom =58
p < 0.01 (Significant)
p was found to be significant in all the three tests.
Chest Expansion:

The following table shows the chest expansion of all 90 participants in cm.

<table>
<thead>
<tr>
<th></th>
<th>HEALTHY NON-SMOKER</th>
<th>HEALTHY SMOKER</th>
<th>TRUMPET BLOWER SMOKER</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEAN</td>
<td>4.54</td>
<td>3.867</td>
<td>4.763</td>
</tr>
<tr>
<td>S.D</td>
<td>0.607</td>
<td>0.611</td>
<td>0.498</td>
</tr>
</tbody>
</table>

A graph is plotted taking the mean and standard deviation of chest expansion of the three groups.

It was found that chest expansion of Trumpet Blower Smokers is nearly same as Healthy Non-Smokers but that of Healthy Smokers is low.

HEALTHY NON-SMOKERS vs HEALTHY SMOKERS

SD=0.61

\( t = 0.16 \) (by STUDENT’S \( t \)-TEST)

Degree of freedom=58

\( p > 0.1 \) (Non-significant)

HEALTHY SMOKERS vs TRUMPET BLOWER SMOKERS

SD=0.56

\( t = 25.23 \)

Degree of freedom=58

\( p < 0.01 \) (Significant)

HEALTHY NON-SMOKERS vs TRUMPET BLOWER SMOKERS

SD=0.56

\( t = 24.15 \)

Degree of freedom=58

\( p < 0.01 \) (Significant)

\( p \) was found to be significant between H-Sm & T B Sm and H N Sm & TB Sm but was found to be insignificant between H Sm and H N Sm.

Discussion:

A number of studies like “MAXIMUM RESPIRATORY PRESSURE IN TRUMPET PLAYERS” and “LUNG FUNCTION IN WIND INSTRUMENT PLAYERS AND GLASS BLOWERS” have already shown that maximum respiratory pressure and FEV1 remains high in Trumpet players than the control group, who do not play trumpet.

The present study also showed that even for addicted smokers, blowing exercise had beneficial effect. The forceful inspiration and expiration cleans away the respiratory tree up to certain extent and makes the lung and chest wall stronger.

Summary:

Thus to summarise, as we find that the FEV1 and chest expansion of Trumpet Blower smokers were nearly same and even better than Healthy Non Smoker, so a regular habit of using a blowing instrument, will definitely protect an addicted smoker from development of obstructive lung disease.

Even if one cannot measure his FEV1 regularly, at least they should measure their chest expansion after doing the blowing exercise.

References:

2. The Lung By Aliya N Hussain And Vinay Kumar-robbins Pathologic Basis Of Disease, 7th Edi;720.
3. Copd By John J Reilly, Edwink Silverman, Stevend Shapiro-harrison’s Principle Of Internal Medicine(vol-ii); 1635.
Abstract:

Objective: The present study was an attempt to measure and to evaluate the role of Prostate Specific Antigen (PSA) as a new biochemical marker of androgen excess in Polycystic Ovary Syndrome (PCOS) women undergoing ovulation induction.

Method: 35 infertile women within age group 18-38 years diagnosed as PCOS and 32 healthy fertile women were enrolled for the study. Lipid profile, hormone parameters (serum insulin, total testosterone, LH/FSH ratio) and serum PSA levels were estimated in the early follicular phase.

Result: At baseline, serum PSA levels were significantly higher in PCOS cases in comparison to control (p< 0.05). Also significant high levels of serum insulin, Total Testosterone (TT) and LH/FSH ratio were documented. The most relevant finding of the study was the significant positive correlation between serum PSA & TT, the most potent androgen (r =0.9, p<0.001).

Conclusion: Serum PSA level could be detected in high significant concentration in PCOS infertile women. Thus it could be used as a promising biochemical marker of hyperandrogenism, one of the important criterias for diagnosis of PCOS.

Key words: Prostate Specific Antigen, Polycystic Ovary Syndrome, Androgen

Introduction:

Polycystic ovary syndrome (PCOS) is a common multisystem endocrinopathy in women of reproductive age, affecting 5-10% of population worldwide [1]. It is characterized by menstrual irregularities, chronic anovulation and hyperandrogenism [2]. Several studies have highlighted that insulin resistance, with consequent hyperinsulinemia may play an early & central part in the pathogenesis of PCOS [3]. Insulin can promote ovarian androgen production, either directly by stimulating ovarian enzyme complex p450c17 á or indirectly by stimulating pituitary luteinizing hormone (LH) secretion [4, 5]. Furthermore in vitro studies suggest a potentiation of ACTH-stimulated adrenal androgen secretion by hyperinsulinemia [6]. It is also hypothesized that as a consequence of hyperinsulinemia, women with PCOS, exhibit greater risk of dyslipidemia, an established risk factor for cardiovascular disease [7].

Prostate specific antigen (PSA) is a serine protease. Previously it was thought to be confined exclusively to male prostate. Subsequently with the development of ultrasensitive immunoassay, several studies could identify the presence of PSA in a wide variety of female tissue (breast, ovary, endometrium) and body fluids (amniotic fluid, milk, breast cyst fluid) [8,9]. Presence of PSA in these female tissues is closely associated with steroid hormone regulation (especially androgen, glucocorticoid, progestin), which has been established in cell culture studies as well as in breast tumors & in breast tissues obtained from androgenised females [10,11]. Also indirect in vivo evidence was provided by Yu et al in his study on primary ovarian carcinoma [12]. High level of PSA in response to androgen therapy was illustrated by Obiezu et al [13], where as much lower level was noted in normal female, not receiving steroid hormone. Data from another group confirmed that serum PSA is higher in hirsute than in nonhirsute [14].

Based on the above considerations, it is speculated that PSA level may be elevated in response to high level of androgen, present endogenously in PCOS women. So the present study was an attempt to measure PSA levels and total testosterone (the most potent androgen) levels in PCOS infertile women undergoing ovulation induction and to correlate different parameters including serum PSA, serum total
testosterone (TT), serum insulin, which may have some clinical implications.

Materials And Methods:

35 young women, within age group 18-38 years, diagnosed to have PCOS (Rotterdam criteria) [2] and 32 age matched healthy female controls were enrolled in this study, after giving informed consent. Women with prior history of glucose intolerance (including gestational diabetes mellitus, non insulin dependent diabetes mellitus), endocrinopathies (late onset congenital adrenal hyperplasia, thyroid dysfunction) were excluded from the study. No subjects suffered from any other disease or were taking medications to alter hormonal or biochemical profile. None of them had been treated with oral contraceptives or antiandrogen drugs in the last year. Moreover all the study participants were not pregnant.

Blood samples were collected from both cases and controls and were estimated for lipid profile, hormonal parameters (serum insulin, serum TT, serum LH/FSH ratio) and serum PSA. Hormones were analyzed by ELISA method using commercial kits. Lipid profile was estimated using auto-analyzer Erba XL 300. Specific tests for serum PSA assay were performed using ultrasensitive chemiluminescent enzyme immune assay (ELECYS-2010, with a sensitivity of 3 pg/ml). preferably blood samples were collected in the early follicular phase of menstrual cycle (2nd or 3rd day). The study protocol has been approved by hospital ethical committee.

The results obtained were analyzed by student’s t test, ANOVA and Pearson’s correlation coefficient using SPSS version 16.

<table>
<thead>
<tr>
<th>Sl No</th>
<th>Parameter</th>
<th>Control(n=32)</th>
<th>Case(n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Total cholesterol(mg/dl)</td>
<td>140.21±15.10</td>
<td>165.13±28.34**</td>
</tr>
<tr>
<td>2</td>
<td>Triglyceride(mg/dl)</td>
<td>115.09±24.46</td>
<td>144.0±53.4*</td>
</tr>
<tr>
<td>3</td>
<td>LDL(mg/dl)</td>
<td>67.78±15.20</td>
<td>92.63±23.77**</td>
</tr>
<tr>
<td>4</td>
<td>HDL(mg/dl)</td>
<td>49.8±4.84</td>
<td>43.77±5.75**</td>
</tr>
<tr>
<td>5</td>
<td>VLDL(mg/dl)</td>
<td>22.96±4.91</td>
<td>28.65±10.84*</td>
</tr>
<tr>
<td>6</td>
<td>Serum Insulin(μIU/ml)</td>
<td>8.03±3.16</td>
<td>14.73±7.09**</td>
</tr>
<tr>
<td>7</td>
<td>Serum total testosterone(ng/ml)</td>
<td>0.5±0.22</td>
<td>1.24±0.70**</td>
</tr>
<tr>
<td>8</td>
<td>LH/FSH ratio</td>
<td>1.03±0.52</td>
<td>2.3±0.87*</td>
</tr>
<tr>
<td>9</td>
<td>Serum PSA(pg/ml)</td>
<td>4.5±0.7</td>
<td>13.1±1.5*</td>
</tr>
</tbody>
</table>

*p<0.05  
**p<0.001

<table>
<thead>
<tr>
<th>Variables</th>
<th>r value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA vs Total Testosterone</td>
<td>0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin vs Total Testosterone</td>
<td>0.42</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
Results:

Table-1 shows baseline characteristics (including lipid profile, hormone parameters & serum PSA) of PCOS cases and controls. Mean PSA levels of cases were significantly higher (13.1±1.5 and 4.5±0.7 pg/ml) than control group. This was similar to the observations of Melegos et al [15] & Gullu et al [16] who conducted their study on hirsute women and confirmed that hyperandrogenemic states such as PCOS are expected to be present with higher level of PSA. Mean total testosterone (TT) levels appeared to be significantly higher (1.24± 0.70 ng/ml, p<0.001) in PCOS cases which was in agreement to other studies [15, 17], explaining the excess ovarian androgen production which is central to the diagnosis of PCOS. Yet conflicting results have also been reported which may be attributed to low normal sex hormone binding globulin. Present study revealed a marked rise in fasting serum insulin in cases which confirmed the observations of other workers showing the role of hyperinsulinemia in the pathogenesis of PCOS [3, 4]. Elevated LH/FSH ratio explains the role of hyperinsulinemia acting on hypothalamic-pituitary axis and further androgen secretion by theca cells within ovarian follicle. Marked dyslipidemia was observed in PCOS cases in comparison to controls. This may be due to hyperinsulinemia stimulating synthesis & secretion of VLDL in liver resulting in hypertriglyciedemia, which in turn enhances post-prandial accumulation of lipoproteins (LDL, VLDL) with lowering of HDL cholesterol [20].

The most relevant finding of the study was the significant positive correlation between basal serum PSA and serum TT (r =0.9, p<0.001) in Table-2 & Fig-1. This may be attributed to the hypothesis that expression of PSA gene is under androgenic regulation [11]. Similar observations have been registered by other workers [17] who were in agreement that higher PSA is expected in hyperandrogenemic state. Also higher PSA results have been documented after testosterone therapy [13]. Some researchers [15] have also illustrated correlation between PSA and 3’androstenedione, a specific metabolite of androgen. On the contrary, Bayatti et al [21] found no association between PSA and TT, which might be attributed to the study participants (PCOS with hirsutism but not PCOS in general). Significant positive correlation between fasting serum insulin and serum TT was illustrated in Table-2. This indicates the aetiological role of hyperinsulinemia in stimulating ovarian androgen production which was in concurrence with the result of other researchers. Moreover insulin infusion studies have shown a clear association existing between serum insulin and testosterone in PCOS suggestive of a cause & effect relationship [7]. It has also been proved from the study by Valezquez et al that reduction in androgen levels correlated with a reduction in hyperinsulinemia. But it is difficult to determine whether ovarian androgen production per se was reduced or, alternatively, whether free androgen concentration declined because of insulin related decrease in sex hormone binding globulin.

Discussion:

PSA can no longer be regarded as tissue specific marker only for prostate tissue. Rather it is regarded as an ubiquitous molecule that can be synthesized & secreted by cells bearing specific hormone receptors under conditions of steroidal regulation [10]. This is confirmed from the present study which demonstrated a significant rise in serum PSA in PCOS cases. There are strong experimental evidences to indicate the role of excess androgen in aetiopathogenesis of PCOS [3]. Many investigators also claim a strong association between antiandrogen therapy and reduced PSA level.
This lends further support to the above described hypothesis that PSA synthesis is under androgen regulation. Moreover it is strongly evident that hyperinsulinemia plays a pathogenetic role in PCOS by acting at multiple sites (hypothalamic-pituitary axis, liver, ovary, adrenal cortex), resulting in increase GnRH pulse frequency, decrease SHBG, increase ovarian androgen production and decrease follicular maturation respectively [2,3]. All these findings adequately explain the cause of hyperandrogenism. So the clinical implication is the use of therapeutic measures directed at lowering insulin secretion which in turn can ameliorate hyperandrogenism. But recent data concludes this mechanism to be unlikely. Further researches are needed to understand the heterogeneity of expression of hyperandrogenism.

Conclusion:

Present data show statistical evidences of significantly high PSA in the serum of PCOS infertile women, which might be used as a promising marker of androgen action in androgen sensitive tissues. So elevated PSA, a baseline predictor of PCOS, along with hyperandrogenism, may open new modalities for treatment of this syndrome.

Reference:

Microbes at the root of Non-Communicable Diseases

Prakash Chandra Panda¹, Smita Kumari Panda²

Idiopathic to immune mediated or autoimmune:

A few decades ago the medical text books mentioned the etiology of many diseases as idiopathic or unknown; we can give the examples of diseases like gullaine barre syndrome, multiple sclerosis, systemic lupus erythematosus, idiopathic thrombocytopenic purpura, rheumatoid arthritis, type-I diabetes mellitus and so on and so forth. With time and with new insights traversed by the medical science the word, ‘idiopathic’ or ‘unknown’ has at many places been replaced by the coinage like ‘immune mediated’ or ‘autoimmune’. And in all these diseases the original insult or agent that heralds the pathogenesis have been one or other microbe.

Has the time really come when we can declare ‘infections are the root cause of all non-communicable diseases we have encountered so far’? Are microbes the root of all medical maladies of man?

The ‘hygiene hypothesis’ and the allied researches have been the corner stone of all these speculations in a novel school of thought, one can claim.

The hygiene hypothesis:

In the late 1980s, a British Pediatrician David Strachan noticed, in the developed world children increasingly live cleaner lives, growing up with smaller families in apartment buildings and suburban areas far from the dirt and pollen and yet rates of childhood allergies, hay fever, and asthma have risen sharply all over Europe and America in the past few decades while remaining almost nonexistent among children growing up in less developed parts of the world. He reviewed records of 17,000 British children and detected that Hay fever and eczema is less prevalent in larger families with more older siblings, in children from small families who enter daycare centers before age of 1 year and in children who don’t get oral antibiotics before age of two years. Dr. Erika Von Mutius, a health researcher compared the rates of allergies and asthma in East and West Germany and found out that children in the polluted areas of East Germany had lower allergic reactions and fewer cases of asthma than children in the cleaner and modern (1)

This led to a new hypothesis called the ‘Hygiene Hypothesis’ which goes like ‘children who are around numerous other children or animals early in life are exposed to more microbes, and their immune systems develop more tolerance for the irritants that cause asthma.’ It implies ‘reduction/lack of in infections and microbial exposures early in life may be associated with increased risk of allergy, asthma and autoimmune diseases.’

Initially proposed and linked to asthma and allergy, the hypothesis over the time has been tested for a whole lot of other medical disorders with variable types and levels of evidences to further it.

The immunological basis:

a. The pet dog analogy:

If one brings home a pet dog it takes time and training to acquaint it with near and dear ones and to detect strangers and respond accordingly. And before training and even after an incomplete training it is not abnormal if the pet responds erratically to people known or unknown, i.e. it barks and attacks the domestic maid or even allows new vegetable vendor to venture into the house. The same is true for our bodily immune system to deal with bacteria and other infectious microorganisms with whom we share our habitat willingly or unwillingly at early age or at a later age.

b. Thymocyte -1 and Thymocyte-2:

Stimulation with different cytokines leads to the development of two types of T-helper cells specialized for orchestrating two very different immune
responses. Th-1 and Th-2 strongly down-regulate each other.

IL-12 drives T-cells to develop into Th1 cells. Th1 cells orchestrate a response directed to inhibit intracellular pathogens like viruses, certain bacteria (mycobacteria) or certain protozoan parasites (leishmania). They secrete Interferon-gamma which activates intracellular killing mechanisms. They activate macrophages and cytotoxic T-cells.

The ‘choice’ towards a Th2 response is driven by the cytokine IL-4. Th2 cells suppress the activation of macrophages and activate eosinophils and mastcells. Th2 cells promote a strong antibody response based on neutralizing IgGs and IgEs. A Th2 response is most effective to combat extracellular pathogens.

This may be better understood with two distinct and opposite variety of disorders with the host and the microbe being the same; infection with Mycobacterium leprae shows two main clinical forms associated with Th1 and Th2 responses. In Tuberculoid leprosy there is low infectivity, localised infection, normal serum immunoglobulins and normal T cell response which lead to poor growth of mycobacteria in macrophages. In Lepromatous leprosy there occurs high infectivity, disseminated infection, hypergammaglobulinemia and florid growth of mycobacteria in macrophages.

At birth, an infant’s immune system appears to rely primarily on the Th2 system. Th1 system can grow stronger only if it gets exercise, either through fighting infections or through encounters with certain harmless microbes. Without such stimulation the Th2 system flourishes and the immune system teeters toward allergic responses.

The ‘choice’ towards a TH2 response is driven by the cytokine IL-4. Th2 cells suppress the activation of macrophages and activate eosinophils and mastcells. Th2 cells promote a strong antibody response based on neutralizing IgGs and IgEs. A Th2 response is most effective to combat extracellular pathogens.

Thus all types of infection might protect against the development of atopy and/or autoimmunity by driving the production of regulatory cytokines such as IL10, TGFb which down regulate both Th1 and Th2 responses in varying proportions.

The impact of microbial antigens on the immune response of the individual and the consequences appear to depend on timing of exposure, genetic susceptibility, nature of the organism other poorly defined factors.

**Evidences**

1. **Childhood infections and allergy:**

   Though there is a genetic component to atopic diseases, genetics cannot account for a marked increase in...
in the incidence and prevalence of allergic manifestations within a few generations. Both outdoor and indoor pollution, along with a long list of other environmental factors, have been proposed as a causal/contributory factor. But, in many developed countries, certain types of pollution have decreased, whereas the prevalence of atopic disease has increased. Prevalence of allergies in urban areas appears higher than in rural environments.

Generally children who grow up in rural areas of the developing countries or in farming communities are as much as 50 times less likely to have allergic conditions or manifest allergic sensitization or BHR than children raised in nearby metropolitan areas.

2. Helminthes and Asthma:

As the prevalence of helminthic infections decline the load of allergic disorders simply rise. The overall prevalence of helminthes in the global population is 25% whereas the allergy prevalence is as low as 2%. Contrastingly the US population shares a allergy prevalence of as high as 13% with a worm prevalence of meager 1%.

3. Common cold and Asthma:

Illi et al show that episodes of uncomplicated common colds during infancy may also protect against episodes of wheezing in later childhood. Other childhood infections such as herpetic stomatitis, exanthema subitum, and chickenpox also seemed protective. By contrast, episodes of wheezy lower respiratory tract infection were strongly associated with subsequent episodes of wheezing by the age of 7 (odds ratio >6). The important conclusion is that the risk of a diagnosis of asthma by the age of 7 is reduced by about 50% percent in children with two or more reported episodes of common cold (without associated wheeze) by the age of 1 year.

4. Infections and Immune Disorders:

During second half the 19th century the load of common infectious diseases like rheumatic fever, measles, hepatitis A, mumps and tuberculosis is gradually phasing out in the western world; parallelly there is a surge in the prevalence of immune mediated disorders like multiple sclerosis, asthma, crohn’s disease, type-1 diabetes. Can this be simple coincidence?

5. Type -1 Diabetes and chronic non-fatal infections:

The six common chronic infections like filariasis, onchocerciasis, trachoma,schistosomiasis, soil borne helminthiasis and leprosy are on the decline in the developed world; simultaneously the prevalence of the type-1 diabetes is on the rise in an inverse relationship.

6. Appendicitis increasing:

The hygiene hypothesis attributes the rise in appendicitis that occurred in the United Kingdom at the beginning of this century to improvements in sewage disposal and water supplies in the late 19th century. These improvements in hygiene greatly reduced the exposure of infants to enteric organisms that programme the immune system of the gut, thereby rendering the bowel more susceptible to triggering infection later in life. They explain, the appendix acts as a good store house for bacteria and can reboot the system whenever the gut is microbe depleted.

7. Early age antibiotic usage:
Children who received oral antibiotics by age 2 were more susceptible to allergies than children who had no antibiotics. Antibiotic treatment, which depletes the harmless bacteria within the gut, derails normal immune development in early life. Children from families that avoid antibiotics and vaccinations have fewer

8. IBD and worms:

An Israeli study covered 400,000 teenagers including 768(0.2 percent) diagnosed cases of IBD. Those with one sibling were found to be 2-3 times more likely to have IBD than teens with five or more siblings. Those who lived in an urban setting were 38 percent more likely to suffer than their rural counterparts. Crohn’s disease was first identified in the 1930s, and it is far more common in developed, urbanized areas than in poor, undeveloped areas. Statistical studies indicate that any country that gets rid of worms begins to see more cases of inflammatory bowel disease.

Helminths are parasitic animals that have evolved over 10^7 years to live in the intestinal tract or other locations of their hosts. Colonization of humans with these organisms was nearly universal until the early 20th century. More than 10^8 people in less developed countries carry helminths even today. Until the 1930s, most kids in North America had intestinal worms; most kids in underdeveloped countries still do. IBD probably results from an inappropriately vigorous immune response to contents of the intestinal lumen. Helminths must quell their host’s immune system to successfully colonize. It is likely that helminths sense hostile changes in the local host environment and take action to control such responses. Helminths interact with both host innate and adaptive immunity to stimulate immune regulatory circuitry and to dampen effector pathways that drive aberrant inflammation.

9. Atypical mycobacteria and asthma:

In a Japanese study, children who were given a tuberculosis vaccine made from an attenuated atypical mycobacteria, had a much lower rate of allergies and asthma than kids who didn’t receive the vaccine. Studies are underway to see if inhaling or injecting mycobacteria can prevent asthma attacks, and preliminary results are promising.

10. Toxoplasmosis and psychiatric disorders:

Rats infected with T. gondii exhibit suicidal behaviors. Otherwise normal men and women infected with T. gondii exhibit alterations in their behaviors: Infected women are likely to be more warmhearted and outgoing, and infected men often are more jealous and suspicious.

11. H. pylori disappearing:

H pylori colonization is the default human state, but it’s a state from which we’re swiftly drifting. A generation ago the global colonization rate was 90%; it is 50% as of now. In the US it is 10%, in Sweden and Germany 5%. So H pylori is disappearing really fast. It’s notable that people with H pylori have a large mass of gastric lymphoid tissue which plays an important role in the development of the immune system.

12. Multiple sclerosis and enterovirus infection:

Several studies have reflected the rising trend of Multiple Sclerosis to be associated with childhood infections of later onset, especially Epstein-Barr virus (EBV) infection. A Study of 62439 US women reported, 4-fold difference in titers of antibodies to Epstein-Barr virus antigens was associated with a 4-fold increase in risk of multiple sclerosis. (3)

13. IDDM and worms:

Professor Anne Cooke at the University of Cambridge experimentally revealed that showed that mice of the NOD strain (which spontaneously develop IDDM) had a significantly reduced incidence of this disease when infected with the helminth S. mansoni.

14. Helminth therapy:

Helminthic therapy is currently being studied as a treatment for several auto-immune diseases including Crohn’s Disease, Multiple Sclerosis, Asthma Ulcerative Colitis, Autoimmune hepatitis. In a double blind study with 54 patients suffering from acute ulcerative colitis the patients received either a placebo or 2500 T. suis ova every 2 weeks for 12 weeks. 43.3% of the patients given T. suis improved compared with those given placebo (16.7%). The study also included a 12 week crossover limb where patients originally on placebo where switched to T. suis and those on T. suis were switched to placebo. In the crossover limb, 56.3% of the patients given T. suis
improved compared with 13.3% of patients given placebo. There is yet another supportive study of skin application of the larvae of N. Americanus in single or multiple doses and its positive effect on the patients of ulcerative colitis.

15. Probiotics and immunity:

Bifidobacterium infantis-35624, a probiotic strain isolated from healthy human gastrointestinal tissue, was administered to mice in freeze-dried powder at least three weeks prior to salmonella infection (Salmonella typhimurium). Animals that received the probiotic showed dramatically increased numbers of T-regulatory cells which protected the host from excessive inflammation during the course of infection by limiting pro-inflammatory damage caused by superfluous activation of the innate immune system.

16. Asthma less in early cat exposure:

We know cats are forbidden for many asthmatics. At three years of age, children who had made antibodies to cats early in life were more likely to have wheeze, a respiratory symptom associated with asthma. However, by age five, the same children who had grown up with a cat were then found to be less likely to have wheeze. This finding suggests that prolonged cat ownership and early life exposure to cats may have a protective effect against early asthma indicators, such as wheeze, as children reach age five.

17. Obesity and gut microflora:

Numerous animal models consistently demonstrated that gut microbiota can modulate host energy homeostasis and adiposity through different mechanisms, e.g., energy harvest from the diet, LPS-induced chronic inflammation, modulation of tissue fatty acid composition, and gut-derived peptide secretion. Although extensive experimental data suggested gut microbiota manipulation can beneficially affect host adiposity and glucose metabolism, human studies so far have been able to establish an association between gut microbiota, western diet, and obesity.(2)

18. Mite sensitization and asthma:

Even when the 30% kids show antibodies against dust mite allergen in both parts of the world, only 12% of kids from Europe and Australia, only 3% have asthma in Gambia and Nigeria.(3)

19. Cancers and microbes:

It is proved beyond doubt that chronic infections have definitive links to yet another group of non-communicable diseases like malignancies. Human papillaoma virus and carcinoma cervix, EB virus and lymphoma, hepatitis-B virus and hepatocellular carcinoma, HIV and related malignancies are examples from the ever growing list.

20. The Diab-immune project:

The European Union has allocated 6 million Euros to the University of Helsinki to establish whether the decrease in the infection load is connected to type 1 diabetes and the emergence of allergies. The project comprises 12 partners from five countries and will include 7,000 children. Based on earlier reports in the project, it is known that the incidence of type 1 diabetes is six times higher and the prevalence of celiac disease five times higher among Finnish children than among Russian Karelian children. The HLA gene variants that predispose people to autoimmune diseases are however approximately equally common in both populations. Russian Karelian school children have helicobacter antibodies 15 times more often, toxoplasma antibodies five times more often, and hepatitis A antibodies 12 times more often than Finnish children.

Epilogue:

There has been some proof to say that microbes are somehow or other linked to the genesis (etiopathogenesis) of disorders like multiple sclerosis, type-1 diabetes, asthma, allergy, inflammatory bowel disease, obesity, schizophrenia, etc. And in years to come the list may include other non-communicable disorders like atherosclerosis, hypertension, etc.

Humans have 10 times more bacterial cells in their bodies than human cells. We are a minority on this planet and we must learn how to work with the majority.

Reference:

Glycemic Control in the Intensive Care Unit
Sidharth Routray¹, Basant K Pradhan²

Introduction:
Critically ill patients’ illness are associated with so-called stress-induced hyperglycemia, which is defined as transient hyperglycemia during illness in patients without previous evidence of diabetes mellitus.¹ The relationship between stress hyperglycemia and poor outcome is largely established for both conditions. In 2001, a large randomized controlled trial (RCT)² in critically ill surgical patients demonstrated that tight glucose control (TGC) (defined as the restoration and maintenance of blood glucose concentration [BG] between 4.4 and 6.1 mM) by intensive insulin therapy (IIT) was associated with a decreased mortality and rate of complications. However, subsequent studies performed in other intensive care units (ICUs) failed to reproduce the beneficial effects of IIT.

These conflicting results raise the following clinically relevant question: How can glycemia be controlled in ICUs? This commentary summarizes the current understanding of the physiologic regulation of glycemia, the toxicity of hyperglycemia, the mechanisms and consequences of stress hyperglycemia, and the available clinical data from observational and interventional studies. In addition, the unsolved issues and implications for daily clinical practice will be discussed. Updated formal recommendations will be suggested for glucose control in critically ill patients.

Physiologic Regulation of BG:
BG is tightly regulated by the following two types of mechanisms¹: (1) the hormonal system, which consists of a balance between the hypoglycemic insulin hyperglycemic counterregulatory hormones (i.e., glucagon, epinephrine, and cortisol); and (2) the neural mechanism, which consists of the activation of messages issued from glucose sensors of various organs. These hormonal and neural signals modulate carbohydrate metabolism by controlling glucose fluxes, including endogenous production and the entrance of glucose into the cells. The translocation of glucose transporters (GLUTs) is the prominent mechanism for the modulation of glucose transport across cell membranes. Among those transporters, GLUT 1 is the predominant transporter for non–insulin-mediated glucose uptake. GLUT 2 regulates the flow of glucose across liver cell membranes. GLUT 4 is the main insulin-responsive GLUT and therefore modulates the insulin-mediated glucose uptake in adipose tissue and cardiac and skeletal muscles. Some lipids, including ceramides, can interfere with the reading of the GLUT transporter-4 gene and the translocation of the protein to the membrane. This mechanism of insulin resistance can represent a target for future treatment.

Toxicity Associated with High Glucose Concentrations:
Because glucose is the preferential substrate during critically ill conditions, stress hyperglycemia was considered for a long time as a beneficial response, allowing an adequate provision of energy to tissues. However, in stress conditions, an overall massive glucose overload happens in non–insulin-mediated glucose uptake tissues. This accumulation results from the inhibition of the down-regulation of GLUT 1 transporters by proinflammatory mediators, counterregulatory hormones, and hypoxia. Several deleterious effects have been associated with these high glucose concentrations in cells.³ Damages to mitochondrial proteins occur, and the formation of reactive oxygen species is increased as a consequence of the shift from glycolysis toward accessory metabolic pathways (i.e., pentose phosphate, hexosamines, and polyols). Other effects of excess glucose concentrations include the exacerbation of inflammatory pathways, decreased complement activity, modifications in the

¹Asst. Prof.
²Assoc. Prof.
Dept. of Anesthesiology
SCB Medical College, Cuttack
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innate immune system, impairment in endothelial and hepatic mitochondrial functions, abolishment of ischemic preconditioning, and protein glycosylation.

**Mechanisms of Stress Hyperglycemia:**

Although sharing some similarities, the pathogenetic mechanisms of type 2 diabetes and stress hyperglycemia are different. In diabetes, the cause of hyperglycemia is a combination of insulin resistance and defective secretion by pancreatic β-cells. During stress hyperglycemia, complex interactions between counterregulatory hormones (e.g., catecholamines, growth hormone, and cortisol) and cytokines lead to excessive hepatic glucose production and peripheral insulin resistance. This highly complex interplay is largely variable over time. The increase in hepatic output of glucose results from gluconeogenesis and, to a lesser extent, from glycogenolysis. Gluconeogenesis is triggered to a larger extent by glucagon than by epinephrine and cortisol. Glycogenolysis is triggered primarily by catecholamines and perpetuated under the influence of epinephrine and cortisol. Tumor necrosis factor α might promote neoglucogenesis by stimulating glucagon production. The increase in peripheral resistance is characterized by the inability of skeletal muscles and adipocytes to absorb glucose, related to an alteration of insulin signaling and down-regulation of GLUT transporter-4. Central insulin resistance is used to define the decreased ability of insulin to suppress hepatic glucose production and seems less affected than peripheral insulin resistance during stress.

**Glycemic Control: Observational Clinical Studies:**

Recent and older observational data in various populations of critically ill patients consistently reported admission hyperglycemia as an independent marker of mortality and morbidity.[5] This relationship was the strongest in patients with acute myocardial infarction, stroke, and cerebral hemorrhage. The beneficial effect of decreasing the BG to lower than 8.0 mM in large populations has been suggested by retrospective analysis of large cohorts of critically ill patients. Consistently, in these series, patients with an average BG lower than this threshold had a better outcome than those with an average BG higher than this threshold.[6]

**Glycemic Control: Interventional Clinical Studies**

**Glycemic Control in ICUs:**

The first large landmark RCT included 1,548 surgical ICU patients (mainly cardiac surgery) randomized to IIT (target BG, 4.4–6.1 mM) or to conventional glycemic management (target BG, 10–11.1 mM).[2] In this study, IIT was associated with a reduction in ICU mortality from 8% to 4.6% and in-hospital mortality from 10.9% to 7.2%. These beneficial effects were even larger in patients who spent longer than 5 days in the ICU. In addition, IIT decreased ICU morbidity, expressed by a decreased incidence of systemic infection, acute renal failure, need for transfusion polyneuropathy, duration of mechanical ventilation, and length of stay in the ICU. The Leuven, Belgium, team performed a second study[7] using a comparable method and objectives in a medical ICU population. Considering the whole cohort of 1,200 patients, no significant decrease of in-hospital mortality in the TGC group versus the control group was found, although a benefit was found in those staying a long time. The external validity of the Leuven studies and the optimal BG target were assessed in large single- and multiple-center prospective trials of TGC by IIT comparing two ranges of BGs. The design of these trials was similar but not identical (table 1). All trials aimed to compare the effects of insulin therapy dosed to restore and maintain the BG between 4.4 and 6.1 mM. They differed in the target range of BG for the control (non-IIT) group. The Glucontrol[7] and the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation) trials used a target value of 7.8–10.0 mM, whereas both Leuven studies, [2], the VISEP study (Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis), and two other single-center large-scale trials used a target value of 10–11.1 mM.
TABLE 1 — Major Differences between the Seven Major Interventional Studies Evaluating Glycemic Control in ICUs:

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of eligible patients</th>
<th>Number of patients included</th>
<th>Percentage of medical patients</th>
<th>Percentage of surgical/postoperative admissions</th>
<th>Mean admission APACHE II score</th>
<th>Percentage of calories given intravenously</th>
<th>Target control (mM)</th>
<th>Target IIT (mM)</th>
<th>BG values reached [mM - mean (SD) or median (IQR 25–75)]</th>
<th>Mortality rate (%)</th>
<th>Hypoglycemia rate (%)</th>
<th>Mean amount of insulin infused (U/day)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van den Bergh et al. [2]</td>
<td>1,562</td>
<td>1,548</td>
<td>0</td>
<td>96.0</td>
<td>9.0</td>
<td>87.0</td>
<td>10.1–11.1</td>
<td>4.4–6.1</td>
<td>8.5+/−1.8, 8.5+/−1.7, 8.1+/−1.4, 7.7+/−1.9, 8.4+/−1.8, 8.2(6.8–10)</td>
<td>8.0</td>
<td>0.8</td>
<td>3.3</td>
<td>39</td>
</tr>
<tr>
<td>Van den Bergh et al. [7]</td>
<td>2,110</td>
<td>1,200</td>
<td>100</td>
<td>0</td>
<td>23.0</td>
<td>87.0</td>
<td>10.1–11.1</td>
<td>4.4–6.1</td>
<td>6.1+/−1.1, 6.1+/−1.6, 6.6+/−1.4, 6.1+/−2.0, 6.2+/−1.0, 6.5(5.6–7.8)</td>
<td>26.8</td>
<td>3.1</td>
<td>0.5</td>
<td>70</td>
</tr>
<tr>
<td>NICE-SUGAR [10]</td>
<td>7,294</td>
<td>6,022</td>
<td>62.9</td>
<td>37.1</td>
<td>21.1</td>
<td>29.5</td>
<td>7.8–10.0</td>
<td>4.4–6.1</td>
<td>8.1+/−1.4, 8.1+/−1.4, 8.6+/−1.4, 8.6+/−2.0, 6.6+/−1.4, 6.6+/−2.0</td>
<td>24.9</td>
<td>0.5</td>
<td>2.7</td>
<td>69</td>
</tr>
<tr>
<td>Preiser et al. [13]</td>
<td>1,108</td>
<td>1,101</td>
<td>40.4</td>
<td>56.1</td>
<td>15.0</td>
<td>27.0</td>
<td>7.8–10.0</td>
<td>4.4–6.1</td>
<td>7.8+/−1.9, 7.8+/−1.9, 8.1+/−1.9, 7.8+/−1.9, 7.8+/−1.9, 7.8+/−1.9</td>
<td>15.3</td>
<td>2.7</td>
<td>4.1</td>
<td>17</td>
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<tr>
<td>Brunkhorst et al. [12]</td>
<td>600</td>
<td>488</td>
<td>46.9</td>
<td>NA</td>
<td>20.2</td>
<td>66.0</td>
<td>10.1–11.1</td>
<td>4.4–6.1</td>
<td>8.4+/−1.8, 8.4+/−1.8, 8.4+/−1.8, 8.4+/−1.8, 8.4+/−1.8, 8.4+/−1.8</td>
<td>35.4</td>
<td>4.1</td>
<td>1.7</td>
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<td>De La Rosa et al. [9]</td>
<td>812</td>
<td>504</td>
<td>48.8</td>
<td>48.8</td>
<td>20.2</td>
<td>66.0</td>
<td>10.1–11.1</td>
<td>4.4–6.1</td>
<td>8.2(6.8–10), 8.2(6.8–10), 8.2(6.8–10), 8.2(6.8–10), 8.2(6.8–10), 8.2(6.8–10)</td>
<td>31.2</td>
<td>8.5</td>
<td>8.5</td>
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<tr>
<td>Arabi et al. [8]</td>
<td>780</td>
<td>523</td>
<td>83.2</td>
<td>16.8</td>
<td>15.6</td>
<td>7.9</td>
<td>10.1–11.1</td>
<td>4.4–6.1</td>
<td>9.5+/−1.9, 9.5+/−1.9, 9.5+/−1.9, 9.5+/−1.9, 9.5+/−1.9, 9.5+/−1.9</td>
<td>17.1</td>
<td>31.1</td>
<td>31.1</td>
<td>99</td>
</tr>
</tbody>
</table>

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APACHE II = Acute Physiology and Chronic Health; ICU = intensive care unit; IIT = intensive insulin therapy; IQR = interquartile range; NA = not analyzed; NICE-SUGAR = Normoglycaemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation.

In the NICE-SUGAR study, IIT was associated with an increased 90-day mortality, whereas in the other confirmatory trials, no difference in the outcome of the two groups was found. As expected, IIT was associated with a 4- to 6-fold increase in the incidence of hypoglycemia (reported in 5–25% of the patients randomized to IIT). This high incidence of hypoglycemia represents the major concern when starting IIT and is the major cause of increased medical and nurse workload. In the VISEP and Glucontrol studies, the rates of hypoglycemia and mortality in patients who experienced at least one such episode (defined as a BG of lower than 2.2 mM) were higher than in patients who did not experience hypoglycemia. In contrast, in both Leuven studies, [2]–[7] hypoglycemic patients had no detectable differences in outcome compared with patients without any hypoglycemic episodes. This does not exclude the possibility that long-lasting hypoglycemia, with consequent decreases in glucose availability for tissues that are glucose dependent, may be deleterious or even life-threatening. An accurate understanding of the consequences of hypoglycemia in critically ill patients requires further investigations.

Glycemic Control in Critically Ill Patients: The Unsolved Issues:

The discrepancies between the results of the prospective trials of IIT led to various discussions and speculations. Several variables, including the quality of glucose control assessed by the actual BG value achieved, may influence the effect of IIT on outcome. Sampling site and type of devices can interfere with the determination of glucose concentration, especially in cases of vasoconstriction, arterial hypotension, shock, ischemia, and edema. Arterial blood samples and laboratory measurements (or blood gas analyzer devices) provide the most accurate BG values. Depending on the patient’s condition, the impact of glycemic control in the ICU could vary. The underlying condition, type of admission, and preexistence of diabetes can also influence the effects of IIT.

Furthermore, a high rate of hypoglycemia and high glucose variability were associated with increased mortality in retrospective studies and in subsets of patients of prospective trials. However, causal relationships between the occurrence of hypoglycemia and poor outcome in the ICU are not established. In addition to insulin infusion, other markers of severity (i.e., mechanical ventilation, renal removal therapies, sepsis, and catecholamines) predispose to hypoglycemia in critically ill patients. Observational studies have reported a clear relationship between poor outcome in critically ill patients and BG variability.

Obviously, several issues are left unsolved, including the optimal BG target, the categories of patients who could benefit from IIT, and the logistical requirements for safe and reliable glucose control. Several technical advances that could improve the quality and safety of glucose control include continuous intravascular glucose monitoring and computerized automated algorithms for insulin infusion. Meanwhile, recommendations for daily practice are needed. In the absence of unequivocal evidence from clinical trials, formal expert recommendations have been issued for hospital diabetic inpatients and critically ill and postoperative patients.

Main Practical Recommendations for Critically Ill Patients:

Formalized recommendations that focused on glycemic control in the perioperative period and in critically ill patients have been elaborated by an international group of experts. Most of these recommendations are summarized in this paragraph.

Glucose Target in ICUs:

1. Avoid severe hyperglycemia (more than 10 mM) in adult ICU patients; a universally acceptable upper limit cannot be specified. (2) TGC should be avoided in an emergency situation. (3) Avoid large variations in glucose concentrations in ICUs. (4) Intravenous insulin is the only medication to be used for glucose control in ICUs.
Hypoglycemia:
(1) A glucose threshold of 2.2 mM is used to define severe hypoglycemia. Early detection and correction of hypoglycemia are needed, even in the absence of clinical signs. (2) Arterial or venous blood samples are more reliable than capillary samples in ICU patients with suspected hypoglycemia; capillary samples often overestimate glucose concentration.

Carbohydrate Intake:
(1) Hyperglycemia may be decreased by restricting intravenous glucose concentration in critically ill patients. (2) Intravenous insulin infusion by electric syringe pump can be discontinued when the patient has resumed food intake while maintaining glucose monitoring for at least three preprandial controls. (3) The daily energy intake in ICU patients must follow the international recommendations of approximately 25 kcal/kg per day. However, optimal carbohydrate intake has still to be established according to the type, severity of pathology, and delay from onset of disease.

Glucose Monitoring:
Glucose concentrations should be measured in the laboratory or with a blood gas analyzer device. The preferential order of sampling is as follows: arterial, venous, and capillary. The specifications of the device and paper strips used must be known to interpret BG values and to account for possible interferences.

Algorithms and Protocols:
A standard protocol for glucose control should be used. A specific route of administration should be used for continuous intravenous insulin infusion. A formal protocol must be dynamic (determination of insulin delivery rate on the basis of the last glucose measurement) and must include at least recommendations on the use of rapid-action insulin as a continuous infusion by electric syringe pump, on the correction and monitoring procedures for episodes of hypoglycemia. Implements in protocols for glycemic control could be obtained by accounting for carbohydrate intake and using a computer-assisted glucose control protocol. Before implementing a glucose control protocol, time should be devoted to train the staff and to account for the increase in workload.

Conclusion:
The adverse effects of excessive hyperglycemia in critically ill patients are undeniable. Data strongly support that BG should be carefully controlled in these populations. However, the concept of TGC by IIT must be revisited because several large RCTs have shown inconsistent results, revealing no effect or an increased mortality in the glycemic control group. Therefore, TGC cannot be used in routine practice regardless of the settings, type of patients, and education of the team. New strategies should be developed to achieve glycemic control with a minimal risk of hypoglycemia and of large glucose variations. More efforts should focus on the quality of BG measurement devices and BG monitoring modalities, thanks to a computer-assisted algorithm and education of medical and nursing staff. Until such optimizations, each team must implement its own protocol by considering its technical and human resources.

References:
The 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care marks the 50th anniversary of modern CPR. In 1960 Kouwenhoven, Knickerbocker, and Jude documented 14 patients who survived cardiac arrest with the application of closed chest cardiac massage.\(^1\) That same year, at the meeting of the Maryland Medical Society in Ocean City, MD, the combination of chest compressions and rescue breathing was introduced.\(^2\) Two years later, in 1962, direct-current, monophasic waveform defibrillation was described.\(^3\) In 1966 the American Heart Association (AHA) developed the first cardiopulmonary resuscitation (CPR) guidelines, which have been followed by periodic updates.\(^4\) During the past 50 years the fundamentals of early recognition and activation, early CPR, early defibrillation, and early access to emergency medical care have saved hundreds of thousands of lives around the world. These lives demonstrate the importance of resuscitation research and clinical translation and are cause to celebrate this 50\(^{th}\) anniversary of CPR.

Challenges remain if we are to fulfill the potential offered by the pioneer resuscitation scientists. We know that there is a striking disparity in survival outcomes from cardiac arrest across systems of care, with some systems reporting 5-fold higher survival rates than others.\(^5\)\(^\text{-}^9\) Although technology, such as that incorporated in automated external defibrillators (AEDs), has contributed to increased survival from cardiac arrest, no initial intervention can be delivered to the victim of cardiac arrest unless bystanders are ready, willing, and able to act. Moreover, to be successful, the actions of bystanders and other care providers must occur within a system that coordinates and integrates each facet of care into a comprehensive whole, focusing on survival to discharge from the hospital. This executive summary highlights the major changes and most provocative recommendations in the 2010 AHA Guidelines for CPR and Emergency Cardiovascular Care (ECC).

On the basis of the strength of the available evidence, they developed recommendations to support the interventions that showed the most promise. There was unanimous support for continued emphasis on high-quality CPR, with compressions of adequate rate and depth, allowing complete chest recoil, minimizing interruptions in chest compressions and avoiding excessive ventilation. High-quality CPR is the cornerstone of a system of care that can optimize outcomes beyond return of spontaneous circulation (ROSC). Return to a prior quality of life and functional state of health is the ultimate goal of a resuscitation system of care.

The 2010 AHA Guidelines for CPR and ECC are based on the most current and comprehensive review of resuscitation literature ever published, the 2010 ILCOR International Consensus on CPR and ECC Science With Treatment Recommendations.\(^10\) The 2010 evidence evaluation process included 356 resuscitation experts from 29 countries who reviewed, analyzed, evaluated, debated, and discussed research and hypotheses through in-person meetings, teleconferences, and online sessions during the 36-month period before the 2010 Consensus Conference. The experts produced 411 scientific evidence reviews on 277 topics in resuscitation and emergency cardiovascular care. The process included structured evidence evaluation, analysis, and cataloging of the literature.
### Basic Life Support

<table>
<thead>
<tr>
<th>2010 Recommendation</th>
<th>2005 Recommendation</th>
<th>. Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A change in the basic life support (BLS) sequence of steps for trained rescuers from</td>
<td>Use of the “A-B-C” basic life support sequence</td>
<td>• In the majority of cardiac arrests, the critical initial elements of CPR are chest compressions and early defibrillation.</td>
</tr>
<tr>
<td>“A-B-C” (Airway, Breathing, Chest compressions) to “C-A-B” (Chest compressions,</td>
<td></td>
<td>• In the C-A-B sequence, chest compressions will be initiated sooner and ventilation only minimally delayed until completion of the first cycle of chest compressions.</td>
</tr>
<tr>
<td>Airway, Breathing) for adults and pediatric patients (children and infants, excluding</td>
<td></td>
<td>• The A-B-C sequence could be a reason why fewer than a third of people in cardiac arrest receive bystander CPR. A-B-C starts with the most difficult procedures: opening the airway and delivering rescue breaths.</td>
</tr>
<tr>
<td>newborns). Also applies to BLS for healthcare providers.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Look, Listen and Feel” has been removed from the BLS algorithm Also applies to BLS</td>
<td>“Look, Listen and Feel” Included in BLS algorithm</td>
<td>Performance of “Look, Listen and Feel,” is inconsistent and time consuming.</td>
</tr>
<tr>
<td>for healthcare providers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A compression rate of at least 100/min. Also applies to BLS for healthcare providers</td>
<td>A compression rate of “approximately” 100/min</td>
<td>The number of chest compressions delivered per minute during CPR is an important determinant of return of spontaneous circulation (ROSC) and survival with good neurologic function. In most studies, delivery of more compressions during resuscitation is associated with better survival, and delivery of fewer compressions is associated with lower survival.</td>
</tr>
<tr>
<td>The new recommendation for chest compression depth: push down on the adult breastbone</td>
<td>Depress adult breastbone approximately 1 1/2 to 2 inches (approximately 4 to 5 cm).</td>
<td>Compressions generate critical blood flow and oxygen and energy delivery to the heart and brain. Rescuers often do not push the chest hard enough.</td>
</tr>
<tr>
<td>at least 2 inches (5 cm). Also applies to BLS for healthcare providers</td>
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</tr>
</tbody>
</table>
If a bystander is not trained in CPR, the bystander should provide Hands-Only (compression-only) CPR for the adult victim who suddenly collapses, with an emphasis to “push hard and fast” on the center of the chest, or follow the directions of the EMS dispatcher. All trained lay rescuers should, at a minimum, provide chest compressions for victims of cardiac arrest. In addition, if the trained lay rescuer is able to perform rescue breaths, compressions and breaths should be provided in a ratio of 30 compressions to 2 breaths.

The new guidelines more strongly recommend that dispatchers instruct untrained lay rescuers to provide Hands-Only CPR for adults who are unresponsive, with no breathing or no normal breathing. Dispatchers should provide instructions in conventional CPR for victims of likely asphyxial arrest (such as drowning).

The new guidelines do not recommend routine use of cricoid pressure in cardiac arrest.

| The 2005 AHA Guidelines for CPR and ECC did not provide different recommendations for trained versus untrained rescuers but did recommend that dispatchers provide compression-only CPR instructions to untrained bystanders. The 2005 AHA Guidelines for CPR and ECC did note that if the rescuer was unwilling or unable to provide ventilations, the rescuer should provide chest compressions only |
| The 2005 AHA Guidelines for CPR and ECC noted that telephone instruction in chest compressions alone may be preferable. |
| Hands-Only (compression-only) CPR is easier for an untrained rescuer to perform and can be more readily guided by dispatchers over the telephone. In addition, survival rates from cardiac arrests of cardiac etiology are similar with either Hands-Only CPR or CPR with both compressions and rescue breaths. However, for the trained lay rescuer who is able, there recommendation remains for the rescuer to perform both compressions and ventilations. |
| • Hands-Only (compressions-only) bystander CPR substantially improves survival after adult out-of-hospital cardiac arrests compared with no bystander CPR. |
| • Other studies of adults with cardiac arrest treated by lay rescuers showed similar survival rates among victims receiving Hands-Only CPR versus those receiving conventional CPR. |
| • It is easier for dispatchers to instruct untrained rescuers to perform Hands-Only CPR than conventional CPR for adult victims, so the recommendation is now stronger for them to do so, unless the victim is likely to have had an asphyxial arrest |
| Cricoid pressure should be used only if the victim is deeply unconscious. This usually requires a third rescuer, not involved in rescue breaths or compressions. |
| Cricoid pressure can prevent gastric inflation and reduce the risk of regurgitation and aspiration during bag-mask ventilation, but it may also impede ventilation. Seven randomized studies showed that cricoid pressure can delay or prevent the placement of an advanced airway and some aspiration can still occur despite application of cricoid pressure. In addition, it is difficult to appropriately train rescuers in use of the maneuver. |
| Cricoid pressure can be used to prevent gastric inflation and reduce the risk of regurgitation and aspiration during bag-mask ventilation, but it may also impede ventilation. Seven randomized studies showed that cricoid pressure can delay or prevent the placement of an advanced airway and some aspiration can still occur despite application of cricoid pressure. In addition, it is difficult to appropriately train rescuers in use of the maneuver. |
**Electrical Therapies**

If one is available, the rescuer should use a pediatric Dose-attenuator system for attempted defibrillation of children 1 to 8 years of age with an AED. If the rescuer does not have an AED with a pediatric dose-attenuator system, the rescuer should use a standard AED. For infants (<1 year of age), a manual defibrillator is preferred. If a manual defibrillator is not available, an AED with pediatric dose attenuation is desirable. If neither is available, an AED without a dose attenuator may be used.

For children 1 to 8 years of age, the rescuer should use a pediatric Dose-attenuator system if one is available. If the rescuer provides CPR to a child in cardiac arrest and does not have an AED with a pediatric attenuator system, the rescuer should use a standard AED. There are insufficient data to make a recommendation for or against the use of AEDs for infants <1 year of age.

The lowest energy dose for effective defibrillation in infants and children is not known. The upper limit for safe defibrillation is also not known, but doses >4 J/kg (as high as 9 J/kg) have effectively defibrillated children and animal models of pediatric arrest with no significant adverse effects. Automated external defibrillators with relatively high-energy doses have been used successfully in infants in cardiac arrest, with no clear adverse effects.

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**Advanced Cardiovascular Life Support (ACLS)**

<table>
<thead>
<tr>
<th>2010 Recommendation</th>
<th>2005 Recommendation</th>
<th>Explanation</th>
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<tr>
<td>Continuous quantitative waveform capnography is now recommended for intubated patients throughout the peri-arrest period. When quantitative waveform capnography is used for adults, applications now include recommendations for confirming tracheal tube placement and for monitoring CPR quality and detecting return of spontaneous circulation based on end-tidal carbon dioxide (Petco2) values</td>
<td>An exhaled carbon dioxide (CO2) detector or an esophageal detector device was recommended to confirm endotracheal tube placement. The previous guidelines noted that Petco2 monitoring can be useful as a noninvasive indicator of cardiac output generated during CPR.</td>
<td>Continuous waveform capnography is the most reliable method of confirming and monitoring correct placement of an endotracheal tube. Because blood must circulate through the lungs for CO2 to be exhaled and measured, capnography can also serve as a physiologic monitor of the effectiveness of chest compressions and to detect return of spontaneous circulation. Ineffective chest compressions (due to either patient characteristics or rescuer performance) are associated with a low Petco2. Falling cardiac output or re-arrest in the patient with return of spontaneous circulation also causes a decrease in Petco2. In contrast, return of spontaneous circulation may cause an abrupt increase in Petco2.</td>
</tr>
</tbody>
</table>
The conventional ACLS Cardiac Arrest Algorithm has been simplified and streamlined to emphasize the importance of high-quality CPR. The new guidelines include a new circular algorithm. The same priorities were cited in the 2005 guidelines. The box and arrow algorithm listed key actions performed during the resuscitation in a sequential fashion.

Before 2005, ACLS courses assumed that excellent CPR was provided, and, therefore, focused mainly on added interventions, such as manual defibrillation, drug therapy, and advanced airway management, as well as alternative and additional management options for special resuscitation situations. Although adjunctive drug therapy and advanced airway management are still part of ACLS, in 2005 the emphasis in advanced life support (ALS) returned to the basics, with an increased emphasis on what is known to work: high quality CPR. While continuing this emphasis, the 2010 guidelines note that CPR is ideally guided by physiologic monitoring and includes adequate oxygenation and early defibrillation, while the ALS provider assesses and treats possible underlying causes of the arrest. There is no definitive clinical evidence that early intubation or drug therapy improves neurologically intact survival to hospital discharge.

Atropine is no longer recommended for routine use in the management of pulseless electrical activity (PEA)/asystole. Adenosine is recommended in the initial diagnosis and treatment of stable, undifferentiated regular, monomorphic wide complex tachycardia (this is also consistent in ACLS and PALS recommendations).

Atropine was included in the ACLS Pulseless Arrest Algorithm: for a patient in asystole or slow PEA, atropine could be considered.

Evidence suggests that the routine use of atropine during PEA or asystole is unlikely to have a therapeutic benefit. On the basis of new evidence of safety and potential efficacy, adenosine can now be considered as recommended.
Summary of Key BLS Components for Adults, Children, and Infants*

<table>
<thead>
<tr>
<th>Component</th>
<th>Adults</th>
<th>Children</th>
<th>Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recognition</strong></td>
<td>No breathing or no normal breathing (i.e., only gasping)</td>
<td>No breathing or only gasping</td>
<td></td>
</tr>
<tr>
<td><strong>CPR sequence</strong></td>
<td>C-A-B</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Compression rate</strong></td>
<td>At least 100/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Compression depth</strong></td>
<td>At least 2 inches (5 cm)</td>
<td>At least 1/2 AP diameter About 2 inches (5 cm)</td>
<td>At least 1/4 AP diameter About 1 1/2 inches (4 cm)</td>
</tr>
<tr>
<td><strong>Chest wall recoil</strong></td>
<td>Allow complete recoil between compressions</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Compression interruptions</strong></td>
<td>Minimize interruptions in chest compressions</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Airway</strong></td>
<td>Head tilt—chin lift (HCP suspected trauma; jaw thrust)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Compression-to-ventilation ratio (until advanced airway placed)</strong></td>
<td>30:2 1 or 2 rescuers</td>
<td>30:2 Single rescuer</td>
<td>15:2 2 HCP rescuers</td>
</tr>
<tr>
<td><strong>Ventilations: when rescuer untrained or trained and not proficient</strong></td>
<td>Compressions only</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ventilations with advanced airway (HCP)</strong></td>
<td>1 breath every 6-8 seconds (8-10 breaths/min) Asynchronous with chest compressions About 1 second per breath Visible chest rise</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Defibrillation</strong></td>
<td>Attach and use AED as soon as available. Minimize interruptions in chest compressions before and after shock; resume CPR beginning with compressions immediately after each shock.</td>
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</table>

*Note: AED, automated external defibrillator; AP, anterior-posterior; CPR, cardiopulmonary resuscitation; HCP, healthcare provider.

*Excluding the newly born, in whom the etiology of an arrest is nearly always asphyxial.

Circular ACLS Algorithm

CPR Quality
- Push hard, 2 1/2 inches (5 cm) and fast (100/min) and allow complete chest recoil;
- Minimize interruptions in compressions;
- Avoid excessive ventilation;
- Rotate rescuers every 2 minutes;
- If no advanced airway, 30:2 compression-ventilation ratio;
- Quantitative waveform capnography;
- If MAP < 60 mm Hg, attempt to improve CPR quality;
- Intra-arterial pressure;
- If hypotension (diastolic pressure < 20 mm Hg), attempt to improve CPR quality.

Return of Spontaneous Circulation (ROSC)
- Biphasic: Manufacturer recommendation (120-200 J); if unknown, use maximum available. Second and subsequent doses should be equivalent, and higher doses may be considered.
- Monophasic: 260 J
- Drug Therapy
  - Epinephrine 1:1000 Dose: 1 mg every 3-5 minutes
  - Vasopressin 1:1000 Dose: 40 units can replace first or second dose of epinephrine
- Amiodarone 400 mg: First dose: 300 mg bolus. Second dose: 150 mg

Advanced Airway
- Supraglottic advanced airway or endotracheal intubation.
- Waveform capnography to confirm and monitor ET tube placement
- 6-10 breaths per minute with continuous chest compressions

Reversible Causes
- Hypovolemia: Tension pneumothorax
- Hypoxia: Pneumonia, cardiac
- Hypo-glycemia: Drug or alcohol
- Hypo-hypertension: Thoracotomy, coronary
References:


Announcement

63RD ANNUAL CONFERENCE
Indian Medical Association
ODISHA STATE BRANCH
Venue: Hotel Shreekshetra International, Kendujhar
on 18th & 19th February 2012
Theme of conference: “Health Care at Periphery”

REGISTRATION FEE

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<td>Spouse/ Child&gt;10y / Accompanying Person/ Students</td>
<td>300</td>
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<tr>
<td>Non IMA Doctors</td>
<td>700</td>
<td>900</td>
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ALL ARE INVITED
Diabetic Retinopathy
Soumyava Basu

Introduction:
Diabetic retinopathy is one of the most significant complications of diabetes. It is responsible for 4.8% of the 37 million cases of blindness throughout the world (i.e., 1.8 million persons). Though management of diabetic retinopathy has improved greatly in recent years, the ever increasing diabetic population makes diabetic retinopathy a challenging public health problem. The following text is an overview of diabetic retinopathy for general practitioners, who commonly deal with diabetic patients and not an exhaustive review of the topic.

How common is diabetic retinopathy? Various studies from across the world show the presence of retinopathy in 32% to 52% of the diabetic population. In India, these figures have been found to range between 7.8 to 18% of the diabetic population. Such low figures could be due to ethnic differences and lesser mean duration of diabetes in Indian studies.

Classification: The current classification of diabetes is based on the Early Treatment for Diabetic Retinopathy Study (ETDRS).

Non-proliferative stage: The earliest clinical signs of diabetic retinopathy are microaneurysms, small outpouchings from retinal capillaries, and dot intraretinal hemorrhages. These signs are present in nearly all persons who have had type 1 diabetes for 20 years and in nearly 80 percent of those with type 2 disease of this duration. As the disease progresses, these patients have an increase in the number and size of intraretinal hemorrhages. This increase may be accompanied by cotton-wool spots; both of these signs indicate regional failure of the retinal microvascular circulation, which results in ischemia. The non-proliferative stage is divided into mild, moderate, severe and very severe, based on extent of clinical signs.

Proliferative stage: This happens when new blood vessels start budding from the retinal circulation. Untreated, it may result in marked visual loss. New vessels can extend into the vitreous cavity of the eye and can hemorrhage into the vitreous, resulting in visual loss, and also cause tractional retinal detachments from the accompanying contractile fibrous tissue. Late in the course of the disease, new blood vessels may form within the iris and may extend into the angle of the anterior chamber, blocking the circulation of aqueous humor, leading to disastrous rise in intraocular pressure (neovascular glaucoma).

Diabetic macular edema: This occurs due to breakdown of the blood–retinal barrier, with leakage of plasma from small blood vessels in the macula, the central portion of the retina that is responsible for the major part of visual function. This causes swelling of the central retina. Resorption of the fluid elements from plasma leads to the deposition of its lipid and lipoprotein components and the formation of hard exudates. Although diabetic macular edema does not cause total blindness, it frequently leads to severe loss of central vision.

Mechanism of disease: The relatively selective loss of pericytes from the retinal capillaries is a characteristic lesion that occurs early in the histopathology of diabetic retinopathy. Normal pericytes are thought to have a contractile function that helps to regulate capillary blood flow. Loss of pericytes is followed by loss of capillary endothelial cells. Since neurons in the retina have high metabolic requirements, the hypoxia that results from extensive retinal capillary cell death is a probable stimulus for the increased expression of molecules (e.g., vascular endothelial growth factor [VEGF]) that enhance the breakdown of the blood–retinal barrier and lead to vascular proliferation.

Clinical evaluation:
The two common manifestations of diabetic retinopathy that require treatment – clinically significant
macular edema (CSME) and proliferative diabetic retinopathy (PDR) are essentially clinical diagnoses. Hence the importance of clinical evaluation. Retinal examination is done with slit lamp biomicroscopy and indirect ophthalmoscopy. During clinical evaluation, it is also important to rule out co-morbid conditions that are frequently seen in diabetics, like cataract, retinal vein occlusions, and anterior ischemic optic neuropathy.

**Investigations:**

Though CSME and PDR are diagnosed clinically, investigations like fundus fluorescence angiography (FFA) and optical coherence tomography (OCT) have a vital role in planning the course of treatment. FFA helps us in identifying focal or diffuse leakage at the macula (guides laser therapy), foveal ischemia (poor prognosis) and early PDR (when clinically indistinguishable). OCT quantifies retinal thickening at a given point of time and thus helps in monitoring response to therapy. It also identifies attachments of the vitreous on the fovea (vitreo-macular traction), which may need surgical intervention. Besides FFA and OCT, B-scan ultrasonography is sometimes used to evaluate retinal integrity in the presence of dense vitreous hemorrhage.

**Risk factor assessment:**

The most important risk factors for the development and progression of diabetic retinopathy are – duration of diabetes, blood glucose control, insulin therapy, hypertension, hyperlipidemia, nephropathy, anemia and pregnancy. The importance of regular monitoring and control of the above factors cannot be overemphasized. Of particular mention are hypertension, whose importance is as much as blood sugar control, and hyperlipidemia, which plays a key role in the formation of hard exudates.

**What do we treat in diabetic retinopathy?**

- Clinically significant macular edema (as defined by ETDRS)
- Proliferative diabetic retinopathy – retinal neovascularization, vitreous hemorrhage, tractional retinal detachment.

**How do we treat diabetic retinopathy?**

- Systemic – risk factor management
- Local – Laser photocoagulation (focal/ pan-retinal), Intra-vitreal injections, Surgery

**Laser photocoagulation:**

Light rays of a given wavelength (commonly 532 nm) can be absorbed by retinal pigments to generate heat. This thermal effect of laser light is utilized in the treatment of diabetic retinopathy. In diabetic macular edema, focal laser is done on leaking microaneurysms, while grid-pattern laser is done to facilitate movement of intra-retinal fluid into the underlying choroid. The reduction in retinal thickening takes 2-3 months, and can be accurately monitored on OCT.

Proliferative diabetic retinopathy needs pan-retinal photocoagulation (PRP). This involves laser-induced ablation of extensive areas of ischemic retina, and is done in 2-3 sittings. Since ischemic retina is the source of pro-proliferation molecules like the VEGF, PRP helps in reducing the stimulus for formation of new blood vessels, leading to resolution of the proliferative process. Timely PRP can be very useful in preventing the sequelae of proliferation viz. vitreous hemorrhage and tractional retinal detachment. Patients with severe NPDR may also need PRP, in case they are unlikely to follow-up regularly.

**Pattern-scan laser (PASCAL)** is a new laser delivery system that delivers laser pulses in a predetermined pattern that greatly increases the accuracy and reduces the time required for laser photocoagulation.

**Intra-vitreal injections:**

These include anti-VEGF agents and long-acting corticosteroids. Anti-VEGF agents like bevacizumab (Avastin) and ranibizumab (Lucentis) are typically used in treating severe macular edema especially when it is associated with sub-retinal fluid or cystoid spaces in retina. Occasionally, anti-VEGF agents are also used for temporary resolution of proliferative retinopathy. These drugs need to be supplemented with laser photocoagulation for better long-term outcome of treatment. Recent clinical trials have shown that both Avastin and Lucentis are equally effective as anti-VEGF agents.

The other group of drugs used as intra-vitreal injections in diabetic retinopathy is long-acting corticosteroid. Intra-vitreal triamcinolone acetonide is now used sparingly because of risk of complications like intractable glaucoma (rise in intra-ocular pressure)
and cataract. Newer drug delivery systems like sustained-release dexamethasone (Ozurdex) have shown promising results.

**Surgery:**

The most common indications for vitreo-retinal surgery are: vitreous hemorrhage (non-resolving), tractional retinal detachment that is involving or threatening the macula, florid neovascularisation, and vitreo-macular traction. Surgery involves removal of the vitreous gel, separation of vitreo-retinal adhesions and endolaser photocoagulation. In most cases, such surgery can be done by 23-guage sutureless technique, which allows faster recovery and less post-operative pain and inflammation.

**Follow-up schedule:**

No retinopathy – 6-12 months (depending on glycemic control)

Mild NPDR – 3-6 months
Moderate NPDR – 2-3 months
CSME/ PDR – depending on response to treatment

**Counseling:**

Counseling plays a key role in the management of diabetic retinopathy. Three important points that need to be emphasized to the patient are:

- The eye condition is a diabetic eye disease – hence its treatment depends on control of blood sugar and associated conditions like hypertension, hyperlipidemia and nephropathy.
- The disease will stay as long as the diabetes. Therefore regular follow-up and treatment are essential.
- Treatment of diabetic retinopathy is often aimed at maintaining existing vision. Thus early check-up results in better visual prognosis.

**Management of diabetic retinopathy**

![Diagram showing steps in management of diabetic retinopathy]

- Diagnosis of diabetes mellitus by physician
- Retinal evaluation by ophtalmologist
- No retinopathy
- Mild to moderate NPDR/No CSME
- Follow-up every 6-12 months
- Follow up 3-6 months
- CSME/ PDR (severe NPDR)
- FFA - Leakage, brain ischemia, early PDR
- OCT - retinal thickening, cystoid changes, vitreomacular traction
- CSME - Focal laser photocoagulation/ Anti-VEGFs (Avastin/ Lucentis)
- Thorough systemic evaluation - HbA1c, BP, lipid profile, kidney function
- PDR - Pan-retinal laser photocoagulation/ Anti-VEGFs
- Vitreous hemorrhage/ Trabeculectomy: vitreo-retinal surgery
- Close follow-up
- Patient counseling
An Unusual Foreign Body in Ileum
Srikanta Kumar Patro¹, Banbihari Mishra²

Introduction :
Small round or oval objects that enter the stomach nearly always pass uneventfully through the gastrointestinal tract without requiring intervention¹. But passage of a non-malleable long pointed metallic foreign body to distal ileum is unusual. We describe here an adult asymptomatic male with no features of intestinal obstruction for more than a year after ingestion of a long non-malleable pointed metallic foreign body which surprisingly passed down up to distal ileum.

Case presentation :
It is a case of a 32 year male having history of ingestion of a large sewing needle [size more than that of a spinal needle i.e. 12-14 cm] about one year back, but strangely having no complaints till operation. The cause of medical attention was only constant anxiety of the family members. No history of bowel / urinary disturbance, on physical examination only slight tenderness in the RIF region, DRE and proctoscopy finding were normal. Straight x-ray abdomen showed a long metallic foreign body like that of a large sewing needle in the RIF. After relevant investigation the case taken up for surgery under general anaesthesia and abdomen opened by right lower paramedian incision. On exploration there were two points of fixation, one - at 20cm proximal to ileo-caecal junction fixed to hernial site with omentum and pus pocket, second - adherent to infracolic tissue with omentum and pus pocket. Procedure - adhesiolysis and removal of the foreign body through tip end, and resection of the segment involved and end-to-end anastomosis. Cut section of the involved gut showed FB lodged in mesenteric border having mucosal atrophy and fibrosis and both ends partially penetrating the lumen. The postoperative recovery was smooth and patient discharged on 10th postoperative day.

Discussion :
Long, sharp objects may perforate the duodenum and have been known to migrate widely in the abdomen. Early removal of such objects has been advised. In addition, objects longer than 5 cm frequently fail to negotiate the C-curve and become impacted² and hence should be removed using an endoscope if possible.

For blunt objects, some authors have also recommended intervention if the foreign body remains in the same location for more than a week.

Small round, oval, or cuboidal foreign objects nearly always pass through the gastrointestinal tract promptly, and stasis of such objects in the stomach or duodenum is extremely uncommon². The retention of such foreign objects within the duodenum suggests partial obstruction, usually of congenital origin.

In adults, there are rare case reports of impaction by foreign bodies leading to detection of bowel stricture due to acquired diseases such as Crohn’s disease.

Generally, laparotomy is performed for diagnosis and management in cases of impacted foreign bodies in the gut. However, with increasing expertise, laparoscopy can be equally effective with all of the other advantages of a minimal access approach. Hence, laparoscopy is now increasingly being employed for removal of ingested foreign bodies impacted in the gastrointestinal tract.

Present case is the first case of such type being reported as non of the previous cases have reported regarding of such a long [12-14 cm] non-malleable pointed metallic foreign body passing down to distal ileum although instances of such ingestion is there but in almost all cases it either perforated the duodenum or stomach.

References :


State executives/Branch secretary/presidents are requested to send photographs with description of activities or short announcements to be published in next issue of OMJ to reach Editor/State HQ Office Before end of August, 2011.
Diabetic Ketoacidosis in Pregnancy

Sudhanshu Sekhara Nanda¹, Subhalaxmi Dash¹, Sujata Misra²

Introduction:
Diabetic ketoacidosis (DKA) is an acute medical emergency commonly associated with type-1 diabetes in pregnancy. Fetal mortality is more than 50% and maternal mortality is 1-2% in such cases. In this article we report a typical case of diabetic ketoacidosis in a 30-year primigravida with type 1 DM in her third trimester.

Case Report:
Thirty year old primigravida at 34 weeks of gestation with type 1 Diabetes Mellitus for 2 years presented with pain abdomen, nausea and vomiting for 3 days and decreased fetal movement for 1 day. She had three antenatal visits in this pregnancy and 1st and 2nd trimester were uneventful. She was on insulin since 2 years. Further history revealed she had missed last three doses of insulin. She had taken isoxsuprine for two day for preterm contraction. Her previous menstrual cycles were normal.

Examination:
On examination she was conscious, tachypnoeic, dehydrated and had mild pallor.

Pulse rate -110/min, BP-90/60mmHg, RR-40/min, temp-99°F. Respiratory system examination revealed acidoic breathing with fruity odour. Other systems revealed no abnormalities. There were no foci of infection. Abdominal examination revealed 34 weeks irritable uterus with a single fetus in cephalic presentation and absent fetal heart sound. On pelvic examination cervix was uneffaced and closed with adequate pelvis.

Investigations:
Hemoglobin-9g%, TWBC-11000/cmm, Total Platelet Count-1.4 lacs/cmm, Venous plasma glucose was 320mg/dL, sodium 135 meq/L, chloride 109meq/L, potassium 5.4 meq/L, urea 50 mg/dL, creatinine 1.4 mg/dL. Arterial blood pH 7.26, bicarbonate 10 meq/L, anion gap 16meq/L. Urinalysis showed 2+ ketones, 3+ glucose, 2+ protein. Glycated haemoglobin (HbA1c) was 8%. The chest radiograph was normal. Urine, cervical swab and blood cultures were negative.

Management:
She was admitted to Labour Room and resuscitated with supplemental oxygen, intravenous fluids, and insulin infusion as per the guidelines for diabetic ketoacidosis. Ultrasound confirmed intrauterine death of the fetus. After maternal stabilisation and reversal of acidosis, delivery was induced with dinoprostone gel. 1st and 2nd stages were uneventful. Moderate amount of atonic PPH occurred during the 3rd stage which was controlled with oxytocics. Examination of the fetus confirmed stillbirth with no congenital anomalies. Five days later her fasting and PPBS were 128mg/dl and 168mg/dl and discharged with insulin advice as per endocrinology consultation.

Discussion:
Diabetic ketoacidosis (DKA) in pregnancy, although rare, is a possible complication in women with GDM and common in pregnant women with pre-existing type-1 DM ¹. Various factors can precipitate and contribute to the occurrence of ketoacidosis in pregnancy. These factors are emesis, infection, non-compliance, insulin pump failure, beta sympathomimetic drugs, corticosteroids, poor management ². In this instance a combined occurrence of vomiting, insulin omission, and beta adrenergic drugs may have predisposed to DKA.

DKA episodes usually occurs in late 2nd and third trimester. Factors responsible are
- Increased insulin resistance due to increased production of human placental lactogen, cortisol and prolactin ³.
- Relative state of accelerated starvation in third trimester as fetus and placenta use large amount of glucose in third trimester ¹.
Nausea and vomiting due to increased esophageal refluxes.

Loss of immune suppression effect of pregnancy in third trimester.

Fetal condition is adversely affected by

- Decrease in uteroplacental blood flow from maternal acidosis.
- Maternal acidosis leading to fetal acidosis and electrolyte imbalance.
- Fetal hyperinsulinaemia resulting from maternal hyperglycemia increases fetal oxygen requirement by stimulating oxidative metabolic pathway.

**Salient points for management of diabetic ketoacidosis in pregnancy**

1. **Fluid replacement**
   - 1–2 litres of isotonic saline in the first hour.
   - 300–500 ml/hour of 0.9% or 0.45% saline thereafter.
   - Add 5% dextrose when serum glucose approaches 12 mmol/l.

2. **Insulin therapy**
   - Loading dose 0.4 U/kg regular insulin.
   - Continuous infusion at 6–10 U/hour
   - Double infusion rate if no response in 1 hour.
   - Decrease infusion to 1–2 U/hour as serum glucose drops to 12 mmol/l.
   - Continue infusion 12–24 hours after resolution of ketosis.

3. **Electrolyte replacement**, Search and treat precipitating factor like infection, Admit to high dependency unit, Supplemental oxygen, Place in left lateral position to avoid aortocaval compression, Monitor fetal heart rate, Monitor urine output.

**Conclusion:**

While the outcomes of diabetic ketoacidosis in pregnancy have improved over the years, significant maternal and fetal mortality still remains. Prevention, early recognition and hospitalisation, and aggressive management remain the cornerstones to minimise the outcomes of this dreaded complication.

**References:**

Abstract:
Leukocytoclastic vasculitis (Cutaneous small vessel vasculitis) is characterized by immune complex deposition in postcapillary venules resulting in an inflammatory infiltrate, red cell extravasation, fibrinoid necrosis of the vessel wall, and fragmentation of nuclei (leukocytoclasis). The lesions typically develop 7 to 10 days after exposure to the offending antigen. Palpable purpura is the classic clinical finding associated with cutaneous small vessel vasculitis.

Introduction:
Cutaneous small vessel vasculitis (Leukocytoclastic vasculitis) can occur due to infections, (group A Streptococcus, viral hepatitis), drugs, chemicals, food allergens or it may be idiopathic. It generally presents as palpable purpuric lesions appearing in crops on legs or other dependent areas; may become vesicular or ulcerative; usually resolves over 3-4 weeks. It occurs in a wide spectrum of diseases, including connective tissue diseases, cryoglobulinemia, malignancy, Henoch-Schönlein purpura (HSP); more common in children.

In this case report we present 2 cases; one of which was Henoch-Schönlein purpura (HSP) and another one was due to food allergy.

Case Report:
CASE - 1
A 15 yr old girl from Kendrapada admitted to PG DEPT. OF MEDICINE, SCBMCH, Cuttack with chief complaints of red coloured spots over both lower limbs and buttocks & pain and swelling of hands and feet for 10 days, pain abdomen for 8 days, blood in stool with clots 4 times and vomiting for 1 day. There was no history of blood in urine or decreased urination. She did not have any history of similar episodes before. During her stay in the hospital she developed another crops of fresh lesions over both legs and elbows and forearms and this was also 1 day after sea fish intake.

On clinical examination she was found to be conscious, oriented, afebrile, pulse- 80/ min, BP- 118/78 mm of Hg, no pallor, no icterus, urine colour was normal and urine output was 1.5 lit/day. There were presence of purpuric spots which were palpable & these were present over lower portion of legs, dorsum of both the ankles and buttoks. These were varying in size ranging from 3-5 mm in diameter. These did not blanch on pressure.

Laboratory investigations showed Hb- 12gm%, TLC- 12600/ cumm, DC-N-82%, L-15%, E-3%, TPC-3.76 Lakhs/ cumm, PT-12.4 sec (cont-11 sec), INR-1.13, APTT-29.7 sec (cont- 27.2 sec), BT- 2 min 15 sec, CT- 9 min 10 sec, ESR-12 mm in 1st hr, RBS-81mg/dl, S.Urea-54mg/dl, S.Creat-0.8mg/dl, S.Na+-133mEq/L, S.K+-4.6mEq/L, S.Total protein- 6.2gm/dl, S.Albumin- 3gm/dl, S.Albumin- 3gm/dl, S.Albumin- +++, RBC-20-30/ HPF, S.Albumin- ++, RBC-20-30/ HPF, Stool for occult blood- +ve, ANA- 0.24(Normal<2.5), HIV- (+ve), HBsAg-(-ve), HCV-(-ve), USG of abdomen and pelvis- Normal, Punch biopsy of skin from a lesion of right leg- small vessel leukocytoclastic vasculitis.

She was discharged after 5 days of hospitalization with Tab. Prednisolone 30mg/day (as 1mg/kg body wt.) in a tapering manner over 6 weeks. After 3 weeks of follow up it was seen that all the lesions were subsided with hypopigmented macules.

CASE - 2
A 25yr old hindu female from Kendrapada was admitted to PG DEPT. OF MEDICINE, SCBMCH, Cuttack with chief complaints of red coloured spots over both upper and lower limbs and buttocks for 10 days, vomiting 3-4 times/day for 8 days, pain abdomen and blood in vomitus 5 times for 1 day. There was history of sea fish intake 10 days back. There was no history of blood in stool or urine, decreased urination, joint pain or swelling neither she had any history of similar episodes before this. During her stay in the hospital she developed another crops of fresh lesions over both legs and elbows and forearms and this was also 1 day after sea fish intake.

On clinical examination she was found to be conscious, oriented, afebrile, pulse- 84/min, BP-124/70 mm of Hg, no pallor, no icterus, urine colour was normal and urine output was 1.2 lit/day. There was presence of...
palpable purpura over both of the lower limbs extending from knee downwards up to dorsum of foot. In the upper limbs these were present over both the forearms, more on flexor surface than on extensor surface and few lesions were present over buttocks. These were of varying size ranging from 3-8 mm in diameter. Some of these spots were discrete and in some places these were confluent. These did not blanch on pressure.

**Laboratory investigation** showed Hb- 12.2gm%, TLC- 7900/cumm, DC- N-58%, L-35%, M-6%, TP- 3.26 Lakhs/ cumm, PT- 13.7sec( cont- 11 sec). INR- 1.26, APTT- 25.5 sec( cont- 27.2 sec), BT- 2 min 20 sec, CT- 6 min 30 sec, ESR- 30 mm in 1 hr, RBS- 96mg/dl, S.Urea- 44mg/dl, S.Creat- 1mg/dl, S.Na- 130mEq/L, S.K+4.3mEq/L, Urine Albumin- +, RBC-nil, Pus cells- 2-4/HPF, HIV(-ve; both screening and ELISA), HBsAg- (-ve), HCV(-ve), USG of abdomen and pelvis-Normal, Punch biopsy of skin from a lesion on right forearm- small vessel leukocytoclastic vasculitis.

She was discharged after 6 days of hospitalization with Tab. Prednisolone 30 mg/day( as 1mg/kg body wt.) in a tapering manner over 6 weeks. After 2 weeks of follow up she was found to have the lesions subsided.

**Discussion :**

Henoch-Schönlein purpura is the most common vasculitis occurring in children. It is an acute vasculitic syndrome with features of colicky abdominal pain, nephritis, arthritis, and lower extremity eruption of diffuse urticarial plaques and palpable purpura. It predominantly affects patients 2 to 20 years old; 90 percent of patients are younger than 10 years. In pediatric cases, boys are more commonly affected than girls (2:1); however, adult males and females are affected equally.

Renal involvement is more common in adults than in children, but the long-term prognosis is similar; approximately 90 percent of children and adults recover renal function. Testicular pain and scrotal swelling can occur. The white cell count, platelet count, and C-reactive protein levels usually are elevated in pediatric patients.

Henoch-Schönlein purpura usually is self-limited, and treatment is supportive. Uses of immunosuppressive drugs, such as glucocorticoids, are reserved for patients with renal involvement. Persistent purpura, severe abdominal symptoms are predictive of renal involvement and should prompt initiation of glucocorticoid therapy at the onset of disease in appropriate patients. The self-limited course of the disorder may result from enhanced apoptosis of offending immune cells that reduces the severity of the acute inflammatory response.

**Conclusion :**

Palpable purpura is the classic clinical finding associated with cutaneous small vessel vasculitis. The lesions are the result of extravasation of erythrocytes into the inflamed dermis; therefore, the lesions do not blanch with pressure. The lesions range in size from pinpoint to several centimeters in diameter and are most prominent on the lower legs. They are abundant on the ankles, knees & elbows. The diagnosis should be confirmed by skin biopsy. Evaluation for the etiologic agent can be challenging and requires a detailed history to identify causative agents. Helpful laboratory studies include complete blood cell count, blood cultures, serum protein electrophoresis, cryoglobulins, hepatitis screen, rheumatoid factor, antinuclear antibody, antineutrophil cytoplasmic antibodies (ANCAs), and complement. Systemic involvement should be determined by the history and physical as well as a urinalysis, chest radiography, and electrocardiogram.

**Suggested Reading :**

1. **Harrison’s Principles of Internal Medicine 17th /e**
2. **Williams Hematology 7th /e**
3. **Wintrob’s Clinical Hematology 12th /e**
Introduction:

Myiasis is caused by parasitic dipterous fly larvae feeding on the host’s necrotic or living tissue. Colloquialisms for myiasis include flystrike and fly-blown. In Greek, “myia” means fly.

It is the infestation of live human and vertebrate animals with dipterous larvae, which at least for a period, feed on the host’s dead or living tissue, liquid body substances, or ingested food. Although infestation by fly larvae is much more prevalent in animals, it is a relatively frequent occurrence in humans in rural, tropical and subtropical regions.

Myiasis can come in all sorts of variations, depending on the fly species and where the larvae are located. Some flies may lay eggs in open wounds, other larvae may invade unbroken skin or enter the body through the nose or ears, and still others may be swallowed if the eggs are deposited on the lips or on food.

The Reverend Frederick William Hope coined the term myiasis in 1840 to refer to diseases resulting from dipterous larvae as opposed to those caused by other insect larvae (the term for this was scholechiasis).

Case report:

An 8yr old girl came to us with a small subcutaneous swelling on the scalp with a small ulcer on its centre of one month duration. She complained of little difficulty except mild pain and uncomfortable sensation. On close examination moving creatures (maggots?) were seen. After incision of the swelling and trimming of the margins, a large crateriform lesion was found with many live crawling larvae/maggots.

CBC count showed leukocytosis and eosinophilia.

The clinical diagnosis of myiasis was done.

The larvae were surgically removed after through cleaning of the wound. Daily dressing was done. Antibiotics and topical ivermectin was administered. The wound achieved complete healing within a period of 3 weeks.

Discussion:

The invasion of mammalian tissues by dipterous (fly) larvae is known as myiasis. The eggs/living larvae or both are deposited on the skin/mucus membranes. The eggs hatch and produce larvae that burrow into the skin and cause mild/severe inflammation. Others migrate to folds of skin and burrow into the subcutaneous tissue producing inflammatory reaction giving the appearance of a furuncle at the centre of which maggots may be seen.

Cutaneous myiasis comes in different forms:

1. Furuncular myiasis: in this case flies puncture the skin and extrude the ova beneath the surface. Mostly caused by the human botfly Dermatobia hominis, tumbu fly/ver du cayor-Cordylobia anthropophaga; in tropical Africa. Wohlfahrita vigil in North America mostly causes furuncular myiasis in infants.

2. Traumatic/wound myiasis: here the flies lay their eggs on open wounds and ulcers. Later larvae hatch out on the skin and maggots crawl about in the ulcerated area.

3. Creeping eruptions: in this case the larvae wander intradermally. An itching pink papule develops which gradually extends as a tortuous line. Found in the Indian sub-continent in people who walk barefoot mostly. It is usually caused by the larvae of Gastrophilus.

The various flies causing the cutaneous symptoms:

- Dermatobia hominis (botfly, Endemic to tropical Mexico, South America, Central America, Trinidad)
• Cordylobia anthropophaga (tumbu fly) - Endemic to sub-Saharan Africa
• Cochliomyia americana/Chrysomyia bezziana - Wound myiasis
• Oestrus ovis (sheep botfly) causes ophthalmomyiasis
• Hypoderma bovis (infested cattle) and Gasterophilus intestinalis (infested horses) both cause creeping (migratory) myiasis.
• Cochliomyia hominivorax (America) and Chrysomyia bezziana (Africa, Australia, Asia) both cause wound myiasis.
  Wohfahrtia vigil, Hypoderma lineatum, Cuterebra cuniculi, Callitroga hominivorax are also responsible in many cases.

Apart from the cutaneous variety how myiasis affects the human body depends on where the larvae are located. Larvae may infect necrotic (dead) or living tissue in various sites: the skin, eyes, ears, stomach and intestinal tract, or in genitourinary sites. They may invade open wounds and lesions or unbroken skin. Some enter the body through the nose or ears. Larvae or eggs can reach the stomach or intestines if they are swallowed with food and cause gastric or intestinal myiasis.

Several different presentations of myiasis include:
- Nasal Myiasis
- Aural Myiasis
- Ophthalmomyiasis
- Hematophagous myiasis
- Nosocomial Myiasis

**Treatment** consists of:
- Essentially surgical
- Picking up with surgical forceps and removing them manually
- Asphyxiation with pork fat/mineral oil
- Douching the wound with 15% chloroform followed by manual removal
- Oral/topical ivermectin

**References:**
1. Andrews diseases of skin - 9th edn p-556-8
2. Arosemena etal; JAMA, 93, 28; 254
3. Jelinek T etal; cutaneous myiasis IJD – 95, 34; 624

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Members are requested to enroll more colleagues as members of IMA and join AMS and CGP in large nos for formation of local branches and extra academic activities.
Rheumatic mitral stenosis in a patient aged above 80 years

Madhusmita Patnaik1, Sarat Chandra Singh1, Bibhuti Sethi2, Sidhartha Das3,

Abstract:
A 85 yrs male presented as cerebro vascular accident (CVA) with right frontal lobe infarction due to right anterior cerebral artery territory embolism, with atrial fibrillation. He was hypertensive and on 2D-echo, found to have rheumatic heart disease with mitral stenosis, mitral regurgitation, pulmonary arterial hypertension and tricuspid regurgitation.

Keywords: Rheumatic heart disease, Mitral stenosis, Cerebrovascular accident.

Introduction:
Rheumatic heart diseases (RHD) is usually considered as disease of young. It is important to point out that the prevalence of RHD is below 0.5/1000 in school children in the western countries1. There has been a 58% decline of RHD in last 30 years in India1. The clinical presentation in India is slightly different from the established literature. There is no predominance of RHDS in women at younger age but in elderly the incidence is much higher than we commonly presumed1,2. In the clinical series of studies (Brenner 1934 and Coombs 1924) the percentage of patients with mitral valve disease over the age of 50 years varies from 6 to 10%.2 The mean age at death for patient suffering from acute RHD is 24.4 years, as published at Heart Journal 20023.

Case Report:
A 85 years Hindu male from Puri was admitted on 17.01.2011 with a chief complaint of sudden onset of loss of consciousness and weakness of left upper and lower limb for 1 day. The patient was apparently all right 3 years back. To start with he developed breathlessness on exertion which was gradually progressive. He was unable to do normal activities for last 3 months and paroxysmal nocturnal dyspnoea with orthopnoea for last 10 days. He developed hemoptysis along with weakness of left half of body for past three days. Past history revealed features suggestive of transient ischaemic attack twice within 1 year. He was a hypertensive for last ten years on treatment but had no documented history of rheumatic fever, tuberculosis or diabetes mellitus. Personal history revealed that he was a farmer by occupation, married having three children and had no addiction nor habituation.

On examination patient was stuporous with moderate pallor having bilateral pitting pedal edema. The pulse was 80/min, irregularly irregular in nature suggesting arterial fibrillation. Peripheral pulses were well felt with pulse deficit of 20/min. His blood pressure was 140/90 mm Hg. On cardiovascular examination, the apex was at the left 6th intercostal space 2 cm lateral to mid clavicular line having forceful and ill sustained in nature along with grade-1 parasternal lift. On auscultation, 1st heart sound was loud and variable over the apex and Pulmonary component of 2nd heart sound was loud in the pulmonary area. Interestingly no murmurs or extra sounds were heard in the mitral and other areas. CNS examination revealed that the patient was stuporous with grade 2/5 power in left upper and lower limb with classical hemiplegia and bilateral extensor plantar response.

Investigations:
The laboratory investigations revealed: Hb- 8 gm%, ESR -40 mm 1st hour, TLC- 8,200/cmm, N-58%, FBS - 84 mg/dl, Sr.urea-50 mg/dl, Sr.creatinine-1.2 mg/dl; Sr. Na+ -139 mM/dl, Sr. K+ -5.1 mM/dl; Sr.cholesterol- 135 mg/dl, Tg-53 mg/dl, HDL cholesterol - 44 m/dl, LDL cholesterol – 80 mg/dl and VLDL cholesterol-11 mg/dl with no abnormality in urine on routine examination. Chest x-ray was found to have non-homogeneous opacities in upper
lobe, cardiomegaly with RV contour. ECG reading was found to have absent 'p' wave in lead II with fibrillatory waves in V1 and LVH with strain pattern in V2-V6 leads. 2D-Echocardiography revealed Rheumatic Heart Disease having Mitral Stenosis (size- 1.8cm²) and Mitral Regurgitation with RA/RV dilation, pulmonary artery hypertension, tricuspid regurgitation but normal LV function. CT scan of brain showed a right frontal lobe infarction in the right anterior cerebral artery territory.

Discussion:

Acute rheumatic fever usually affects children or young adults and it is a more common cause of rheumatic heart disease in childhood and adolescence. 4

Rheumatic Mitral stenosis is compatible with normal life until old age and is often associated with complete freedom from symptoms. The reason why some do live until old age is not yet clear. 5 Some authors (White and Bland 1941) suggested the following reasons: (1) relatively mild mitral stenosis, (2) rheumatic fever late in life, (3) quite careful living, and (4) ancestral longevity. 5 Other authors suggested causes for longevity in mitral valve disease are coexistent hypertension, the absence of arterial fibrillation (Kossmann and Connor 1942) and involvement of the mitral valve alone (Cabot, 1926) which can explain as to why this male patient who presented as a hypertensive at the age of 80 did not ever have features to suggest mitral stenosis.5

Conclusion:

Mitral stenosis in elderly is very rare and more so in our population. This is an unusual case where the patient in his ninth decade presented with features of hypertensive heart disease and CVA but on investigation found to have significant rheumatic mitral stenosis.

References:

2. Appel SB, Kossmann CE. Rheumatic heart disease in patient over sixty years of age; JAMA 1951; 146(16); 1474-8.
Scrotal Grapes – An uncommon encounter
Srikanta Kumar Patro

Abstract: Scrotal grapes or multiple sebaceous cyst of scrotum is quite rare and needs surgical attention mostly due to cosmetic reasons. As it involves most part of scrotum, reconstruction followed by excision is the practical problem. In the present case normal scrotal skin was available for cover so, only median raphe was reconstructed.

Keywords: scrotal grapes; multiple sebaceous cyst of scrotum

Introduction: Grapes look beautiful on a plant, but are they cosmetically acceptable on a scrotum? We may have come across several cases of sebaceous cysts [epidermoid cysts] at several locations on body, even scrotum is quite common site, but it is very rare to get a bunch of such benign tumors over the scrotum.

Case presentation: It is a case of a 32 year male having history of small beads gradually developing all over the scrotum up to root of penis over a period of three years. They gradually increased in size slowly to attain sizes like grapes. There is history of mud like material coming out from the structures on accidental pressure. On examination those tiny lumps(largest was of 2 cm size) were non-tender with visible punctum over some. They were free from deeper structures and were free from deeper structures. USG of scrotum revealed no fluid collection inside the tunica vaginalis testes. FNAC of some of them done randomly and found out to be epidermoid cysts. The need for surgery for the patient was cosmetic problem. After all routine investigations the patient was posted for surgery under local anaesthesia. After acquiring asepsis and adequate anaesthesia the affected scrotal skin was excised from a vertical diamond shaped incision. After achieving hemostasis, median raphe was reconstructed and skin closed. The post-operative period was uneventful and patient discharged after stitch removal on 7th post-op day.

Discussion: Sebaceous cysts are formed either due to blockage of ducts of sebaceous glands or implantation of skin due to minute injuries. Multiple sebaceous cysts of scrotum is still a rare condition. Often men present late as the cysts are painless unless infected. The need for surgery in an uninfected multiple sebaceous cyst scrotum is cosmetic as well as prevent to get infected [proximity to genitor-urinary tract]. [1]

Median raphe reconstruction give more anatomical look as well as prevents torsion of testes in future.[2]

References:
1. P. Mohite & A. Bhatnagar : A Case Of Multiple Sebaceous Cysts Over Scrotum In A 35 Years Old Male . The Internet Journal of Surgery. 2007 Volume 9 Number 1
2. Surgical treatment of lymphedema of the penis and scrotum, Clinics vol.61 no.4 São Paulo Aug. 2006
Solitary Fibrous Tumor of the Pleura – A rare entity

P. Biswal¹, K.P. Gouda¹, P. Mohanty¹, L. Mohanty¹, P.K. Palai², M.K. Pattnaik³, N. K. Pattnaik⁴

Abstract:
A Case of solitary fibrous tumour of the pleura is presented in a 52 years old male with a recurrence within a span of 6 months only. The patient presented with the chief complaints of pleuritic chest pain & cough. Radiographic features & histopathological findings confirmed it to be Solitary Fibrous Tumor. The Pt. became asymptomatic after surgery, only to return back within 6 months. Radiographic findings showed it to be a recurrent mass at the same site, however the size was small. The patient was again operated & histomorphological pictures was that of SFTP. The Pt. now is asymptomatic & receiving radiotherapy. We present this case because of its rarity & recurrence.

Key words = Solitary Fibrous Tumor, pleura, recurrence.

Introduction:
SFT is a rare primary tumour arising from the mesenchymal cells in the areolar tissue subjacent to the mesothelial lined pleura. Only about 800 cases have been reported in medical literature. It can occur at any age (40yrs - 70yrs). A similar tumor has been described at other extra thoracic site. Fortunately 80% of this tumor are benign in nature, as is in our case. Localized SFTP’s are almost always cured with complete surgical resection though recurrences have occurred as long as 17 years after initial resection. More sessile benign tumors appear deceptively localized but deserve liberal resection margins as of up to an 8% recurrence rate. Resection of benign recurrences is usually curative.

Case Report:
A 52 yrs old male presented to the cardio-thoracic department with a 6 yrs. history of cough & 2 months history of associated chest pain. The patient reported recent onset of sharp chest pain and shortness of breath.

His heart rate was 92 per mint. and Blood Pressure 130/84 mmHg. Physical Examination of lung’s showed diminished breaths sound and dullness to percussion on side of chest. There was no cyanosis or clubbing. Other lab parameters were within normal limits. CT (Computed Tomography) with a contrast revealed a well-circumscribed predominantly homogeneously solid, pleura based mass. The mass had irregular & indistinct margin, infiltrating into the surrounding adjacent areas including ribs. There was no internal calcification, pleural effusion, fibrosis, mediastinal adenopathy, vascular involvement or mass effect. There was slight adherence to the lung parenchyma. Basing on the clinical presentation & radiographic findings, a D/D of malignant pleural lesion was considered. The patient was operated and the mass was removed in piece meal due to extensive adherence. Removal of the mass led to collapse of the lung of the same side.

Gross specimen was received in piecemeal, together @ 6x4x4cm. Cut-section was soft to firm with areas of haemorrhage and necrosis. Histopathological sections was studied by using normal haematoxylin and Eosin stain. They depicted a “pattern less pattern” with alternating areas of short fasicles of spindle cells interspersed between variable areas of extensive collagens. The collagens was mostly hyalinised. The individual tumor cells are spindle cells with scant cytoplasm, indistinct border, dispersed chromatin with a vesicular nucleus. Mitosis was absent. So a diagnosis of solitary Fibrous Tumor of pleura was given.

However, the patient again returned after 6 months with history of recurrences. Again he was operated. Histomorphological picture revealed the same findings.

Discussion:
Solitary Fibrous Tumor of Pleura is a rare neoplasm with fewer than 800 cases reported in literature. There is a strong immunohistochemical evidence for a mesenchymal cell origin. Similar solitary fibrous tumor have been reported to arise from extrathoracic locations including meninges, nose, oral cavity, pharynx, epiglottis, salivary gland thyad, breast & kidney, bladder. SFT occurs in a wide age range (40-70yrs) with a fairly equal
frequency in both the sexes. There is no apparent genetic predisposition or no relationship to exposure to asbestos, tobacco or any other environmental agent. Majority of patients present with commonly cough, chest pain, dyspnoea, PUO, wt loss, haemoptysis & pneumonitis. The larger the tumor, the more likely that symptoms will be present. Over 75% of malignant tumors cause symptoms as compared to only 54% of Solitary Fibrous Tumor of Pleura who have symptomatic.

Usual CT scan, clinical presentation & HP studies aids in the diagnosis of SFTPs. Xray, bronchoscopy sputum or pleural fluid cytology has no role. The tumor most commonly arises as a pedunculated, discrete mass on a stalk attached to visceral pleura of the lung. They are usually benign. Sessile mass or inverted tumors requires a wide surgical resection. Histological characteristics is useful in estimating the risk of recurrence is SFTPs.

Malignant SFTPs are predominantly hypercellular showing cellular atypical, tumor necrosis, mitosis infiltrative margin. Unfortunately malignant potential may not always correlate with histological findings, and some cases of SFTP may progress to the malignant type of disease.

However, in our case, though it clinically behaved as malignant, but histomorphologically it was confirmed to be Benign SFT of pleura.

Reference:

Rare Foreign Body in Trachea

Chinmay Sundarray¹, Rajlaxmi Panigrahi²

Abstract: Foreign body in airway has been a major cause of morbidity and mortality. Although it is frequently encountered in children, adults are not spared either. In our case, a tracheostomy tube, that too PVC, not metallic was found lodged in carina towards left bronchus.

Case Report: A 80 year old male patient, previously diagnosed with laryngeal growth was admitted with PVC tracheostomy tube in situ in casualty with mild respiratory distress. He gives a history of another broken PVC tube inside his trachea. He had undergone tracheostomy 8 months back and had also undergone radiotherapy with this PVC tracheostomy tube. One day his daughter was changing the PVC tube when she noticed that the tube had separated from its flanges and accidently went into the trachea. In panic, she inserted another spare PVC tracheostomy tube into the trachea to relieve the cough. Patient had minimal respiratory distress when he presented to us. However to confirm diagnosis, he underwent x-ray chest – AP/ Lateral view. Since the broken tube was behind the cardiac shadow, it wasn’t clear in AP view but was clearly marked in lateral view. (Fig. 3) We planned for removal under spontaneous TIVA. Under bronchoscopic guidance the tube was dislodged and pulled up, however the stoma had to be widened by giving releasing incision (Fig.1). The PVC tube was splitted into two halves near the stoma by sharp (15 No.) knife as the tube was tough and unyielding and was safely removed. The stoma was widened and a larger tube was inserted and next day the patient discharged with advice of regular follow up.

Discussion: Tracheobronchial foreign body is uncommon in adults and tracheostomy tube as foreign body in tracheobronchial tree is one of the rare cases encountered. Several cases²,³ of broken metallic tracheostomy tube have been reported and several theories¹ responsible for its breakage like erosion, manufacture defect etc. has been proposed.

However, in this case the tube is PVC (not metallic) so either it is defective manufacturing or extra force used to insert the tube through stoma. Since the stoma was narrow for the tube probably following radiotherapy. Eventhough, the tube was PVC, due to the presence of radioopaque line given on all pvc tubes, it could be easily detected on radiography. However no other changes was noted in chest X-ray.

Tracheobronchial foreign body may result in a spectrum of presentations from minimal symptoms, often unobserved, to respiratory compromise or even death. However, history leads to diagnosis in most of the cases. Choking and coughing is present in 95% of cases. In our case such a situation did not arise as the tube was hollow.

The best way to prevent such cases is probably to train the patient’s attendant properly. Regular follow up and advise to use new tubes if slight damage is noted.

References:

2) Bossoe H.h and Boe J(1960). ‘ Broken tracheostomy tube as foreign body’ Lancet, 1:1006
Carcinomatous Meningitis Secondary to Follicular Carcinoma of Thyroid

Madhusmita Patnaik, Sarat Ch. Singh, Bibhuti Sethi, Sidhartha Das

Abstract: Carcinomatous meningitis (CM) is a rare and often devastating complication in patients with follicular carcinoma of thyroid and the treatment is far from consensus. We report a patient with CM with lymphnode metastasis which is a rare presentation in follicular carcinoma of thyroid. The patient presented with a small thyroid nodule and adjoining cervical lymphadenopathy along with multiple focal neurological symptoms and signs. Diagnosis was confirmed by analysis of the cerebrospinal fluid, fine needle aspiration cytology (FNAC) of lymphnode and USG of thyroid gland.

Introduction: Carcinomatous meningitis (CM), synonymous with leptomeningeal metastasis, neoplastic meningitis, meningeal carcinomatosis, is the seeding of cancer cells through cerebrospinal fluid (CSF) into the central nervous system (CNS). The hallmark of carcinomatous meningitis is multiple cranial nerves and spinal root lesions. CM is diagnosed in 1–5% of patients with solid tumors. The most common tumors that metastasize to the meninges are breast carcinoma, lung carcinoma, gastrointestinal tract carcinoma and melanoma. (1,2) CM as a complication of follicular cancer of thyroid is however extremely rare. Unlike thyroid nodules, differentiated thyroid carcinomas are relatively rare. Clinically detectable thyroid carcinomas constitute less than 1 percent of all human cancers. The annual incidence rate in various parts of the world ranges from 0.5 to 10 cases per 100,000 populations. Follicular cancers are rare in children and adolescents, whereas its incidence increases with age in adults. Frequency of thyroid carcinomas in women is two to four times higher than in men. Metastasis to bones and lungs are common in follicular carcinoma due to hematologic spread. Whereas less common sites of metastasis in follicular carcinoma are lymph node, brain, liver and skin. (3) Here we report a case of CM metastatized from thyroid with an accompanying brief review of the existing literature.

History: A 26yrs Hindu female was admitted on 29th Nov 2010 with complains of altered sensorium for one day. She was apparently alright 6 months back after which she gradually developed generalized weakness, loss of weight, loss of appetite with low grade fever. Subsequently she had developed frontal headache, projectile vomiting, diplopia and neck pain with stiffness for last 1month. One day prior to hospitalization, she had altered sensorium. She had no history of convulsion, weakness of limbs and respiratory problem. She was not a diabetic or hypertensive and having no past history of tuberculosis. A housewife with two children, without any history of menstrual irregularities and her obstetrical history was uneventful.

On examination, patient had average built with 38kg wt., and 140cm height having mild pallor, lymphadenopathy (3 nodes on right cervical, 2 on left cervical, 1 on left axilla and 1 on submandibular region). All lymph nodes were 2cm-4cm in diameter, nontender, firm and mobile. An oval thyroid nodule of 2×2 cm size was visible on right side of neck which was firm in consistency, nontender and moved on deglution but on protrusion of the tongue. She was afebrile with stable vitals. On CNS examination, patient was confused but responded to verbal commands. Ptosis and dilated pupil not reacting to the light on right eye suggested 3rd cranial nerve palsy as presented in Figure 1. She was also having bilateral lateral rectus palsy due to paralysis of both 6th cranial nerves. Other cranial nerves, motor, sensory and cerebellar system examination revealed no abnormality. Spine examination revealed neck rigidity with positive Kernig’s sign.

Investigation: Routine blood examination showed Hb-10gm%, TLC-11.200/cmm, N-75%, L-20%, ESR-5mm/1st hr, FBS-95mg/dl, Sr. Urea-25mg/dl, Sr. Creatinine-0.8mg/dl, Sr. Na+-129meq/l and Sr. K+-3.5meq/l. Routine and microscopic examination of urine,
serological tests for HIV, HBsAg and HCV were negative. Chest X-ray, CT scan of brain and USG of abdomen revealed no abnormality. CSF study showed total cell count to be 130/dl(L-95%,N-5%), no malignant cells,sugar-nil,protein-247mg/dl and adenosine deaminase level 3.5u/l. FNAC of right upper cervical lymph node revealed metastatic follicular carcinoma of thyroid. Ultrasonography of thyroid gland detected multiple hypoechoic foci in right lobe due to malignancy (Figure 2). Patient was referred to cancer institute for further evaluation and management. However the patient’s attendant deferred treatment and left the hospital and she was died on 25th Dec, 2010.

Discussion: As discussed, CM and lymphnode metastasis as the complications of follicular carcinoma of thyroid are extremely rare. On searching the literature through net,there are two reported cases of follicular carcinoma of thyroid leading to CM till date. The clinical features that are observed in this patient with CM were headache, disorientation, 3rd and 6th cranial nerves palsies. These observations are consistent with other studies. CSF study revealed lymphocytic pleocytosis, high protein and absence of glucose which are akin to other study. Lymphnode metastasis from follicular carcinoma of thyroid, as seen in this patient, is one of the rare clinical findings. Observations made in other studies had shown that most differentiated thyroid carcinomas present as asymptomatic thyroid nodules, but the first sign of the disease is occasionally lymph-node metastases or in rare cases lung or bone metastases. On physical examination, the carcinoma usually presents as a single mass, firmin consistency, moves during swallowing and not distinguishable from a benign nodule. Thyroid ultrasonography is useful for assessing the size of the nodule, detecting other nodules, and guiding fine-needle biopsy in the case of a nodule that is small or difficult to palpate. CM is a rare complication of solid tumours which is associated with a median survival of approximately 2-3 months depending on the origin of the tumour. CM and lymphnode metastasis as complications of follicular carcinoma of thyroid are extremely rare. Because of the rare incidence of the tumour most research institutes have managed patients according to standard protocols that largely include radiotherapy to the brain and areas of symptoms or disease bulk, together with chemotherapy given either intrathecaally or intravenously. However, there is no evidence to support these regimens and prospective randomised trials in a single disease type are required.

Conclusion: This case report pertains to a multiparous young lady presenting with altered sensorium with preceding history of constitutional symptoms and features suggestive of raised intracranial presuure. At presentation found to have lower motor neuron palsy of 3rd cranial nerve on the right and bilateral 6th nerve palsies with signs of meningitis. On evaluation found to have follicular carcinoma of thyroid with metastasis to lymph node and carcinomatous meningitis. She had a galloping clinical course and succumbed within one month of detection.

References:
Down’s Syndrome

A K Sahu¹, P C Sahu¹, J K Panda², S Dutta¹, B Bellam¹, PK Padhy³

A 22yr old male presented with vision loss for 3yrs, breathlessness on exertion for 6months. He is mentally retarded. Past history of delayed milestone was there. There was no history birth asphyxia. Mother’s age at conception was 26yrs.

General examination revealed height 132cm, arm span 132cm, upper segment- 66.5cm, lower segment- 65.5cm, body weight-60kg, BMI-34.4kg/m². presence of short neck, mongoloid slant of eyes, epicanthic folds, bilateral mature cataract, depressed nasal bridge, macroglossia, low set small ears; presence of single simian crease, 4 ulnar loops on each palm, sandle gap in common foot.

CVS examination revealed apex at 5th ICS 1cm medial to midclavicular line, normal character. no parasternal heave. Loud S1, P2 normal. pansystolic murmur of grade 3 heard over a wide area best heard in left sternal border at 3rd & 4th ICS.

Thyroid function tests were normal. 2D ECHO revealed large inlet VSD.

DOWN’S SYNDROME is the commonest chromosomal disorder occurring more often in offsprings of mothers conceiving at greater age e.g., 1 in 1550 if maternal age is 15-29yrs, 1 in 800 at 30-34 yrs, 1 in 270 at 35-39yrs, 1 in 100 at 40-44yrs, 1 in 50 after 45 yrs.

Cytogenetics :- 94% cases are due to meiotic nondisjunction leading to Trisomy 21, 5% cases due to Robertsonian translocation, 1% due to mosaicism.

Most common CVS anomaly associated with DOWN’S syndrome is endocardial cushion defect followed by VSD.

References :
1. Harrison’s principle of internal medicine; 17th ed; p 412
2. Textbook of paediatrics; OP Ghai; 6th ed; p-587
3. Nelson’s textbook of paediatrics; 17th ed

¹PG Students, ²Asst Professor, ³Professor
SCB Medical College, Cuttack
E-mail : drashwiniscbmed@gmail.com
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An Unusual Presentation of Hemophilia

P.C. Das¹, A.K. Sahu¹, M Naik², J.K. Panda³, P.K. Padhy⁴

Introduction:
Hemophilia is a X-linked recessive disorder of coagulation. It affects males, whereas females are asymptomatic carriers. It affects 1 in 10000 males worldwide. Hemophilia is mainly of 2 types; type A & B; occurring due to the deficiency of clotting factor VIII & IX respectively.

Haemophilia A is due to mutation in F8 gene and B is due to mutation in F9 gene. More than 500 mutations have been identified, but haemophilia A most commonly results from an inversion of intron22 sequence, which is seen in 40% of cases.

Clinically Hemophilia A & B are indistinguishable. It usually presents early in life even at circumcision or as hemarthroses in knee, elbow, ankle joints when the child starts walking. Hematomas in other areas like upper airway or retroperitoneum may be seen.

Case History:
A 32 year old male patient was admitted to PG DEPT OF MEDICINE, at SCB MEDICAL COLLEGE, CUTTACK with history of 4 episodes of hematemesis & 3 episodes of melaena within last 2 days. He had no history of any bleeding episodes in the past. He was resuscitated with blood transfusion, IV Tranexamic acid, Pantoprazole. He was kept nil orally. On the 3rd day he again had 4 episodes of hematemesis and it continued upto 5th day.

Routine investigations done. Hemoglobin on Day 1 = 11 gm%, day 2 = 7 gm%, day 3 = 6 gm%. TLC=10600/mm³, DC – N-62 L-28 E-5 M-5, ESR-30mm, Total Platelet Count-236000/mm³, FBS-100mg/dl, BUN-81gm/dl, Serum creatinine-1.1mg/dl.

On 6th day he did not have hematemesis, so he was sent for UGI endoscopy. It revealed an ulcer in the antrum with active bleeding. On 7th day he again had hematemesis. Then he was sent for coagulation profile – Bleeding time - 1 min 45sec, Clotting time – 9min 20 sec, Prothrombin Time-control 11sec, test-12.4sec, INR-1.13, APTT-control-27.2sec, test-43.6 sec. FACTOR VIII level – 17% (normal range-50-150%), FACTOR IX level – 110% (normal range-50-150%). After 1 month, FACTOR VIII level – 20%, FACTOR IX level – 106%. Finally he was diagnosed as a case of Hemophilia A.

Discussion:
Severity of Hemophilia may be graded according to level of factor VIII, i.e. mild – 6 - 50 %, moderate -1 – 5%, severe < 1 %. Moderate to severe grade of haemophilia may present early with classical features. Bleeding and coagulation disorders can not be neglected as the cause of GI bleed.
Oral Antidiabetic Drugs in Gestational Diabetes

Tapan Pattanaik¹, Babita Panda¹, Sarat Kumar Mahapatra²

Introduction:

Diabetes mellitus is a heterogeneous disorder of glucose intolerance. Due to direct relationship between maternal glycaemic control and neonatal outcomes, protocols during pregnancy emphasize strict glycaemic control by combination of diet and medication. Insulin therapy has been considered the gold standard for management because of its efficacy in achieving tight glucose control and the fact that it does not cross the placenta.

Role of Oral hypoglycemic agents:

Since Gestational Diabetes Mellitus (GDM) is characterized by insulin resistance and relatively decreased insulin secretion, treatment with oral hypoglycemic agents that target these defects is of potential interest. Possibility of fetal teratogenesis and prolonged neonatal hypoglycemia, due to trans-placental passage has been a concern. The sulfonylurea’s were the first hypoglycaemic drugs that reached approval for use in non-pregnant woman. These drugs appear to exert their beneficial effects by acting directly on pancreatic beta cells to enhance secretion.

The use of first generation sulfonylurea compounds such as chlorpropamide and Tolbutamide, in pregnant woman was discouraged in the U.S. based on limited scientific evidence. These drugs do cross the placenta and their use was associated with severe, prolonged hypoglycemia in neonates. In contrast to the first generation drugs, very little Glyburide appears to cross the placenta to the baby. Elliot et al (American journal of Obstetrics & Gynecology 1994) Furthermore glyburide was not detected in the cord serum of any infant.(Am j Ob& Gyn 2006)

Safety Of OAD In First Trimester:

Numerous trials have been conducted to support the use of OHA in first trimester.


In a retrospective review, in which 78 patients with GDM used Oral hypoglycemic agents in the first trimester 93 did not use it.

There was no significant difference in the fetal outcome & result in blood sugar control were comparable.

Gulzin etal Can j. Clin. Pharmacology (223)

In a meta-analysis of 10 studies (only those fulfilled the criteria) conducted in University of Toronto, there was no significant difference in the rate of congenital anomalies between exposed and non exposed. Odds ratio was 1.05 (95%CI 0.65 TO 1.70)& and the risk difference was 0.00 (95%CI 0. 67 to 2/ .00)and the risk difference was -0. 03(95%CI-0.17 to 0.12)the difference was not statistically significant. So their conclusion was first trimester exposure to OHAs did not significantly increase rates of major malformation or neonatal death

Langer etal Am. j. Obst. & Gynecol (2005) & three more studies that compared Glyburide and insulin for the management of gestational diabetes in first trimester, the results showed no difference in the blood glucose level, no difference in congenital anomalies & Glyburide was not detected in the cord blood of any of the fetuses of the Glyburide group. There were no significant differences between the Glyburide and insulin groups in terms of lung complications (8 % and 6 %), hypoglycemia (9% and 6 %)and admission to neonatal intensive care unit (6 %and 7%). Thus concluding that, Glyburide is clinically effective alternative to insulin. Secondary analysis of the trial also concluded Glyburide and insulin are equally efficient for treatment of GDM at level of severity
Dose of Glyburide:

In all the trials usually started at a low dose of 2.5 mg once or twice per day. It generally takes 4 to 5 days or longer before an impact is seen on fasting and two-hour post-prandial blood sugar levels, but if the response has been inadequate within a week, it is usually safe to double the initial dose. If glycaemia control is inadequate during the day, but fasting blood sugars are normal, the morning dose can be increased independently of the evening dose, just as we do with insulin. It is generally recommended that the total 24-hour dose of glyburide not exceed 20 mg and if adequate glycaemia control is not achieved within 3 weeks, consider changing over to insulin. Side-effects are usually minimal, episodic hypoglycemia might be a complain.

Role of Metformin:

The other class of oral hypoglycaemic agents which has received considerable attention in recent years is the biguanides group of which Metformin appears to work primarily by increasing the sensitivity (reducing the resistance) of the liver and peripheral tissues (muscle and fat) to insulin. To a lesser extent, it also appears to decrease absorption of glucose in the gastrointestinal tract. The actions of metformin have the combined effects of reducing glucose production by the liver and enhancing peripheral glucose utilization. Like glyburide, metformin is also classified by the FDA as a category B drug. When dosing metformin, we usually begin at 500 mg twice per day. Usually a beneficial effect on glycemic control will be seen within 3-5 days. Again, if the response has been inadequate within a week, the dose can be increased by 500 mg per day on a weekly basis until 2,000 per day is reached. If adequate glycemic control is not achieved within three weeks, change to or add insulin to the current metformin regimen.

Glueck et al, pilot study (Fertility & sterility 2001)

In patients with polycystic ovarian disease (risk of GDM is high)

Metformin use in the first trimester does not increase the incidence of major congenital anomaly. Continuing metformin throughout pregnancy in women with PCOD is safe and decrease the incidence of first trimester abortion.

Glueck et al (human reproduction 2004)

Metformin Therapy throughout pregnancy reduces incidence of GDM, also shows promise in preventing miscarriage

Jakubarez (Journal Of Clinical endocrinology & Metabolism 2020) Metformin is safe if used throughout pregnancy, with no effects on babies up to 4 year follow up, also helps to reduce early pregnancy loss in PCOD

OAD In Lactation:

Metformin, glyburide, and glipizide appear to be compatible with breast-feeding

Conclusion:

New generation of oral hypoglycemic agent glyburide does not cross the placenta and may be used to replace insulin between 11 to 33 weeks of gestation.

Metformin can be used in P.C.O.D patients during the whole pregnancy, it reduces miscarriages & also the incidence of G.D.M

No significant difference in the rates of major malformations between those exposed and those not exposed oral hypoglycaemic agents.

Further well-conducted, large-scale clinical studies will be needed to confirm the safety in very early (<10 weeks) pregnancy.

References:


2) Kenneth F. Trofatter, jr, MD, PhD(2008); Diabetes in pregnancy-Use of OHA


# BRANCH PRESIDENTS & SECRETARIES OF ODISHA 2011-12

<table>
<thead>
<tr>
<th>BRANCH NAME</th>
<th>PRESIDENT</th>
<th>SECRETARY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANANDAPUR</strong></td>
<td>Dr. Sisir Kumar Das&lt;br&gt;SAI Colony, Anandapur, Keonjhar – 758021&lt;br&gt;Ph: 06731-240202, M-9438802808</td>
<td>Dr. K.C. Das&lt;br&gt;Sub.Div. Hospital, Anandapur, Ghasipura, Keonjhar – 758015, Orissa&lt;br Mob: 9437336723</td>
</tr>
<tr>
<td></td>
<td><strong>ANGUL (New)</strong></td>
<td><strong>Dr. Pravat Kumar Panda</strong>&lt;br&gt;At: Hanuman Bazar, NH-55, Amalapada, Angul – 759122, Orissa&lt;br Mob: 9777443536</td>
</tr>
<tr>
<td><strong>ASHA</strong></td>
<td>Dr. P. Sibaji Patro&lt;br&gt;M.G. Road, Aska, Ganjam - 761110&lt;br&gt;Ph. 06822-273315</td>
<td>Dr. V. Santaram&lt;br&gt;R.L.T.R.I. ASKA&lt;br&gt;P.O.: Babanpur, Via: Nuagaon, Ganjam - 761111&lt;br&gt;Ph. (06822) 273079 Mob: 9337001458&lt;br&gt;E-mail: <a href="mailto:rlti@sancharnet.in">rlti@sancharnet.in</a>; <a href="mailto:rlti338@bsnl.in">rlti338@bsnl.in</a></td>
</tr>
<tr>
<td><strong>BALASORE</strong></td>
<td>Dr. Bijoy Kumar Panda&lt;br&gt;Bateswar, Balasore-756002, Orissa&lt;br Mob: 9861525654&lt;br Ph.: 06782 – 250868</td>
<td>Dr. J. K. Das&lt;br&gt;Anand Clinic, Motiganj, Balasore - 756001&lt;br Ph.06782-262909(R), 262678(C)&lt;br Mob: 9437295244</td>
</tr>
<tr>
<td><strong>BALUGAON-BANPUR</strong></td>
<td><strong>Dr. B.K. Panda</strong>&lt;br&gt;Banpur Road&lt;br&gt;Balugaon, Khurda - 752030&lt;br&gt;Ph. (06756) 220363&lt;br Mob: 9437423888, 943733776</td>
<td>Dr. S. N. Patra&lt;br&gt;Banpur&lt;br&gt;Khurda - 752031&lt;br Ph. (06756) 223100, 223224(Fax)&lt;br Mob.: 9437286098</td>
</tr>
<tr>
<td><strong>BARAGARH</strong></td>
<td><strong>Dr. Jogesh Chandra Padhi</strong>&lt;br&gt;Padhi Clinic, Gandhi Bhawan Marg, Baragarh – 768028&lt;br&gt;Ph. (06646) 234112&lt;br Mob: 9861380880</td>
<td>Dr. Mahendra Kumar Tripathy&lt;br&gt;Gayatri Nursing Home, N.H.-6, Baragarh - 768028&lt;br Ph.06646-247101(C), 247102(R)&lt;br Mob. 9437257080, 231078 (Fax)&lt;br E-mail: <a href="mailto:gayatrinh@yahoo.com">gayatrinh@yahoo.com</a></td>
</tr>
<tr>
<td><strong>BARBIL</strong></td>
<td><strong>Dr. S.C. Das</strong>&lt;br&gt;Kalinga Iron works, Barbil, Matkambeda, Keonjhar – 758037</td>
<td>Dr. Anil Kumar Dash&lt;br&gt;At/po: Bonaikela, Via: Joda, Keonjhar - 758038&lt;br Ph.(06767) 272198(R)&lt;br Mob: 9437027219&lt;br Email: <a href="mailto:dr.anilkumardas@yahoo.in">dr.anilkumardas@yahoo.in</a></td>
</tr>
<tr>
<td><strong>BARIPADA</strong></td>
<td><strong>Dr. C.R. Dash</strong>&lt;br&gt;THE BRAIN&lt;br&gt;Station Road&lt;br&gt;Baripada - 757001&lt;br Ph. (06792) 257999,&lt;br Mob: 9861041904</td>
<td><strong>Dr. S.S. Khandelwal</strong>&lt;br&gt;Durga Nursing Home&lt;br&gt;Badabazar, Baripada - 757001&lt;br Ph. (06792) 254112, 258919 (C)&lt;br Mob: 9437038919, 252663 (Fax)</td>
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<tr>
<td>BERHAMPUR</td>
<td>Dr. Gayatri Kar</td>
<td>Gandhi Nagar 3rd Line, East Berhampur, Ganjam– 760001, Orissa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph. 0680-2225003, Mob: 9861385003, Email: <a href="mailto:gayatri.kar@gmail.com">gayatri.kar@gmail.com</a></td>
</tr>
<tr>
<td></td>
<td>Dr. K.K. Panigrahy</td>
<td>Doctor’s Lane, Aurobindonagar New Lines Berhampur - 760001, Orissa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph. 0923817277(R) 0680-2200627 (O), Mob: 09437066627 (M), Email: <a href="mailto:kkp1000@hotmail.com">kkp1000@hotmail.com</a></td>
</tr>
<tr>
<td>BHADRAK</td>
<td>Dr P.K. Behuria</td>
<td>CDMO, Bhadrak - 756100.</td>
</tr>
<tr>
<td></td>
<td>Dr. Harekrishna Nayak</td>
<td>Nalinikanta Diagnostic Center, College Road, Po/Dist: Bhadrak-756100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mob: 9437138343, E-mail: <a href="mailto:mithun25nalini@gmail.com">mithun25nalini@gmail.com</a></td>
</tr>
<tr>
<td>BHUBANESWAR</td>
<td>Dr. Bijayananda Patnaik, M.D.</td>
<td>HIG-A-15, H.B.Colony, Baramunda Bhubaneswar - 751003</td>
</tr>
<tr>
<td></td>
<td>Dr. Saroj Kumar Sahu</td>
<td>SADITSA, 250/10, Paika Nagar (WEST) Near Baramunda Fire Station</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bhubaneswar – 751 003, Ph. : 0674-2561680 ( R ), Mob: 9437002424 ( M )</td>
</tr>
<tr>
<td>BOLANGIR (NEW)</td>
<td>Dr. Jyostnamayee Mohapatra</td>
<td>Radharani Pada, Bolangir – 767001</td>
</tr>
<tr>
<td></td>
<td>Dr. Narendra Kumar Sahoo</td>
<td>Harihar Hospital D.K.Enterprises Hospital Chowk Balingir</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Orissa - 767 001 PH:06652-233121, 9861381300 , 9437901021</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E-mail: <a href="mailto:dmkshahoo@gmail.com">dmkshahoo@gmail.com</a></td>
</tr>
<tr>
<td>BURLA</td>
<td>Dr. Golak Chandra Behera</td>
<td>Qr. No 3R/29 Doctor's Colony, Burla, Sambalpur – 768 017, Orissa</td>
</tr>
<tr>
<td></td>
<td>Dr. Guna Sagar Das</td>
<td>Associate Professor, Ophthalmology, VSS Medical College, Burla,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sambalpur – 768017 Ph. : 0663-2431525, 2430780, Mob: 9437085825</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Email: <a href="mailto:dr.gsdas@gmail.com">dr.gsdas@gmail.com</a></td>
</tr>
<tr>
<td>CUTTACK</td>
<td>Dr. Anangamohan Dwibedy</td>
<td>Sri Ram Nagar Cuttack</td>
</tr>
<tr>
<td></td>
<td>Dr. Trupti Ranjan Sarangi</td>
<td>IMA House, Medical Road, Ranihat, Cuttack – 753007, Odisha</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph.: 0671-2415255 (R), 2121125 (O), Mob: 9437020050 (M)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>email: <a href="mailto:truptiima@gmail.com">truptiima@gmail.com</a>, <a href="mailto:ima.cuttack@gmail.com">ima.cuttack@gmail.com</a></td>
</tr>
<tr>
<td>DHENKANAL</td>
<td>Dr. Ajaya Kumar Nanda</td>
<td>Muktedepur Sasani, Dhenkanal - 7599001</td>
</tr>
<tr>
<td></td>
<td>Dr. Bibhuti Bhusan Jena</td>
<td>Gudiadandi, Dhenkanal, Orissa - 759 001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph.: (06762) 224872, 9437121877 (M), Email: <a href="mailto:drbibhuti.jena@gmail.com">drbibhuti.jena@gmail.com</a></td>
</tr>
<tr>
<td>GUNUPUR</td>
<td>Dr. Mahakal Bisoyi</td>
<td>SDMO, Gunupur, Dist: Rayagada - 765 022, Orissa</td>
</tr>
<tr>
<td></td>
<td>Dr. Sravan Kumar Sahukar</td>
<td>Bank Street, Gunupur, Rayagada - 765022</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph. : (06857) 250127, 9861542861, email: <a href="mailto:sksahukar@yahoo.com">sksahukar@yahoo.com</a></td>
</tr>
<tr>
<td>JAGATSINGHPUR</td>
<td>Dr. Manoranjan Das</td>
<td>CDMO, AT/PO/Dist: Jagatsinghpur, Orissa – 754103</td>
</tr>
<tr>
<td></td>
<td>Dr. Raghunath Jena</td>
<td>At: Ohala, Badabazar, Jagatsinghpur-754103</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph. (06724) 220196, 220263 (PKR), Mob: 9437666591</td>
</tr>
<tr>
<td>JAJPUR</td>
<td>Dr. Kartik Chandra Rout</td>
<td>Gariapur, Jajpur Town</td>
</tr>
<tr>
<td></td>
<td>Dr. Batakrushna Mohanty</td>
<td>Gariapur, Jajpur Town, Jajpur - 755 001</td>
</tr>
<tr>
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<td></td>
<td>Jajpur - 755 001, Email: <a href="mailto:batarushma@gmail.com">batarushma@gmail.com</a></td>
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<td>Location</td>
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</tr>
<tr>
<td>JAIJPUR ROAD</td>
<td>Dr. Harihar Pati</td>
<td>New Market, Vyasnagar – 755019</td>
</tr>
<tr>
<td></td>
<td>Dr. G. S. Sarangi</td>
<td>Ganesh Bazar, Jaijpur Road, Jaijpur -755019, Orissa. Ph: (06726) 220543, 9437028321 (M) Email: <a href="mailto:gourisankarsarangi@gmail.com">gourisankarsarangi@gmail.com</a></td>
</tr>
<tr>
<td>JHARSUGUDA</td>
<td>Dr. M.J. Dora</td>
<td>MAIN ROAD, JHARSUGUDA-768 201, ORISSA. Mob: 9437117338, E-mail – <a href="mailto:mjdora20@yahoo.com">mjdora20@yahoo.com</a></td>
</tr>
<tr>
<td>KALAHANDI</td>
<td>Dr. Lambodhar Sahu</td>
<td>Mohavirpada Bhawanipatna – 766001</td>
</tr>
<tr>
<td></td>
<td>Dr. Malay Kumar Behera</td>
<td>Mahavirpada, Bhawanipatna - 766001 Ph. (06670) 230339, Mob: 9437070339 Email: <a href="mailto:drmalyabehera@yahoo.com">drmalyabehera@yahoo.com</a></td>
</tr>
<tr>
<td>KENDRAPARA</td>
<td>Dr. S. N. Das</td>
<td>Karuna Hospital Near HQ. Hospital Kendrapara – 754211</td>
</tr>
<tr>
<td></td>
<td>Dr. Ananda Gopal Mohanty</td>
<td>Mahipal, Kendrapara – 754211 Mob: 9437226701 Email: <a href="mailto:anand622@rediffmail.com">anand622@rediffmail.com</a></td>
</tr>
<tr>
<td>Keonjhar</td>
<td>Dr. Chandra Bhanu Sethy</td>
<td>At/Po Jaganathpur, Keonjhar 758001, Orissa Mob: 9437334674</td>
</tr>
<tr>
<td>KORAPUT DISTRICT</td>
<td>Dr. Kedarnath Choudhury</td>
<td>Govt. Sub-Divn.Hospital, At/Po Jeypore-764 001, Dist. Koraput, Orissa. Mob: 9437174666</td>
</tr>
<tr>
<td>NUAPADA</td>
<td>Dr. B.B. Jagat</td>
<td>CDMO, Nuapada – 766104</td>
</tr>
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<td></td>
<td>Dr. J. Chandrakar</td>
<td>Khariar Road Nuapada – 766104</td>
</tr>
<tr>
<td>PARALAKHEMUNDI</td>
<td>Dr. Pradeep Kumar Swain</td>
<td>Serango Christian Hospital Ranipeta Gajapati - Odisha Mob: 9437072868 E-mail: <a href="mailto:serangochristianhospital@yahoo.com">serangochristianhospital@yahoo.com</a></td>
</tr>
<tr>
<td>PRACHI</td>
<td>Dr. Adhiraj Kumar Parida</td>
<td>Niali Cuttack – 754004</td>
</tr>
<tr>
<td></td>
<td>Dr. Chitta Ranjan Mishra</td>
<td>Niali, Cuttack - 754004 Ph. 2803325 (R), Mob: 9437012522, 9438534050 (M) e-mail: <a href="mailto:cssniali@yahoo.co.in">cssniali@yahoo.co.in</a></td>
</tr>
<tr>
<td>PURI</td>
<td>Dr. Bamadev Mohanty</td>
<td>Talamali Sahi, Puri Town, Puri - 752 002, Orissa Ph.: 9437027775</td>
</tr>
<tr>
<td>Location</td>
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<td>Address</td>
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<td>RAJGANGPUR</td>
<td>Dr. Jaydev Dash</td>
<td>Talki Pada, Rajganjpur, Sundargarh - 770017</td>
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<td>Dr. Ghanashyam Soren</td>
<td>GOVT. HOSPITAL, RAJGANGPUR - 770 017, ORISSA.</td>
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<td>RAYAGADA</td>
<td>Dr. Dukkhiyam Dash</td>
<td>Indira Nagar 2nd Line, Rayagada - 765 001</td>
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<td>Dr. K. Krishna Mohan Kumandan</td>
<td>Kumudan Nursing Home, Main Road, Rayagada - 765 001</td>
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<td>Dr. P. K. Satpathy</td>
<td></td>
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<td>Dr. Binayak Rath</td>
<td>Qr. No.1-104, Sector-17, Rourkela - 760003</td>
</tr>
<tr>
<td>ROURKELA CITY</td>
<td>Dr. R.N. Dash</td>
<td>M-5, Chhend Colony, (M.S.Nagar) Rourkela – 769015</td>
</tr>
<tr>
<td></td>
<td>Dr. Rajat Kumar Ray</td>
<td>Ray Ultrasound Centre &amp; Infertility Clinic, S.T.I. Chowk, Rourkela - 769004</td>
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<tr>
<td>SAMBALPUR</td>
<td>Dr. Radheshyam Panda</td>
<td>A7/3, Sarswati Bihar, Ambiranagar, Ainthapali, Sambalpur – 768006, Orissa</td>
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<td>Dr. Sudhansu Sekhar Panda</td>
<td>Modipara (Kultapara), Sambalpur – 768002, Orissa</td>
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<td>C.D.M.O., Sundargarh - 770001</td>
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<td></td>
<td>Dr. Dillip Sarangi</td>
<td>Bijay Talkies Road, Dengibadi, Sundargarh – 770001</td>
</tr>
<tr>
<td>TALCHER-ANGUL</td>
<td>Dr. R.N. Panda</td>
<td>Ex-CDMO, HIG-4, Kalinga Vihar-5, Po: Parapada, Bhubaneswar – 751019, Orissa</td>
</tr>
<tr>
<td></td>
<td>Dr. L.N. Prasad</td>
<td>&quot;Kanta Niwas&quot; Bye-Pass Road, Talcher - 759107</td>
</tr>
<tr>
<td>TITILAGARH</td>
<td>Dr. Hasmukh Lal</td>
<td>Medicare, Main Road, Titilagarh, Balangir - 767033, Orissa. Mob: 9737096677</td>
</tr>
<tr>
<td></td>
<td>Dr. Mohan Lal Jain</td>
<td>Old Bank Chowk, Titilagarh, Bolangir – 767033, Orissa Mob: 9777858888 E-mail: <a href="mailto:drmohanjain@yahoo.com">drmohanjain@yahoo.com</a></td>
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**ODISHA STATE BRANCH 2011-12**

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<td>Dr. Bijay Kumar Mishra Saraswat, A-319, Sahid Nagar, Bhubaneswar - 751007, Orissa.</td>
<td>Bhubaneswar</td>
<td>09437012255, 0674-2547255, 2544055</td>
<td><a href="mailto:bijaykumarmishra@yahoo.co.in">bijaykumarmishra@yahoo.co.in</a></td>
</tr>
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<td>Imm. Past President</td>
<td>Dr. Sarat Kumar Mohapatra T.V. Road, Tulsipur, Cuttack – 753008, Orissa.</td>
<td>Cuttack</td>
<td>09437064510, 0671-2300110, 2300721(C)</td>
<td><a href="mailto:sarat.mohapatra@rediffmail.com">sarat.mohapatra@rediffmail.com</a></td>
</tr>
<tr>
<td>Vice Presidents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Cuttack</td>
<td>0671-2300611, 09437034611</td>
<td><a href="mailto:rudra_biswai7@gmail.com">rudra_biswai7@gmail.com</a></td>
</tr>
<tr>
<td>West Zone</td>
<td>Dr. Bijaya Kumar Dutta Brooks Hill, Sambalpur, Sambalpur-766 001, Orissa.</td>
<td>Sambalpur</td>
<td>0663-2521277, 09337333013</td>
<td><a href="mailto:bijaydutt@yahoo.com">bijaydutt@yahoo.com</a></td>
</tr>
<tr>
<td>North Zone</td>
<td>Dr. Harekrishna Nayak Naliniakta Diagnostic Center, College Road, P/o/Dist: Bhadrak-756100, Orissa.</td>
<td>Bhadrak</td>
<td>09437138343</td>
<td><a href="mailto:mithun25nalin@gmail.com">mithun25nalin@gmail.com</a></td>
</tr>
<tr>
<td>South Zone</td>
<td>Dr. E. Jayanti Rao Prem Nagar, 1st Lane, Berhampur-760 002, Orissa.</td>
<td>Berhampur</td>
<td>09437058282, 0680-2261182</td>
<td><a href="mailto:jayantirao_epari@yahoo.com">jayantirao_epari@yahoo.com</a></td>
</tr>
<tr>
<td>Hony. State Secretary</td>
<td>Dr. Kamala Kanta Panigrahy Doctor’s Lane, Aurobindonagar New Lines, Berhampur – 760001, Orissa.</td>
<td>Berhampur</td>
<td>09437066627, 09236127127 (R) 0680-2200627(Q)</td>
<td><a href="mailto:kkp1000@hotmail.com">kkp1000@hotmail.com</a></td>
</tr>
<tr>
<td>Joint Secretaries</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr. Mrutyunjay Mohapatra Rajendra Nagar, Madhapatna, Cuttack – 753 910, Orissa.</td>
<td>Cuttack</td>
<td>09437023444, 0671-2344446</td>
<td><a href="mailto:dimrutyunjaymohapatra@gmail.com">dimrutyunjaymohapatra@gmail.com</a></td>
<td></td>
</tr>
<tr>
<td>Dr. Banambar Senapati &quot;ABHILASH&quot;, M.I.G.-14, Srikritha HSG Colony Water Works Road, Puri - 752002</td>
<td>Puri</td>
<td>06752- 225363(R), 09437305906 (M)</td>
<td><a href="mailto:banambarsenapati@yahoo.com">banambarsenapati@yahoo.com</a></td>
<td></td>
</tr>
<tr>
<td>Joint Secretary (Nominated)</td>
<td>Dr.Basanta Kumar Dash A/229, Sahidnagar, Bhubaneswar-751007</td>
<td>Bhubaneswar</td>
<td>09437004353, 0674-2344767</td>
<td><a href="mailto:dashpathology@gmail.com">dashpathology@gmail.com</a></td>
</tr>
<tr>
<td>Hony. Finance Secretary</td>
<td>Dr. Janmejaya Mohapatra Qr-No-D-3/1, Medical College Campus, Near JMA House, Cuttack – 753007, Orissa.</td>
<td>Cuttack</td>
<td>09437020333, 0671-2419852</td>
<td><a href="mailto:dr.janmejaya.mohapatra@hotmail.com">dr.janmejaya.mohapatra@hotmail.com</a></td>
</tr>
<tr>
<td>Director, State Faculty IMACGP</td>
<td>Dr. Gayatri Kar Gandhinagar 3rd Line East, Berhampur(Ganjam)-760001, Orissa</td>
<td>Berhampur</td>
<td>09861385003, 0680-2252003</td>
<td><a href="mailto:gayatikar@gmail.com">gayatikar@gmail.com</a></td>
</tr>
<tr>
<td>Secretary State Faculty IMACGP</td>
<td>Dr. Prasanta Kumar Patro Gandhi Nagar, 1st Lane, Berhampur - 760 001, Orissa.</td>
<td>Berhampur</td>
<td>09437062424, 0680-2222424</td>
<td><a href="mailto:dirprasant_patro@yahoo.in">dirprasant_patro@yahoo.in</a></td>
</tr>
<tr>
<td>Jt Secy., State Faculty IMACGP</td>
<td>Dr. Saroj Kumar Mishra Siddhanagar Main Line Ext., Berhampur - 760004, Orissa.</td>
<td>Berhampur</td>
<td>09437075229, 0680-2282598</td>
<td><a href="mailto:sarojmisra3@rediffmail.com">sarojmisra3@rediffmail.com</a></td>
</tr>
<tr>
<td>Chairman, IMA AMS, State Chapter</td>
<td>Dr. Sisir Kumar Mohapatro Surya Niwas, HIG-2, B1/91 Lingaraj Vihar Pokhariput Bhubaneswar-751020</td>
<td>Bhubaneswar</td>
<td>0674-2382366, 09437067855</td>
<td><a href="mailto:drskm_med@yahoo.co.in">drskm_med@yahoo.co.in</a></td>
</tr>
<tr>
<td>Secretary, IMA AMS, State Chapter</td>
<td>Dr. Chanchal Sri Sarkar 3 B, Binayak Villa, 1967, Siritamnagar. Old Town. Bhubaneswar-751002, Orissa.</td>
<td>Bhubaneswar</td>
<td>0977795825, 0674-3261217</td>
<td><a href="mailto:drchanchalsri@yahoo.co.in">drchanchalsri@yahoo.co.in</a></td>
</tr>
<tr>
<td>Editor, Orissa Medical Journal</td>
<td>Dr. Jayant Kumar Panda Ratho Complex, Biju Patnaik Square, Tulsipur, Cuttack – 753008, Orissa</td>
<td>Cuttack</td>
<td>09437028282, 0671-2320300, 2307300</td>
<td><a href="mailto:drjayantpanda@gmail.com">drjayantpanda@gmail.com</a></td>
</tr>
<tr>
<td>Role</td>
<td>Name</td>
<td>Address</td>
<td>Contact Information</td>
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<tr>
<td>Secy. Orissa Medical Journal</td>
<td>Dr. Gautam Patnaik</td>
<td>Qr. No. C-3/CB-8 Campus, Cantonment Road, Cuttack – 753001, Orissa</td>
<td>09861039806 0671-2306868 <a href="mailto:dr.gautam.patnaik@gmail.com">dr.gautam.patnaik@gmail.com</a></td>
<td></td>
</tr>
<tr>
<td>Secretary Social Welfare</td>
<td>Dr. Deba Prasad Mohanty</td>
<td>&quot;Asprua Bhavan&quot;, Kalyani Nagar, Cuttack - 753 013, Orissa.</td>
<td>09437021313 0671-2344767 <a href="mailto:drdev07@yahoo.com">drdev07@yahoo.com</a></td>
<td></td>
</tr>
<tr>
<td>Secy. Women Doctor’s Wing</td>
<td>Dr. Sandhyaarani Panigrahy</td>
<td>Doctor’s Lane, Arvind Nagar 1st Line, New Bus Stand Road, Berhampur - 760 004, Ganjam</td>
<td>09438767684 0680-3296591 <a href="mailto:sandhyaarani_panigrahy@yahoo.com">sandhyaarani_panigrahy@yahoo.com</a></td>
<td></td>
</tr>
<tr>
<td>Member C.W.C.</td>
<td>Dr. Abhoya Kumar Kar</td>
<td>Gandhinagar 3rd Line East, Berhampur (Ganjam)-760001, Orissa</td>
<td>09937064983 0680-2225003 <a href="mailto:abhoya.kar@gmail.com">abhoya.kar@gmail.com</a></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dr. Saroj Kumar Sahu</td>
<td>&quot;Sadatsa&quot;, 250/10, Paika Nagar (West), Near Baramunda Fire Station, Bhubaneswar – 751 003, Orissa</td>
<td>09437002424 0674-2561680 (R) <a href="mailto:sahudsaroj@yahoo.co.in">sahudsaroj@yahoo.co.in</a></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dr. Ananga Mohan Dwibedy</td>
<td>Sriram Nagar, Behind Puri Bus Stand, Cuttack – 753012, Orissa</td>
<td>09437013011 0671-2313011 <a href="mailto:amdwibedy@yahoo.com">amdwibedy@yahoo.com</a></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dr. Jagannath Mohapatra</td>
<td>B-35, Sahid Nagar Bhubaneswar - 751 007</td>
<td>09437004500 0674-2543133 (C) 2545133 (R) <a href="mailto:drjnmohapatra@yahoo.com">drjnmohapatra@yahoo.com</a></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dr. R.N. Panda</td>
<td>HIG-4, Kalinga Vihar-5, Po: Parapada, Bhubaneswar – 751019, Orissa</td>
<td>9437017239 Ph. 0674-2475235 <a href="mailto:rabipanda_2000@yahoo.com">rabipanda_2000@yahoo.com</a></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dr. Sreejoy Patnaik</td>
<td>Shanti Hospital &amp; Research Centre, Patnaik Colony, Thoria Sahi, Cuttack-753001, Orissa</td>
<td>09437024550 0671-2416520 (R) 2415260 (C) <a href="mailto:drsreejoypatnaik@yahoo.com">drsreejoypatnaik@yahoo.com</a></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dr. Dhirendra Kumar Patnaik</td>
<td>T.V.Road, Tulsipur, Cuttack – 753008, Orissa.</td>
<td>09437023001 0671-2300131 <a href="mailto:dkpatnaik1@rediffmail.com">dkpatnaik1@rediffmail.com</a></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dr. Krupasindhu Panda</td>
<td>Panda Medical Center Beparisahi, Kesarpur, Cuttack-753001, Orissa</td>
<td>09861054177 0671-2615829 (R) <a href="mailto:doctorkpanda@yahoo.com">doctorkpanda@yahoo.com</a></td>
<td></td>
</tr>
<tr>
<td>Nominated Members</td>
<td>Dr. Ashok Kumar Singhal</td>
<td>Sambalpur</td>
<td>09437057777 <a href="mailto:drashok_ht@yahoo.co.in">drashok_ht@yahoo.co.in</a></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dr. Trinath Pal</td>
<td>C/O- Dr.M.P.Mohanta, Goudanibeda, Dhurpada, Near Kumar Automobiles, Keonjhar, 758013</td>
<td>09437138227 <a href="mailto:dr.trinath.pal@gmail.com">dr.trinath.pal@gmail.com</a></td>
<td></td>
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</table>
IMA HEADQUARTERS

National President
Dr. Vinay Aggarwal, M.B.B.S.
A-14, Pushpanjali, Vikas Marg Extn.-110092, Delhi

Imm. Past National President
Dr. Goparaju Samaram, M.B.B.S.
Vasavaya Nursing Home, Patamata, Benz Circle, Vijayawada - 520010 Andhra Pradesh.

National President Elect 2011-12
Dr. G.K. Ramachandrappa, M.B.B.S., M.S.
63 Udayaravi Mayura Road, 4th Main, Kadukudure Layout, Nagarabavi, ind State, Bangalore – 560072, Karnataka

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Saketh, Kripa Nursing Home
Kalpetta - 673121, Kerala.

Dr. Sunil Kumar Gope, M.B.B.S., F.C.G.P.
9/A, Central Road, Anandapuri, Po. Nonanchandanpukur
Kolkata -700122 Bengal

Hony. Secretary General
Dr. D.R. Rai, M.B.B.S., F.C.G.P.
Dev Medical Centre, 5, D.d.a. B-block Market, Dilshad Garden, Delhi-110095

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J-71, Kalkaji, New Delhi-19.

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7/13, Rohit Kunj Market, Pitampura, Delhi - 110 034.

Dr. Ajay Gambhir, M.B.B.S., M.D.
D-721, Saraswati Vihar, Delhi-110034

Dr. Hans Raj Satija, M.B.B.S., M.D.
A-5/7, Paschim Vihar, New Delhi-110 063

Dr. Narendra Saini, M.B.B.S., M.D.
81, Saini Enclave, Vikas Marg, -110092 Delhi

Hony. Jt. secretary, Calcutta
Dr. Amitabha Bhattacharya, M.B.B.S., DPH
Ha-330, Flat No. 4, Salt Lake City, Sector-III, Kolkata -700097 Bengal.
**Membership Application Form**

**Annual/Life/Direct Membership Application Form**

(All details to be filled in Block Letters)

**Membership Proposed by Dr.** _______________  
IMA Hqrs.: Membership No. _______________

To,
The Honorary Secretary General, IMA
IMA House, I P Marg, New Delhi-110002

Dear Sir,

I hereby apply to be enrolled as a member of the Indian Medical Association as _______________ member through

Local Branch _______________ under the _______________ State/Territorial Branch of IMA

Member’s Name (as per MCI/SMC Certificate, in BLOCK LETTERS): _______________

Father’s/Husband’s Name: _______________ Date of Birth: _______________

Address (Permanent/Correspondence): _______________

Clinical/Hospital Address: _______________

Mobile No _______________ Tel. (H) _______________ Tel (Clinic/Hospital) _______________

Email ID: _______________ Fax No. _______________

**QUALIFICATION**  
M.B.B.S. (1)  (2)  (3)

**COLLEGE**

**UNIVERSITY**

Designation (Practice/Job): _______________

Registration Details: *(Photocopy of Registration Certificate to be enclosed with IMA Hqrs. Form)*

Registration No. of Medical Council of India/State Council: _______________

Date: _______________

Service (details)

I certify that I am registered with MCI/State Medical Council. I certify that all details furnished are true. If my statement is found to be incorrect, my membership would stand to be cancelled and the fee paid by me to all sections of IMA will be liable to be forfeited by them. I hereby give undertaking that I shall abide by the Rules and Regulations of IMA.

Date: _______________  
Place: _______________  
Signature of the Applicant

(Certified that I have verified the qualifications and registration of the applicant and his eligibility as per rules of IMA for being enrolled as member of the Indian Medical Association. Forwarded to the Honorary Secretary General along with HFC)

Signature & Stamp of Honorary, State Secretary

Forwarded to IMA Hqrs. along with HFC on _______________

Received at IMA Hqrs. along with HFC on _______________

Membership confirmed on _______________

Signature & Stamp of Honorary, State Secretary

Signature & Stamp of Honorary, Local Branch

NB: The Local Branch Secretary will keep a photocopy of this form & forward the original form to State/Provincial Branch Secretary along with Admission Fee & HFC and the State will sign/initial a photocopy of this form & send the original form along with Admission Fee and HFC to IMA Hqrs. for proper record maintaining. The Journal Office will be informed by the Honorary Secretary General by providing admission letter to IMA.

Membership will commence only when it is approved and confirmed by the Honorary Secretary General, IMA (Hqrs.)
Glimpses of Release Ceremony of “OMJ 2010” at IMA State Headquarters, Cuttack on 30th Dec, 2010 by Prof. Manorama Mahapatra, Justice A.S. Naidu & Prof. Pramod Mallick
62ND ANNUAL STATE CONFERENCE OF IMA ORISSA STATE BRANCH
ON 19TH-20TH FEBRUARY 2011 AT PANTHA NIVAS, ROURKELA

Inaugural Function

Felicitation & Awards

Ultrasound Workshop

State Council Meeting
ANNUAL NATIONAL REVIEW WORKSHOP
IMA - GFATM-RNTCP-PPN-RCC PROJECT on 5th & 6th March, 2011
Hotel Hindustan International, Bhubaneswar

1st Office Bearers Meet
IMA State Headquarters, Cuttack
on 19th March, 2011

World Health Day observation
by IMA, Bhubaneswar & Kaling Hospital
on 7th April, 2011

Rare Photographs of Past Activities
1ST ANNUAL CONFERENCE OF IMACGP ORISSA STATE FACULTY AND
46TH ANNUAL CONFERENCE OF IMA STATE BRANCH
at REC, Rourkela on 12th November, 1994
FELICITATION

"We felicitate Prof. Purna Chandra Mahapatra, a born Teacher, Excellant Orator, Compassionate Human Being, Competent Clinician, Skillful Surgeon, Successful Organiser, Committed Academician & Sacrificing Leader for being elected as the National President of FOGSI."

Editor, OMJ

OBITUARY

in beloved memory of our Iconic Past Presidents

Dr. K.S.N. Rao
(Passed away on 18.3.2011)

Dr. (Mrs) Nirupama Rath
(25.10.1925 – 06.04.2011)
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METUM
(Meropenem 1gm Inj.)

VAN
(Methylcobalamin, Anti-oxidant, Anti Mineral Caps.)

PRALIDON
(Pralidoxime Chloride 1gm Inj.)

TOPEP
(Pantoprazole 40mg Tabs)