

## CONFERENCE SUMMARY

# THE MDRF-ADA POST GRADUATE COURSE IN DIABETOLOGY – SCIENTIFIC HIGHLIGHTS

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**KEY WORDS:** Impaired glucose tolerance (IGT), United Kingdom Prospective Diabetes Study (UKPDS), Basal Metabolic Rate (BMR), Continuous Glucose Monitoring system (CGMS), Continuous Subcutaneous Insulin Infusion (CSII), Diabetes in Early Pregnancy (DIEP)

This article covers the scientific highlights of the MDRF-ADA Postgraduate Course in Diabetology, which was held first time in India, at Chennai during 20-22 September, 2002. Topics presented at the course included prevention of diabetes, management of diabetes and its complications like diabetic nephropathy, retinopathy and neuropathy, management of associated comorbidities like obesity and hypertension, pregnancy in diabetic women, newer insulin delivery systems, insulin regimens, oral hypoglycemic agents, current and future trends in self monitoring of blood glucose, developing standards for diabetic education and optimal strategies for delivering effective self management education.

In the opening lecture of the course, **Dr. Aaron Vinik** (Eastern Virginia Medical School, Virginia, U.S.A), spoke on "Prevention of Diabetes". He stated that diabetes had become a global problem. In 1997, 2.1% of world population or 124 million people had diabetes (Type 1 and Type 2). Of these 97% or 120 million people world-wide had Type 2 diabetes. Approximately 1% more were added each year to the existing diabetic population. The natural history of Type 2 diabetes is progression from normal glucose tolerance to impaired glucose tolerance (IGT) to diabetes. Thus the right time for prevention is to intervene at the IGT stage before the beta cell decompensation starts. UKPDS has also proved that beta cell function starts deteriorating approximately a decade prior to diagnosis of diabetes and at the time of diagnosis approximately 50% of the beta cell function is already lost. Type 2 diabetes is the result of deteriorating beta cell function with increasing

insulin resistance (reducing insulin sensitivity). Insulin resistance can be broadly governed by inherited and acquired influences like obesity, aging, glucotoxicity, lipotoxicity and smoking.

The results of Nurses Health Study have shown that even among overweight and obese individuals, the combination of an appropriate diet, a moderate amount of exercise, abstinence from smoking and reduced alcohol consumption can substantially lower the risk of Type 2 diabetes.

Even modest weight loss has shown the benefits like lowering of lipids, better glycemic control and reduced prevalence of coronary artery disease. The Finnish Diabetes Prevention Program showed that lifestyle interventions (diet and exercise) in IGT patients reduced the relative risk of diabetes development by 58%. Conversely, a mere 3% weight gain increases the chances to get diabetes in IGT individuals by 81%.

In the Diabetes Prevention Program done in USA on patients with IGT with diet (reduced calorie with 25% fat) aimed for 7% weight loss, exercise (30 min/day, 5 days a week) or metformin (850mg twice daily) showed that life style modifications (diet and exercise) reduced development of diabetes by 58% but metformin reduced the development by 31%. It has been observed that strength training may serve as an valuable adjunct to aerobic training. Newer evidence suggests that long bouts of exercise have greater effects over weight loss in comparison to short bouts.

Several studies are currently assessing the role of pharmacological intervention to prevent diabetes in individuals with IGT. The current recommendations to prevent or delay diabetes are:

- a. Individuals at high risk should be made aware of benefits of modest weight loss and regular physical activity.

- b. Dietary modifications with moderate calorie diet, high intake of cereal fiber and polyunsaturated fatty acids, low intake of transfatty acids and intake of low glycemic index foods should be preferred.
- c. Anti-obesity drugs can be started in severely obese patients.
- d. While treating the patients for diabetes and associated co morbidities search should be made for alternative drugs that do not promote weight gain.
- e. Smoking should be totally stopped and only modest amount of alcohol intake should be allowed, if any.

**Dr. F. Xavier Pi-Sunyer**, (St. Lukes –Roosevelt Hospital, New York, U.S.A.), discussed the hormonal regulation of body weight. He showed evidence that the body weight is controlled by energy balance equation, whereby energy intake equals energy expenditure when body weight is stable. When the body weight is lowered, the regulatory mechanisms which increase the body weight are increased hunger, decreased activity level, high lipoprotein lipase activity and increased insulin sensitivity acting together to increase the body weight. The regulatory mechanisms for increasing weight are better than mechanisms for lowering weight. Increased BMR, increased satiety, increased insulin resistance and increased adipocyte size are some of the mechanisms to decrease body weight. The peripheral signals that are important to energy balance are the gut peptides, the pancreatic hormones, the peptidases secreted from the adipose tissue and neurotransmitters.

Long term food regulation depends on insulin, leptin and fuel molecules. Increase in adipocyte mass increases leptin (produced by leptin genes) which block hypothalamic receptor and results in reduced food intake and increased thermogenesis. It has ability to cross the blood brain barrier and is known as leptin regulatory system. The effect of leptin is to reduce body weight, food intake, insulin secretion, blood glucose and to activate sympathetic system. Thus leptin deficiency may lead to obesity, hyperphagia, hyperinsulinemia, insulin resistance, diabetes mellitus and autonomic imbalance. Leptin resistance has been documented in obese persons.

**Dr. Francine Kaufman**, (USC School of Medicine, Los Angeles, USA), presented about the newer insulin delivery systems to improve diabetes outcome in patients with Type 1 diabetes. A number

of novel insulin delivery devices like insulin pens, inhaler insulin and continuous subcutaneous insulin infusion have been developed. Insulin pens have been successfully used for almost 2 decades. They are convenient and cause less pain in comparison to conventional injections. The inhaled insulin has also being widely used in Type 1 diabetic patients. 3gm of inhaled insulin roughly equals to 10 units of subcutaneous insulin. The inhaled insulin can also be used in basal bolus regimen – as inhaled insulin can be used as bolus, while injectable insulin could be used as basal insulin. With the availability of short acting (lispro / aspart) and long acting (glargine) insulin analogues, the basal bolus regimen has become more effective and can offer a good measure to control the wider fluctuations in Type 1 diabetic patients. Insulin pump therapy has been widely used since two decades and its use is increasing day by day. It has also been used in children of 1 year of age. The use of continuous subcutaneous insulin infusion pump only at night time in Type 1 diabetic patients has also been shown to have decreased evidence of hypoglycemia and a better fasting plasma glucose levels.

The glucose monitoring systems like Glucowatch biographer and Continuous Glucose Monitoring Systems (CGMS) are now being widely used and they offer a good way to monitor glycemic status of Type 1 diabetic patients. The evolving options could be implantable sensors and pumps and we could thus hope to have a much better monitoring systems in near future.

**Dr. Lois Jovanovic**, (Sansum Medical Research Institute, California, U.S.A.), spoke about management of pregnancy in diabetic women. She classified the diabetes in pregnant women in two classes:

**A. Normoglycemic / Optimal Control.**

- a. Fasting 55 – 65 mg%
- b. 1 hour post meal <140mg%
- c. Mean glucose of 84 mg%

**B. Less than Optimal Control** : blood glucose documented outside of normal range.

Prior to 1922, no infant of a diabetic mother survived. With the advent of insulin and optimally controlling mean maternal blood glucose levels, the infant mortality rate decreased nearer and nearer to

that seen in the general population. The measures by which this glycemic control has been achieved are diet, insulin, moderate exercises and frequently monitored blood glucose.

Diet is the main stay of therapy for pregnant diabetic women. The diet plan that has been successful is a diet that is calculated as 30 Kcal /kg/day in a normal weight woman and 25 kcal/kg/day in an overweight woman with expectations to maintain the body weight around ideal body weight. The caloric requirement from carbohydrate should be around 40% to 60% of the diet.

The normoglycemia or optimal control could only be achieved with 3-4 insulin injections /day. The insulin dose is calculated as 0.7 units/kg/day for the first trimester, 0.8 units / kg/day for the second trimester and 0.9 units per kg/day in the third trimester. The insulin requirement at term is 1.0 unit / kg/day. The total daily dose is divided in half to be delivered as the basal insulin and rest to the meal related insulin (boluses) needs. The use of continuous subcutaneous insulin infusion (CSII) has revolutionized the glycemic control, but multiple insulin injection can also simulate the CSII pump. In monitoring of glycemic control, it must be kept in mind that HbA<sub>1c</sub> is 20% lower in pregnant women in comparison to non-pregnant women.

Animal studies have shown that hyperglycemia during first trimester causes dys-organogenesis. Caudal agenesis / absent lower spine is pathognomic of diabetes. The hyperinsulinemia and hyperglycemia of pregnancy leads to adiposity or big bad baby syndrome which could be prevented by normoglycemia. Results of Diabetes in Early Pregnancy (DIEP) Trial have shown that earlier the diabetic pregnant women starts achieving normoglycemia, the less is the chance of fetal malformations. The diabetic women with well-controlled HbA<sub>1c</sub> have shown normal rate of abortion like general population, but those with HbA<sub>1c</sub> >7% have shown increased incidence of spontaneous abortions.

In pregnancy associated with nephropathy if the serum creatinine is <2mg%, the outcome is good, while serum creatinine of >2 mg% is compounded with hypertension and proteinuria. Rapid normalization of maternal blood glucose may lead to diabetic retinopathy. In DIEP trial, it has been shown that the first trimester retina status guides

towards the risk of progression of retinopathy. The group with a higher HbA<sub>1c</sub> and worst retina at first trimester progressed very faster than group with same HbA<sub>1c</sub> with better retina at first trimester. The DIEP trial has also shown that progression of diabetic retinopathy is independent of glycemic control in pregnancy but the eye needs frequent monitoring. Better glycemic control has also been shown to reduce the prevalence of caesarian sections in pregnant diabetic women. If the baby is normal and the glycemic control is good, there is no need to initiate the pregnancy. Initiation should be planned if the fetus is endangered.

Hypoglycemia is an associated outcome of insulin therapy. But hypoglycemia has not been associated with adverse outcome in diabetic pregnancy in humans. Oral hypoglycemic agents have not been recommended in diabetic pregnancy as their safety is yet not proven. Only human insulin has been approved by the FDA for use in pregnancy. Thus with normalization of maternal blood glucose, the pregnancy outcome could be near normal in a pregnant diabetic women like non-diabetic women, but large clinical trials are necessary.

**Dr. Martha M. Funnell**, (Michigan Diabetes Research and Training Centre, Michigan, U.S.A.) discussed about "Developing standards for diabetic education". Diabetes self management education is the corner stone of care for all persons with diabetes. The development of standards helps to define quality so that diabetes self management education can be implemented to diverse settings and facilitate improvement in health outcomes.

Standards need to be evidence-based, clearly defined, and broad enough to adapt the new trends and changes in the delivery of diabetes care and the health care systems. Standards typically include criteria related to program structure, the educational process including the curriculum and outcome measures. Incorporating recommendations about program organization and operation helps to promote institutional support.

While standards help to ensure consistency in process and outcomes, they are not meant to mandate a particular program or methodology. In order to be meaningful, outcome measures need to be selected that will best match the goals and objectives of the program and the patient population and include behavioral psychosocial and metabolic measures.

**Dr. John Buse** (University of North Carolina, U.S.A.) discussed about Oral agents. When and How to use them in type 2 diabetes. The basic pathophysiology of Type 2 diabetes mellitus is defective insulin secretion and insulin sensitivity. The measures which improve the insulin secretion are sulphonylureas and glinides while measures improving insulin sensitivity are diet, exercise, glitazones and metformin. The ADA recommends premeal plasma glucose between 90-130mg% and HbA1c of <7% while they have not recommended any glycemic range for post prandial glucose. The American College of Endocrinology recommends premeal plasma glucose value of <110 mg%, 2 hour postprandial plasma value of <140mg% and a HbA1c value of <6.5%. DCCT and UKPDS trials have clearly shown the benefits of intensive diabetes therapy in reducing complications. Thus it is mandatory now to maintain stringent glycemic control.

The treatment of Type 2 diabetes should be targeted to the pathophysiology of Type 2 diabetes namely increased insulin resistance and reduced insulin secretion leading to hyperglycemia in diabetic state by causing increase hepatic glucose production, increase glucose absorption from the intestine, decreased insulin secretion by pancreas and reduced peripheral glucose uptake in adipose tissue and muscles. The drugs which reduces the hepatic glucose output are biguanides and thiazolidinediones. The drugs which increases insulin secretion from pancreas are sulphonylureas and glinides (repaglinide, nateglinide). The drugs reducing the glucose absorption from the intestine are alpha-glucosidase inhibitors (acarbose and miglitol). Drugs that increase the peripheral glucose uptake at the level of muscles and adipose tissue are thiazolidinediones (pioglitazone and rosiglitazone) and biguanides.

The combination therapy should be planned if monotherapy fails or to counter insulin resistance as well as to increase insulin secretion. The fasting and the preprandial glucose levels could be controlled by reducing hepatic glucose output (by metformin), increasing insulin sensitivity by glitazones or increasing insulin availability (by sulphonylurea / glinides). The postprandial blood glucose can be controlled by reducing carbohydrate absorption rate (by alpha-glucosidase inhibitors) by reducing carbohydrate intake or rapidly increasing insulin availability with meals (by glinides).

It is important to note that the commonly used oral hypoglycemic agents may produce some side effects. The common side effects of sulphonylureas and glinides are hypoglycemia and weight gain. Biguanides may not cause weight gain but it causes gastrointestinal (GI) upset and they are contraindicated in renal, cardiac and hepatic insufficiency (as they can induce lactic acidosis under these situations). Alpha-glucosidase inhibitors may cause GI upset and flatulence but they have a rare risk of liver enzyme elevation also. Thiazolidinedione may cause edema, weight gain, anemia and rarely cardiac failure.

In her second lecture, **Dr. Francine Kauffman**, discussed about the "Treatment of childhood and adolescent Type 2 diabetes mellitus". 25% of new Type 2 diabetes mellitus cases in the US now belong to this category. The predisposing risk factors for childhood diabetes are obesity, sedentary life style, puberty, genetic defects and gender (girls > boys). There is evidence that breast feeding exclusively upto 6 months and in total upto 12 months prevents obesity. 84% of obesity is due to eating habit with >30% calorie coming from fat. Children of obese parents are 5 times more at risk to be obese.

Puberty is associated with insulin resistance. Lower insulin stimulated glucose disposal has been seen at puberty due to growth hormone and insulin like growth factors. The obesity may be due to increased fat consumption and meal size. As normal pubertal transition has been associated with insulin resistance, healthy beta cells adapt to this, but the failure to adapt this situation results in Type 2 diabetes mellitus in children. The development of Type 2 diabetes mellitus is faster in children in comparison to parents. Presenting symptoms could be weight loss, ketosis, high HbA<sub>1c</sub>, ketoacidosis, acanthosis nigricans and some may have circulating antibodies like GAD and ICA. The children at risk are those with BMI > 85<sup>th</sup> percentile, a diabetic relative, ethnic group with high diabetes prevalence and children with signs of insulin resistance like dyslipidemia, acanthosis nigricans, hypertension and polycystic ovarian syndrome. A child with any of the above symptoms with age of ≥ than 10 years should be screened.

Non-pharmacological treatment modalities include child education, family education about diabetes and nutrition and proper exercises as they

benefit the child by decreasing the weight gain velocity. HbA<sub>1c</sub> should be kept below 7.0%. The drugs of choice to control blood glucose are insulin, insulin analogue, sulphonylurea and metformin. The anti-obesity drugs sibutramine and orlistat are not recommended by FDA for pediatric population. Less than 10% of patients are controlled by diet and exercise while others require oral agents or combination therapy with SU and metformin.

Co-morbidities associated with adolescent Type 2 diabetes mellitus are hypertension (17-32%), high lipid levels (4-32%), sleep apnea syndrome, depression and dyslipidemia. Prediabetes has also been seen in children. In U.S.A. 20-25% obese adolescents have IGT. As obesity is associated with diabetes, a term diabetes has been suggested. The diabetes prevention strategy should be planned. Schools should be the target with promotion of physical activity, supply of better nutritious food and advise to reduce obesity.

**Dr. Claude L. Cowan** (George University Medical Centre, Washington, U.S.A) spoke about the "Pathogenesis and management of diabetic retinopathy". Diabetic retinopathy is a clinical manifestation of a progressive retinal microangiopathy, characterized by a combination of vascular incompetence (localized and diffuse retinal thickening) and vascular insufficiency (localized and diffuse non-perfusion/proliferative retinopathy). Diabetic retinopathy is a major cause of visual morbidity and is highly correlated with duration of diabetes, glycemic control and BP control.

Disordered glucose metabolism is the biochemical abnormality associated with diabetes. Persistent hyperglycemia precipitates alterations to blood vessel walls and the cellular components of the blood. Probable pathogenic mechanisms are sorbitol pathway, hemodynamic and rheologic abnormalities, advanced glycosylation end products and vasoactive factors like VEGF (vascular endothelial growth factors). Persistent hyperglycemia induces a procoagulant state and provides biochemical changes which alter vascular permeability. Expression of vasopermeability and vasoproliferative factors is linked to the severity and duration of disordered glucose metabolism, as is the risk for retinopathy.

Non proliferative diabetic retinopathy is manifested clinically by the presence of microaneurysms, hemorrhage, lipid exudates, retinal

edema, cotton wool spots, venous beading or loops and I.R.M.A. (intraretinal microvascular abnormalities). Proliferative retinopathy develops when retinal ischemia associated with capillary non-perfusion induces the proliferation of newly formed blood vessels over the surface of the retina or optic nerve. The predictors for progression of NPDR (non proliferative diabetic retinopathy) to PDR (proliferative diabetic retinopathy) are venous beading, intra retinal microvascular abnormalities, severe retinal hemorrhage and cotton wool spots. Vitreous hemorrhages occur when the fibrovascular tissues, exposed to tractional forces associated with contraction of the posterior vitreous, ruptures. Traction detachment of the retina may accompany the vitreous hemorrhage or may occur independently.

The management of diabetic retinopathy depends on better glycemic control, management of other vascular disorders, periodic screening for retinopathy, timely laser photocoagulation and vitrectomy. Thus blindness from diabetes is largely preventable. Better glycemic control and laser therapy significantly reduces the risk for vision loss. The promise of new therapies should not overshadow the effectiveness of current approaches to the prevention of diabetic blindness.

In his second lecture, **Dr. Aaron Vinik**, discussed on pathogenesis and management of diabetic neuropathy. Diabetic neuropathies are a family of diseases, encompassing a wide range of abnormalities that affects the peripheral nerves. It is the most common peripheral neuropathy resulting in 50-70% of non-traumatic amputations. It can be classified as focal and diffuse. Focal neuropathy involves the single nerves (mononeuritis) and should be differentiated from entrapment neuropathies. Diffuse diabetic neuropathy can be further subdivided into proximal and distal type. Distal symmetrical mixed sensori motor polyneuropathy is the most common type of neuropathy found in diabetics and it can involve both small and large fibers. Small fiber involvement manifests as pain, hyperalgesia, loss of thermal sensitivity, reduced light touch and pin prick sensation. Large fiber neuropathy manifests as reduced vibration and position sense, weakness, muscle wasting and depressed tendon reflexes. Autonomic neuropathy is another form of diffuse neuropathy that occurs mostly in Type 1 patients, resulting mainly from the small fibre involvement, affecting almost every system of the body from cardiovascular to genitourinary.

Treatment of diabetic neuropathy is based on better glycemic control and symptomatic treatment for pain and other associated symptoms like numbness, postural hypotension and erectile dysfunction. Strengthening exercises for muscle are of great help. The future strategies for treating diabetic neuropathies could be aldose reductase inhibitors and PKC inhibitors like LY333531 which will act at the pathogenic mechanisms causing neuropathy. There are several agents like GLA (gamma linolenic acid) and ALA (alpha lipoic acid) which have shown impressive effects on nerve function. We can hope that some more pathogenesis specific treatment for diabetic neuropathy becomes available in near future.

**Dr. Vivian Fonseca**, (Tulane University Health Sciences Centre, Louisiana, U.S.A), discussed about hypertension and diabetic nephropathy. Hypertension is a very common problem in people with diabetes. Hypertension is the critical determinant of the development and progression of diabetic nephropathy as well as CVD in diabetics.

The pathologic processes leading to glomerular injury and proteinuria has been linked to advanced glycation end products and imbalance in factors affecting vascular tone and structure. The constrictors and growth promoters are angiotensin II, catecholamines and endothelin (endothelium derived constricting factors). The dilators and growth inhibitors could be nitric oxide, prostacyclin, bradykinin and EDHF (endothelium derived hyperpolarizing factors). The renin angiotensin gets activated with production of increased angiotensin II which binds to AT<sub>1</sub> and AT<sub>2</sub> receptors resulting in upregulation of gene expression of NF-Kappa B and TGF resulting in a variety of lesions like glomerulosclerosis, tubular interstitial fibrosis, nephron loss and ultimately renal failure. Angiotensin II also induces oxidative stress on the kidneys resulting in endothelial dysfunction and renal injury.

The United Kingdom Prospective Diabetes Study (UKPDS) has clearly shown the increased diabetes related complications and mortality associated with increased systolic blood pressure. Event rates for select end points have markedly decreased with good control of blood pressure. The HOPE study, Hypertension Optimal Trial (HOT) and the Appropriate Blood Pressure Control in Diabetes (ABCD) trial have also shown the same results. The

recommended BP in diabetic patients is less than 130/80 mmHg. As nephropathy is present at diagnosis in 15 – 25% of patients, the annual screening for microalbuminuria, tighter blood pressure control <125 /75 (with ACE inhibitors, and Angiotensin Receptor Blocker (ARB) as first choice), better glycemic control with cessation of smoking should be done. Use of ACE inhibitors and ARB's is advocated even for normotensive microalbuminuric as microalbuminuria is associated with other cardiovascular risk factors like insulin resistance, lipid abnormalities, increased coagulability and endothelial dysfunction.

The treatment strategies for advanced renal disease are dietary modification (low protein and potassium restricted diet), phosphate binders, calcium maintainers like 1,25 Vit D, diuretics like metolazone or frusemide for high BP or edema, potassium monitoring and use of sodium bicarbonate for mild acidosis. Referral to a nephrologist should be considered for serum creatinine of >2mg%. For end stage renal disease, transplant should be preferable to dialysis, although the latter is also a viable alternative.

**Dr. Om. P.Ganda**, (Joslin Diabetes Center, Boston, U.S.A) discussed about "lipid subfractions and their role in cardiovascular disease". The mystery of premature and accelerated process of atherosclerosis in diabetes remains unsolved. The factors underlying accelerated atherogenesis in diabetes are insulin resistance, diabetic dyslipidemia and hyperglycemia causing damage through glyco-oxidation, sorbitol / myoinositol pathway and diacylglycerol / PKC activation, oxidative stress, hemorrheological alterations like increased platelet aggregation, increased fibrinogen, reduced fibrinolysis, increased PAI-1 and endothelial dysfunction.

Stepwise selection of risk factors for coronary artery disease in Type 2 diabetes in UKPDS study have shown that high LDL cholesterol and low HDL cholesterol are greater risk factors than HbA<sub>1c</sub>, blood pressure and smoking. United Kingdom Prospective Diabetes Study (UKPDS) has also shown that elevated LDL cholesterol, low HDL cholesterol, hypertension and hyperglycemia were identified as the modifiable major risk factors. Multiple mega trials with HMG-COA reductase inhibitors (statins) including 4S, CARE, LIPID, WOSCOPS, TEXCAPS/ AFCAPS and most recently, Heart Protection Study

(HPS) has clearly established the benefits of LDL cholesterol reduction in CVD outcomes (CAD and stroke). The subgroup analysis in most of these trials revealed similar positive benefits in patients with diabetes.

In diabetic patients, statins may not be able to correct all the abnormalities of dyslipidemia completely. The abnormalities unique to diabetes (particularly Type 2 diabetes mellitus) are increased small dense LDL, increased triglyceride rich particles (TGRP's) including VLDL and remnant particles, increased apo-B particles, low HDL and glycooxidation products of various apo proteins. Some studies suggest that apo-B or apo-B / apoA ratios may be better predictors of CVD risk than LDL cholesterol. The VA-HDL intervention Trial (VA-HIT) and Diabetes Atherosclerosis Intervention Study (DAIS) have shown the beneficial effects of fibrate (fenofibrate) in delaying the disease progression in a diabetic. The benefits and adverse effects of combination therapy for dyslipidemia's (adding niacin or fibrate to a statin) should be always borne in mind. The probable side effects could be increased risk of myositis and hepatitis (with niacin). More studies are needed for assessing the better outcome results with combination therapy.

In his second lecture, **Dr. F. Xavier Pi-sunyer**, spoke on the effective use of pharmacologic agents to reduce body weight. Reduction in body weight has been associated with reduced HbA<sub>1c</sub> levels in a diabetic. Even a mild reduction of 1.9% in body weight has been associated with a 0.4% reduction in HbA<sub>1c</sub>, while a modest reduction of 10% body weight reduces the HbA<sub>1c</sub> levels by 1.6%. Thus the plan to reduce body weight should be formulated by:

- a. Diet and exercise.
- b. Drugs
- c. Weight loss surgery

In U.S.A., anti-obesity drugs have been used at BMI is >30 and at BMI of >27 if associated with comorbidities like diabetes, hypertension and coronary artery disease. The weight loss surgery is being recommended at BMI of >40 and at BMI of >35, if associated with comorbidities. The anti-obesity drugs, if used should be continued till the results are obtained. At present two drugs available for long term use are sibutramine and orlistat. Sibutramine (a centrally acting drug) is a serotonin and

norepinephrine reuptake inhibitor in postsynaptic neurons which reduces food intake by enhancing satiety. The effects of sibutramine on glucose and lipid levels are related to weight loss. The usual dosage is 10mg / day (once a day). Though with >15 mg/day – better weight loss has been seen, the drug's usage is associated with increase in systolic blood pressure (4-5 mmHg) and increased heart rate (4-5 beats/min). The STORM trial has recommended that blood pressure and the heart rate should be monitored with sibutramine therapy. If BP is increased by >6 mm of Hg or the heart rate is increased by >4 beats / min, it is better to stop the drug. The other antiobesity drug is Orlistat which acts locally at G.I. tract. It competes with pancreatic lipase thus blocking the triglyceride breakdown and causes fat malabsorption. Fat absorption is reduced by 30% with Orlistat causing the weight loss. The drug should be given 3 times daily with meals. As it also block absorption of fat soluble vitamins, vitamin supplements are necessary. The side effects due to fat malabsorption are fecal urgency, fatty oily stools, flatus and oily evacuation with increased defecation. The GI side effects of Orlistat can be reduced by use of Psyllium with Orlistat. Apart from weight reduction, Orlistat also reduces LDL cholesterol by 16%.

**Dr. Martha Funnel**, in her second lecture talked about optimal strategies for diabetes self management education. Self management education continues to be an integral component of care for diabetic patients. Though there is a lot of improvement in diabetes care, there still exists a gap between promise and reality. Diabetes self management education is the key to closing that gap. In order to be effective, diabetes self management education must be evidence based, practical, proactive and collaborative. The future of diabetes self-management education depends on follow-up to sustain effects, integrate diabetes self management education into ongoing care, expand use and training of health professionals, expand outcome evaluation (costs, quality of life, long term outcomes) and to expand international efforts to promote quality diabetes self-management education.

In his second lecture, **Dr. Om P.Ganda**, discussed about the current status of management of diabetic dyslipidemia. The current recommendations for management of diabetic dyslipidemia are primarily based on the NCEP expert panel and ATP III reports. The goals in diabetic patients for lipids are:

- i. target primarily LDL cholesterol
- ii. As diabetes is a risk factor for coronary heart disease, the LDL cholesterol goal should be <100 mg%.
- iii. The therapeutic options are
  - a. If LDL cholesterol is 100 – 129 mg%, increase therapeutic life style changes; if uncontrolled, add drugs (statin / fibrate / niacin) to modify atherogenic dyslipidemia.
  - b. If LDL cholesterol is  $\geq$  130 mg%, simultaneously initiate therapeutic lifestyle changes and LDL cholesterol lowering drugs.
- iv. After LDL cholesterol goal is met, if triglyceride is  $\geq$  200 mg%, non HDL cholesterol <130mg%, becomes the target.
- v. Target triglycerides <150mg%.

The therapeutic life style modification for patient with diabetic dyslipidemia is weight reduction, physical activity and dietary modifications. Total fat should not exceed 25-30% of the total daily calorie intake. Other therapeutic dietary options include plant stanol / sterol (2mg/day), but they should not be given below the age of 25 years. Larger doses of fish oil should not be prescribed as they can worsen the beta cell function.

In the Heart Protection Study simvastatin v/s placebo was tried and it was clearly shown that a 40mg% reduction in LDL cholesterol resulted in 25% reduction in CHD, stroke, and other cardiovascular disease outcomes even if the baseline LDL cholesterol was <100 mg/dl. No significant side effects were observed. This trial provides evidence that statins have other beneficial effects on endothelial dysfunction, vessel wall inflammation, plaque stability etc. apart from their lipid lowering effects. Newer drugs in the pipeline are ezetimibe, a cholesterol absorption inhibitor and reovastatin, which can further help in management of diabetic dyslipidemia.

**Dr. David L. Horwitz** (Life Scan Inc., U.S.A) spoke about current and future trends in self monitoring of blood glucose. The advancements in the area of self monitoring of blood glucose are:

- a. Newer technologies wherein blood samples can be obtained from other than fingertips (alternative site testing – AST).

- b. Continuous monitoring of blood glucose.
- c. Non-invasive methods for glucose monitoring.

Alternative site testing like (arm and thigh) is made possible by systems that can test very small blood volumes (less than 2.5 microlitre). Available data indicate that AST is useful prior to meals, but not within 2 hours following meals, exercise or insulin injection. With increasing insulin doses and intensive therapy, blood sugar values related to meals and other events must be stored in a data box. Modern data processing and storage technologies offer the potential for summarization and display of large amounts of data in a form that may facilitate use of the data to monitor diabetes management.

Continuous glucose monitoring system is now widely being used as an adjunct to traditional self-monitoring of blood glucose (SMBG). It allows recognition of patterns of glycemic excursions that may not be evident when only a few measurements are made in a day, thus offering a better glycemic controls by understanding the real changes in blood glucose levels. Non-invasive techniques like gluco-watch are now available which measure interstitial fluid glucose through reverse iontophoresis. It should be remembered that interstitial fluid glucose value monitored by CGMS and gluco-watch lags blood glucose value by few minutes and while dose adjustments are made this fact should be kept in mind.

In his second lecture, **Dr. Vivian Fonseca**, discussed about the management of diabetic patients with multiple co-morbidities. Management of patients with multiple advanced complications can be extremely difficult. Diabetes complications themselves have an impact on the diabetes management, as the natural history of the disease has advanced to a stage of poor pancreatic function and severe insulin resistance leading to decreased efficacy of oral medications. Diabetic Nephropathy, Neuropathy, Retinopathy and the cardiovascular diseases are extremely common complications particularly in Type 2 diabetic patients.

The guidelines for the management of Diabetic Nephropathy are treatment of anemia by weekly subcutaneous erythropoietin injections, aggressive treatment of lipids & blood pressure, screening for cardiovascular disease, routine eye checkups and follow ups, dietary modifications (low protein, low

cholesterol, low potassium), maintenance of serum calcium and phosphorus levels and use of diuretics. Diabetic neuropathy is the commonest complication of diabetes and can result in amputations and autonomic disturbances. Use of proper foot wear and taking good care of feet and maintaining good glycemic control can help to prevent amputations.

Diabetic retinopathy is a preventable complication which can be detected early by fundus examination. It can be treated by better glycemic control, better blood pressure control, prevention of renal failure, and cessation of smoking. In the future protein kinase - C inhibitors may be of good treatment option. Cardiovascular disease is an extremely common complication particularly in Type 2 diabetes. It has been proved by the DIGAMI study that good glycemic control at the time of myocardial infarction and thereafter improves the prognosis. Insulin acts as an anti-inflammatory agent apart from acting as anti-hyperglycemic agents. Aggressive management of lipids, blood pressure are necessary in all the diabetics with CAD. Thus in managing a complicated diabetic patient, a team of specialists is required along with a Diabetologist.

In her second lecture, **Dr. Lois Jovanovic**, spoken about management of Gestational Diabetes. Gestational diabetes mellitus occurs when the diabetogenic forces of normal pregnancy are not counterbalanced by increased insulin secretion. The "Diabetogenic Forces" include increased calorie intake, increased adiposity, increased levels of placental hormones : (HPL and Progesterone) and maternal increase in Cortisol and Prolactin. BMI of > 24 kg/m<sup>2</sup> increases the risk of diabetes in women, 8% of pregnant population is having GDM. The prevalence of congenital malformations in a Type 1 pregnancy is 9% and that in type 2 pregnancies is 12%. With better glycemic control, the risk of congenital malformations can be significantly reduced.

The fourth international workshop on GDM has issued guidelines for screening. Random Blood Sugar should be checked after 50 grams glucose load and if values are <140mg%, no further testing is needed. If values are >140mg%, glucose tolerance testing should be done with 100grams glucose load to diagnose GDM. Screening test should be done at first trimester and subsequent tests should be done at the second and third trimesters. The usual prevalence

of macrosomia is 18% in uncontrolled diabetes mellitus, which can be brought down to 7% with good glycemic control. Even the frequency of caesarian section is reduced to 7%. The 1 hour post meal capillary blood glucose predicts the macrosomia best. In the third trimester, peak value of 110mg% is accepted. In a baby born to a mother with uncontrolled diabetes, the visceral fat deposition is increased even at the time of birth. Pregnancy potentiates the dawn phenomenon by increasing the hypercortisolemia, and hence the carbohydrate content of breakfast should be <33%. The euglycemic diet in pregnancy includes 30 kal/kg/day with a 40% carbohydrates diet. The meals size should be small and taken at frequent intervals to minimize the postprandial rise in blood sugar levels.

Exercise causes uterine contraction and causes fetal distress. Walking is permissible as it does not cause heart rate variability. Arm exercises can be allowed, as it helps in blood sugar stabilization and at the same time does not cause fetal heart distress. Oral hypoglycemic agents should not be used as they can cross the placental barrier and cause neonatal hypoglycemia and also increase the risk of congenital malformations. The glycemic control should be achieved by insulin / short acting insulin analogues. The aim of the management is to control the hyperglycemic peaks as it is important to reduce macrosomia and other complications during pregnancy. Thus, with a normal maternal blood glucose levels (i.e. pre prandial of <90mg% and 1 hour post prandial of <120mg%), a normal outcome is possible.

In his second lecture, **Dr. John Buse**, discussed about intensive management of type 2 diabetes. Patients with higher levels of blood glucose (i.e. fasting plasma glucose >200mg%), almost always require agents to increase insulin levels. When two drug therapies are inadequate, the issue arises whether multiple oral agents therapy is reasonable or whether the use of insulin is indicated as a matter of routine. Intensive management strategy aims at increasing insulin sensitization by diet exercise, glitazones and metformin. This regime minimizes the risk of hyperglycemia and weight gain. If the blood sugars are still not in the desired range, a secretagogue may be added (either sulphonylurea or glinides). When the glycemic control is still inadequate, insulin is needed.

The principle of combination therapy of insulin and OHA is to continue OHA as usual and add a single, evening dose of insulin and try to control the FPG in the reasonable range. This addition is limited by hypoglycemia (mid sleep, AM and pre-lunch) and weight gain. If even with this regime, the blood sugar are not controlled then to achieve a normal postprandial glucose value, pre-meal soluble insulin is added. Many type 2 diabetics patients eventually require more than twice daily injections. In this case, split mix insulins, multiple injections or even insulin pump therapy can be used. With the availability of insulin sensitizers and the availability of both long acting (glargine) and rapid acting insulin analogs (lispro), it appears that the majority of patients with Type 2 diabetes can achieve the same levels of glycemic control as laid down by the ADA.

**Dr. Richard Kahn** (American Diabetes Association, U.S.A) discussed about Diabetes Care in America over the last decade. Many studies like Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) have shown that improved diabetes care will greatly reduce the morbidity and mortality associated with diabetes. In addition, a wide variety of pharmaceutical agents that are effective in lowering blood glucose and blood pressure and in adjusting abnormal lipid levels are available. In addition, patients with diabetes have been given

substantial information on proper diabetes self management.

Despite all these efforts and tools, performance rates in the United States on process measures (e.g. eye exam, lipids & HbA<sub>1c</sub> testing), and outcome measures (eg.HbA<sub>1c</sub>, LDL-C, blood pressure levels) remain far from optimal. An analysis of the factors involved in achieving quality medical care reveals that patient characteristics such as age, duration of diabetes, educational level and care affected the results far more than the physician's knowledge and skill. Attempts to change patient behaviour will be essential in order to achieve optimal diabetes care end results.

In addition, to the above lectures, there were 14 Meet the Professor Sessions on topics such as type 2 diabetes in children and youth, insulin resistance, economic burden of diabetes, diabetic foot, diabetic retinopathy and nephropathy, autonomic neuropathy, intrauterine factors and development of diabetes, combination therapy of insulin and OHA, hypoglycemia, endothelial dysfunction, glucotoxicity and lipotoxicity, sexual dysfunction in diabetes, postprandial hyperglycemia and is cure of diabetes a reality. During these Meet the Professor Sessions, eminent Indian Diabetologist teamed up with US faculty and discussed these topics threadbare with a lot of audience participations.