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Diabetes in India-Its Profile and Magnitude in Comparison to the West

B.B. Tripathy. Postgraduate Professor of Medicine (Retd). SCB Medical College, Cuttack.

Epidemiology

Data on prevalence of diabetes was provided by a collaborative study sponsored by the ICMR in which 6 centres (Ahmedabad, Calcutta, Cuttack, New Delhi, Poona and Trivandrum) participated. Among subjects aged 15 years and above clinical diabetes and impaired glucose tolerance was detected in 2% among urban and 1.5% of rural populations. Diabetes was commoner in males than in females. Diabetes (0.48%) and impaired glucose tolerance (IGT) was detected in 0.9% of 2296 tribals living in Koraput district of Orissa.

Due to lack of longitudinal studies in any part of the country, no data is available on the incidence of diabetes.

Clinical Pattern

Classical insulin dependent Type-I diabetes is relatively uncommon in India as in other oriental nations including Japan. Further, a recent increase in the incidence of this type of diabetes in Western countries such as U.K. has not been noticed in this country inspite of special efforts to look for it at Madras and elsewhere. Reports from several parts of India have documented cases of ketosis resistant J-type or pancreatic secondary diabetes. As both these types more commonly affect subjects with poor nutritional status and occur in areas where undernutrition is widely prevalent, they have been classified as malnutrition related or Type M diabetes (WHO 1980).

Even among cases of non-insulin dependent Type-II diabetes, certain differences in the presenting features and incidence of complications are noticeable from those of the West. Preponderance of males, peak incidence about a decade earlier, lower incidence of obesity and a high proportion of grossly under-weight (lean) patients have been documented among diabetics attending hospital clinics in several parts of the Indian subcontinent. Of greater importance may be the lower incidence of coronary heart disease and possibly in consequence, higher incidence of K.W. syndrome. Symptomatic polyneuropathy appears to be more common and autonomic neuropathy less dangerous among our patients compared to those in the West. Mortality and morbidity in our diabetic population is higher from both pyogenic and tubercular infections. Hence there are wide differences in the relative incidence of causes of death between the two locations.

Health Care

At present about 5% of individuals over 40 years of age have diabetes or IGT. By 2000 A.D. the number of diabetics is likely to be doubled. To provide health for all, it is hoped that the centre and the states will soon plan to provide comprehensive health care for all patients of diabetes mellitus.

Aetiopathogenesis of Diabetes Mellitus

J. S. Bajaj. Professor of Medicine. All India Institute of Medical Sciences, New Delhi.

A major advance in our understanding of diabetes mellitus is the fact that it is not a single clinical entity, but a heterogeneous group of disorders with different underlying causes, although with a common diagnostic denominator namely, elevated blood glucose either in a fasting state or in response to a glucose challenge. Thus aetiopathogenesis has to be related to the current classification of diabetes mellitus.

Studies in identical twins have clearly shown the differential role of genetic factors. Concordance rate of IDDM in identical twins is 25-50% in various studies. Susceptibility to IDDM is conferred by genes in the HLA-D DR region of the major histocompatibility complex (MCH) on chromosome6. Genes in this complex control immune response. The trigger may be through a variety of factors including infections (viruses), toxins and chemicals. However, final pathway may be through immunogenetic factors which play a major role in IDDM, as evidenced by a lymphocytic infiltration of the islets and presence of circulating islet cell antibodies in the early stage of IDDM. A variety of such antibodies has been characterized. Recent studies indicate that the presence of such antibodies may precede the development of clinical diabetes mellitus. New technology such as allele specific DNA probes for gene mapping in the HLA-D/DR region, is likely to provide exciting information in the near future.

A relationship between obesity, carbohydrate dysmetabolism, and NIDDM is well recognised. A complete understanding of the pathophysiological interlinkage between these disorders has not yet emerged. NIDDM is characterized by a combination of abnormal insulin secretion and peripheral insulin resistance. The role of genetic factors is well demonstrated in NIDDM as shown by a concordance rate of 90-96% in identical twin studies. The characterisation of insulin gene in 1980 has accelerated the pace of research in identifying genetic marker (s) for NIDDM susceptibility. Although the observations regarding restriction fragment length polymorphism in the 5 flanking region of insulin gene on chromosome 11 has generated a major debate, the synthesis of abnormal mutant insulin(s) has been well documented to be the cause of NIDDM only in a few cases.

Malnutrition related ketosis resistant diabetes as seen in developing countries is receiving major attention by research investigators, and the role of protein deprivation in early infancy, along with dietary toxins is being increasingly recognised.

Insulin Degradation

D.D. Bansal. Reader, Deptt. of Biochemistry. Punjab University, Chandigarh.

Insulin degradation is a complex and incompletely understood process at present. Most of the body tissues have been shown to degrade insulin. However, in terms of overall clearance and metabolism, the liver is responsible for more than half of the total insulin degradation, with kidney responsible for most of the rest. The peripheral tissues, fat and muscle, probably degrade the remainder of the insulin in the body. These peripheral tissues may serve as a reservoir for insulin, presumably by the hormone binding reversibly to membrane receptors.

At the cellular level, in most tissues, insulin degradation is initiated by the hormone binding to specific receptors. The hormone receptor complex is processed, including internalization and degradation of at least some of the hormone receptor complexes. The enzyme or enzymes involved in the degradation process have not been fully established but three systems have been implicated: insulin protease, glutathione insulin transhydrogenase (GIT) and lysosomal enzymes.

The physiological role of insulin degradation by insulin sensitive tissues has not been established. Several possibilities exist, including the possibility that metabolism of insulin is required to produce some of the effects of insulin, perhaps by releasing an active fragment. It has been shown that when receptor is occupied by insulin, there seems to be release of a 1000-1500 dalton heat-labile factor which is responsible for some of the actions of insulin. Another possibility is that insulin degradation is required to terminate insulin action.

Insulin degradative process is affected by age, sex and physiological state of the animal species. Experimental diabetes in different species of animals has been shown to affect insulin degradation; however, these studies are not conclusive.

Insulin and Pro-insulin Dynamics in Evaluation of B-cell Activity in Health and Diabetes

R.J. Dash. Professor and Head, Deptt. of Endocrinology. Postgraduate Institute of Medical Education & Research, Chandigarh.

The normal beta cell secretion includes insulin (IRI) and C-peptide in equimolar concentrations, and 2-5 % pro-insulin. Insulin and proinsulin circulate in blood and is measured collectively as immunoreactive insulin (IRI) using radioimmunologic procedures. Proinsulin like component (PLC) is separately quantitated using sephadex chromatography.

While serum can be processed directly for quantitation of IRI and PLC, acid ethanol extraction is essential prior to their measurement in pancreatic tissues. IRI and PLC are detectable in the pancreas of 6-8 week fetuses. The pancreatic extractable IRI increases progressively upto 34 weeks. In nondiabetic adult pancreas, no significant difference in extractable IRI has been observed between the tissue segments obtained from head,

body and tail. In type II diabetics IRI was extractable from the pancreas but 14 it showed decrements with increase in duration of the disease. In type I diabetics however, pancreatic extracts yield very little of IRI. Circulating IRI measurements in nondiabetic subjects show progressive rise following oral glucose load with peak values corresponding to peak glucose levels. PLC however is highest in the fasting state but it decreased in proportion to IRI with blood glucose increments. While IRI increments following glucose load are similar to those following cooked rice load, those following ingestion of legumenous diets (Channa Dal, Rajmah etc.) are significantly lower (proportionate to increments in blood glucose).

Circulating IRI increments in secondary sulphonylurea failure patients are lower in comparison to those in the responder group, suggesting inadequacy of insulin secretory reserve as the cause of failure.

Insulin Resistance

K. Nalini. Assistant Professor. Deptt. of Endocrinology. PGIMER. Chandigarh.

Insulin resistance is defined as a condition in which greater than normal amounts of insulin are required to elicit a quantitatively normal response. Conventionally the term is used when the insulin requirement exceeds 200 units per day for two days or more in the absence of ketoacidosis and infection. But a state of relative insulin resistance is considered when there is unexplained increase in insulin requirement by 50 percent.

Exogenous insulin therapy leads to development of insulin binding IgG antibodies and in 0.1% of patients the antibody titre rise is significant enough to produce immune insulin resistance. Hyperinsulinaemia due to hyperphagia in obesity down regulates insulin receptors producing an adaptive insulin resistance. Alternatively intracellular abnormalities like increase in fattyacids leading to defective glucose utilisation can act as a primary post-receptor abnormality, producing hyperinsulinaemia. Obesity and related hyperinsulinaemia contribute to insulin resistance in 80-90% of type 1I diabetics. In addition, a primary B cell defect either due to genetic abnormality (glucose receptor defect) or B-cell exhaustion produces inappropriately low stimulus induced insulin secretion. Thus the basal hyperinsulinaemia coupled with impaired glucose induced insulin scretion produces cellular insulin resistance in type II diabetics. Extreme insulin resistance in association with acanthosis nigricans with hyperandrogenaemia (Type-A) and auto-immune manifestations (Type-B) is a well recognised clinical entity. Leprechaunism, lipoatrohic diabetes, Alstrom syndrome and ataxia telangiectasia are listed as rare causes of insulin resistance.

Insulin resistance in Type II diabetes responds to weight reduction, exercise, dietary modification with high carbohydrate, high fibre diet and newer generation sulphonylureas. For immune insulin resistance, newer insulin (purified, sulphated, human) and high dose prednisolone are being used with variable response.

Microangiopathy in Diabetes

M.M.S. Ahuja. Prof. & Head. Deptt. of Endocrinologv Metabolism & Diabetes. A.I.I.M.S. New Delhi.

This presentation will cover three aspects, epidemiology, organ involvement and newly recognized pathogenetic mechanisms.

A) Epidemiological features

Prevalence studies in the last decade have indicated that Asiatic populations, considered to have low risk profile for vascular disease (low BMI, low blood pressure and low serum lipids), however, suffer from microvascular disease related to diabetes in the same quantum or even in greater proportion and this too at a younger age.

Analysis of data from W.H.O. multinational study on vascular disease providing information on Asiatic countries (India, Japan, Chinese (H.K.) relates microangiopathy inversely with age of onset of diabetes and type of treatment.

B) Organ Involvement, Early Clinical Recognition

Earlier, specific lesions were recognized in retina, renal glomerulus, skin and muscle capillaries or conjuctiva and the lesions were related to pericytes, mesangium or capillary basement membrane. The glycosylated protein metabolism was considered predominantly contributory for the pathogenicity.

In recent times, there is increasing recognition of microangiopathy also involving the cardiac muscle, brain or neuronal tissues. There is consideration that local metabolic events or peripheral tissue mechanisms have significant role in some of the functional organ involvement in diabetes.

Clinically early recognition of microangiopathy by retinal fluorophotometry or microalbuminuria is being assessed.

C) Newly Recognized Pathogenetic Mechanisms

Conventionally, diabetic microangiopathy is related to the type of diabetes, its duration, glycaemic control, hypertension, or DR antigens.

Recent experimental and clinical evidence brings forth for consideration the role of :

(i) rheological factors (ii) haemodynamic factors (iii) tissue growth factors

in modulating the presence of specific microvascular disease in diabetics.

Reversibility of microangiopathy in experimental models or clinical experience seems related to present severity of tissue alteration : functional recovery is possible in

permeability or immunopathological alterations but not once sclerosis (proliferative changes in retina or mesangial proliferation in glomerulous) has set in.

Diabetes, Hyperlipemia and Immunological Trauma in the Development of Macro and Microangiopathy-An Experimental Study

R.N. Chakravarti. Prof. & Head. Deptt. of Experimental Medicine. PGIMER. Chandigarh.

Diabetes mellitus is known to promote atherosclerosis and precipitate complications such as acute myocardial infraction and peripheral arteriopathy. To elucidate the mechanism of these lesions, both clinical and experimental research have been undertaken. It appears that several factors combine to produce the macro and microvascular complications of diabetic individuals. Among these deranged carbohydrate metabolism, hyperlipemia, abnormal glycoprotein metabolism and certain immunological factors play a major role. In our laboratory an attempt has been made to reproduce same of these changes in a primate model. Diabetes has been induced in male rhesus monkeys by alloxan injection and the animals have been studied for periods of more than 12 months. The diabetic monkeys developed severe hyperglycemia and glycosuria with marked elevation of serum lipids.

To induce immunological trauma, some of the diabetic monkeys were subjected to bilateral vasectomy which caused the formation of sperm antibodies and possibly circulating immune complexes. Immunofluorscent studies revealed deposition of IgG and C_3 in the kidneys of diabetic vasectomized monkeys but not in sham operated non-diabetic monkeys.

Aortic tissues also showed the immunoglobulins but only in a few monkeys. Pathological study revealed a marked and significant increase of coronary and renal atherosclerotic plaque score in diabetic vasectomized monkeys as compared to sham vasectomized non-diabetic monkeys. Significant changes however, were not observed in the aortic plaque and cerebral artery plaque scores.

These studies have been extended now on streptozotocin induced diabetes in primates. Measurement of blood glucose and glycosylated haemoglobin is being carried out in these animals. The studies are planned to evulate whether controlled diabetics have lesser micro and macrovascular disease than those with uncontrolled severe diabetes.

Diabetes and the Heart

P.L. Wahi. Prof. & Head. Deptt. of Cardiologv. PGIMER. Chandigarh.

Diabetes Mellitus (DM) and coronary artery disease (CAD)

During the last 100 years the importance of DM and CAD in preinsulin era was only 2% (many would die of other fatal complications of DM) whereas after the intro-duction of insulin death rate due to CAD in diabetics rose to 45-70 % (because they live long and avoid other complications). Approximately a third of IHD patients show evidence of diabetes. In the diabetic population 15% have IHD on routine examination

and another 15% can be picked up on Master's two step Exercise test. In the west similar figures are reported (20.66%).

The diffuseness of disease in coronary vasculature is observed more in IDDM but not in NIDDM. However, diabetics are more prone to left mainstem disease. The incidence of silent MI and angina is much higher in diabetics (24.42%). Out of all diabetics 20% die of AMI and 13% die of CCF. The incidence of post MI complications and the recurrence rate is higher. The management of diabetics with CAD is similar to non-diabetics except that they need closer supervision for a longer period.

Diabetic cardiomyopathy

In 1972 on the basis of autopsy studies, this new entity was defined. Framingham study showed a 4 to 5 fold increased risk of CCF unrelated to CAD in patients with diabetes. This was more noticeable in patients with IDDM. The type of therapy (insulin or no insulin) was found to be of no importance. Many animal experiments and autopsy studies revealed deposition of PAS positive glycoprotein in myocardium and interstitium as the cause of cardiomyopathy. Invasive studies have shown decreased ejection fraction and cardiac output. Noninvasive studies show involvement of systolic and diastolic functions of the heart. LV dysfunction in diabetes may be subclinical, overt or gross. The abnormal LV function correlates well with increased glycosylated haemoglobin levels. Some of these abnormalities are reversible by good diabetic control. Though the exact pathogenesis of cardiomyopathy is not known, metabolic, microvascular and myopathic factors are implicated. Associated hypertension adds to the LV dysfunction and aggravates the complications. Hypertension is seen in diabetics to the tune of 40-80%. As regards autonomic neuropathy, the parasympathetic function is affected first, which leads to loss of sinus arrhythmia. Sympathetic dysfunction leads to decreased postural alterations in blood pressure.

Infants born of diabetic mothers have cardiomegaly (50%) and reversible hypertrophic cardiomyopathy as a result of maternal hormonal influence.

Diabetic Retinopathy-Current Concepts

O. P. Ahuja, Professor, Retina Service. Institute of Ophthalmology. Jawahar Lal Nehru Medical College, Aligarh University College, Aligarh.

The reported incidence of diabetic retinopathy varies from 33% to 50%. In general, the frequency of retinopathy, in both sexes rises with age, reaching a peak at 50-70 years. While the frequency of retinopathy among the younger individuals rises from 50% after 10-12 years of diabetes to 75% or more after 20 years, it appears following a shorter duration of the disease amongst late age onset diabetics.

Pathogenesis

Basic factors involved in pathogenesis are ischaemia and hypoxia of the retinal tissue brought about by several biochemical and anatomical changes in the retinal circulation as a result of faulty metabolism in diabetes.

Classification

The lesions of diabetic retinopathy are multiple, pathogenesis is obscure, and the course variable. This has resulted in multiplicity of classifications.

It has been presumed, for the sake of simplicity, and to a good extent with clinical justification, that one stage of disease leads to the other. These stages can be remembered easily by the acronym 'VAHEX' (V, venous dilatation; A, microaneurysm formations; H, haemorrhagic activity; E, retinal oedema; and X, exudate formation).

Photocoagulation

There has been a considerable improvement in the overall prognostic outlook of diabetic retinopathy following the use of photocoagulation by Xenon arc and later by lasers of different types. This has been particularly so in eyes with proliferative retinopathy and in selected cases of diabetic maculopathy. The general basis of this treatment relates to the pathogenesis of the disease process, i.e. microinfarcts leading to the development of hypoxic areas in the retina which are responsible for the liberation of a vasoproliferative factor. Theoretically thus, if the liberation of the vasoproliferative factor can be reduced by destruction of hypoxic area, the stimulus to neovascularisation will be diminished, and the neovascular tuffs will regress.

Vitrectomy

In general, the aim of vitrectomy is to clear vitreous of all its opacities, to reduce or eliminate vitreous traction, and glial attachments or membranes on the retina, thus normalizing the vitreous cavity. There is also evidence to believe that a release of traction or a complete posterior vitreous detachment tends to cause regression of the proliferative disease.

Pituitary Ablation

Hypophysectomy has been noted to improve many lesions of diabetic retinopathy as assessed by serial colour photography, visual acuity measurements and fluorescein angiography. The rationale of this procedure is based on the opinion that growth hormone, secreted by the anterior pituitary is aetiologically related to the development of diabetic retinopathy.

Diabetic Nephropathy-An Overview

B.K. Sharma. Prof: & Head. Deptt. of Internal Medicine. PGIMER. Chandigarh.

Diabetic nephropathy is defined as a complex disorder resulting primarily from an alteration in glomerular capillaries due to the diabetic state. It is responsible for renal damage in the majority of diabetics.

Pathology of Diabetic Nephropathy

a) Glomerular lesions : (i) difiuse intercapillary glomerulo-sclerosis, nodular glomerular sclerosis, (ii) hyaline cap. (iii) capsular drop.

b) Arteriolar lesions : (i) Hyaline thickening of afferent and efferent arterioles, (ii) accelerated atherosclerosis of renal arteries and its branches, (iii) degeneration of J. G apparatus.

c) Tubulo-interstitial lesions : Interstitial infiltrates, gylcogen deposits, vacuolisation of tubular cells and thickening of tubular basement membrane.

d) Electron-microscopic changes : Mesangial expansion, thickening of GBM, obliteration of epithelial foot processes.

e) Immunofluorescence : Linear deposit of IgG and albumin along the GBM and TBM and C_3 in some cases, absence of mesangial staining.

Clinical Spectrum of Diabetic Renal Disease

The various stages in diabetic nephropathy are well known (Stage I to stage V)

Although the incidence of asymptomatic bacteriuria is increased in diabetics, the incidence of pyelonephritis is the same as in non-diabetics. One fourth of the episodes of pyelonephritis lead on to acute papillary necrosis. These infections do not correlate with the control or duration of diabetes. The bacteriological profile of UTI is same as in non-diabetics.

Management of Diabetic Nephropathy

The following are the principles of management in diabetic nephropathy :

1. Medical control

Strict euglucemia through the use of continuous subcutaneous insulin infusion (CSII) and insulin infusion pumps have been shown to reduce the GFR and RPF in stage-I. A strict euglycemic control in stage-II and at the onset of stage-III is helpful. In stage-IV & V blood sugar control does not have any effect on progression of the renal disease.

2. Treatment of hypertension

Hypertension usually appears in stage-III and worsens through subsequent stages. Strict control of B. P. decreases proteinuria and prevents decline in renal function at all stages of diabetic nephropathy.

3. Collaborative planning

As the patient with diabetic nephropathy has serious extra-renal problems like retinopathy, IHD, peripheral vascular disease etc., a collaborative planning by all specialists involved in the case is mandatory.

4. Conservative management of renal failure

i) Diet : Modification needs to be imposed from the early stages and includes unrestricted calories with 55% contribution from carbohydrate and a protein intake of 1 gm/kg/day.

ii) Salt restriction, diuretics and drugs for hypertension as required.

iii) The preferred antidiabetic drug is plain insulin. Long acting insulin and oral drugs are to be avoided.

5. Renal replacement therapy

Dialysis or transplantation are to be planned at an earlier stage than in a nondiabetic preferably at a creatinine clearance of 12-l5 ml/min, as the patients are symptomatic at an earlier stage and retinopathy tends to progress fast with advancing nephropathy. The choice of procedure among haemodialysis, peritoneal dialysis continuous ambulatory peritoneal dialysis (CAPD) and renal transplantation depends upon availability of facilities, economic factors and the presence of other complications.

Changing Concept of diet in Diabetics

J. B. Dilwari. Associate Prof. & head. Deptt. Hepatology. PGIMER. Chandigarh.

An ideal diet in a diabetic is one that results in :

a) normal body weight.
b) euglycemia.
c) normo-lipidemia.
d) normal insulin levels.
e) reduced dosage of drugs/insulin when administered if necessary.

Basal calorie requirement would be 22 Kcal/Kg. An addition of 35%, 50% and 100% of the basal calorie requirement would be needed for mild, moderate and severe form of physical activity respectively.

Distribution of Calories

Contrary to previous recommendation of a low carbohydrate diet in diabetes comprising only 40% of the total calculated calories, the present trend is towards a high carbohydrate diet containing 50% to 75% of the total calories; fat should be less than 30% of total calories, while the in remaining calories can be from proteins.

Protein

Dietary protein must be adequate in quantity and quality to maintain synthesis of body proteins and other nitrogen containing substances.

Fats

Small amounts of the essential fatty acids, linoleic acic and arachidonic are probably required in adults as well as infants. The total dietary fat intake should be restricted to 30% of the total calories, the saturated fat intake being less than 10% and total cholesterol intake not exceeding 300 mg/day.

Carbohydrate

Although the controversy regarding the amount of carbohydrate (high carbohydrate - 60%) required for the diabetic diet is settled, the nature of the carbohydrate to be given is not clear. The problem centres around two main aspects : refined versus crude carbo-hydrate.

Refined vs Crude Carbohydrate

A comparison of meals containing 30gm of sucrose or 30g of starch in Type-I diabetics showed no difference in mean blood glucose or mean glycemic excursion after starch meals than after sucrose or starch. Studies carried by us at PGI showed only minor difference between the peak blood glucose values reached when 75g of carbohydrate was given in the form of glucose and rice.

High Fibre Diets

The role of a high fibre diet in reducing the plasma glucose at alt points is well established. Studies carried at this Institute and by Jankins abroad have conclusively proved that it is the high viscous galactomannan containing polysaccharides naturally found in legumes and pulses, that produce the greatest fall in plasma glucose.

The mechanisms of reduction postulated include prolonging the gastric emptying time, viscous polysaccharides reducing the glucose transport across the intestinal muscosa by affecting the rate limiting unstirred layer.

Glycemic Index

Work done on the nature of the carbohydrate and the type of fibre most effective in reducing the blood sugar revealed that different carbohydrates produce varying blood glucose profiles in diabetic and non-diabetic individuals. The legumes showed more than 50% of reduction of the blood glucose values compared to rice, wheat and glucose, thus challenging the concept that the nature of the carbohydrate does not make a significant difference to the plasma glucose profile. Based on similar evidence, Jankins and colleagues formulated the concept of glycemic index. The area under the blood glucose response curve for each food, expressed as a percentage of the area, after taking the same amount of carbohydrate as glucose. Our work has shown glycaemic indices of Rice to be 89.67%, Wheat 87.86%, Green Gram 48.12%, Rajmah 29.55%, Bengal Gram 47.89%:

Alcohol

Small amounts of alcohol can be permitted with the knowledge that it yields 168

Cal/0z or 7 Cal/gram. In addition, it can precipitate lactic acidosis when given along with biguanides.

Artificial Sweeteners

Cyclamates or saccharine may permit the diabetic a deceptive sense of culinary joic de vivre when used in beverages, desserts or in carbonated drinks.

In conclusion the present concept of diet in diabetics is to have not only high carbohydrate diet (60% of total calories) but also a diet containing high fibre of galactomannan nature which will prevent high levels of blood sugar. Glycemic indices for all Indian foods should be evaluated and recommendations should hence worth be based on the same.

Newer Aspects of Oral Hypoglycemic Agents

J.K. Aggarwal. Reader in Endocrinology Institute of Medical Science. Banaras Hindu University. Varanasi.

The oral hypolycemic agents include first generation sulphonylureas (tolbutamide, chlorpropamide and acetohexamide) and second generation sulphonylureas (glybenclamide, glypizide, gliclazide, glybornuride) and biguanides (phenformin and metformin).

The second generation sulphonylureas are more potent weight for weight compared to the first generation ones. Both glybenclamide and glypizide are 450 times more potent compared to tolbutamide whereas glymidime is twice as potent as tolbutamide.

The sulphonylureas act by stimulating insulin release in type-II diabetics through an increase in beta cell sensitivity to glucose. They supress glucagon secretion. They also exert extrapancreatic effects like inhibition of glucagon stimulated hepatic gluconeogensis, increased muscle glucose uptake and increased insulin binding to cells due to increased receptor number, etc.

In addition, gliclazide has antiplatelet actions. It inhibits platelet adhesion and aggregation responses to stimuli. Since platelet function abnormalities are thought to play a role in the genesis of microvascular disease of diabetes, gliclazide has been evaluated for its effect on diabetic retinopathy and has been found useful. The biguanide drugs act similarly assulphonylureas; in addition they inhibit intestinal absorption of glucose and many other nutrients. Biguanides cause lactic acidosis and their use in patients over 60 years of age, in those with cardiac, renal or hepatic disease and in alcoholics is not recommended.

Indications for the use of oral hypoglycemic agents

These drugs are indicated when the age of onset of diabetes is above 35-40 years, when the patient is not obese, when the duration of diabetes is less than 5 years at the initiation of therapy, when the fasting blood sugar is less than 200 mg/dl and when the insulin requirement is less than 30 u/day.

Drug failure

Primary failure of respone to sulphonylureas occurs at rates of 5-40%. Secondary failure (that is, loss of efficacy after 6 months of favourable response) varies from 50-80% when the patients are followed upto 10 years.

Contra-indication to oral hypoglycemic agents

These drugs are not recommended in Type-I diabetes, in pregnancy, surgical operations, stress and when significant hepatic or renal diseases coexist.

Indigenous oral hypoglycemic agents

Innumerable indigenous drugs are suspected to have hypoglycemic action. But only a few have been subjected to detailed animal and human studies:

1. Mamordica Charantica (Karela) :-When an aqueous extract or the fried fruit was given to type II diabetics as a dietary supplement for 8 weeks, the glucose tolerance improved. In experimental studies, normal rats have shown a hypoglycemic response to Karela.

2. Pterocarpus Marsupium (Vijayser) :-An extract of the bark of this tree is known to have hypoglycemic effects. In one study an ethanol extract of the bark caused pancreatic beta cell regeneration in alloxan diabetic rats.

3. Melia Azadirachta (Neem) :-Oil of neem seeds has been shown to have hypoglycemic effects.

Insulin therapy-recent advances

John Punnose. Senior resident, Deptt. of Endocrinology. PGIMER. Chandigarh.

Conventional insulin therapy is known to be associated with problems of immuno-genicity due to contaminants, intermediate products producing resistance, lipodystrophy and various allergic manifestations. Moreover, uniform tight control is difficult with multiple subcutaneous injections. Great progress has been made recently in purification of insulin preparations by sephadex chromatography which excludes large mol. wt. aggregates and by ion-exchange chromatography which eliminates insulin sized particles. Also, efforts are being made to commercialise homologous human insulin by recombinant DNA technique.

Newer insulin delivery systems

The advent of pumps for the management of Type-I diabetes has as its physiological basis the simulation of basal insulin delivery by the continuous subcutaneous infusion of small amounts of regular insulin throughout the day and night.

Open top pumps (portable)

Portable pumps comprise of an etectromechanical device from which insulin is deli vered through a plastic cannula to a subcutaneous needle. None of the currently

available portable devices has a glucose sensor adjustment and blood glucose control requires self monitoring of blood glucose.

Closed Loop Pumps

Presently available closed loop device (Biostator) consists of a glucose sensor system, a computer programmed to calculate the amount of dextrose and insulin to be infused by insulin pump and a printer that provides a minute by minute record of the blood glucose concentration.

Recent Trends in Management of Diabetic Ketoacidosis (DKA)

S.K. Garg. Lecturer, Deptt. of Endocrinology. PGIMER. Chandigarh

DKA is defined as the profound alteration of metabolism due to insulin deficiency resulting in hyperglycemia, increased lipolysis, ketogenesis, acidosis and intra and extra-cellular water and electrolyte depletion.

Management

The key to effective management of DKA is prompt correction of fluid and electrolytes. Patients generally require 4-8 litres of fluid or even more in the first 24 hours. Use of central venous pressure monitoring especially in the elderly, is recommended. Normal saline is the infusate of choice unless the serum Na+ at the start of therapy is more than 155 mEq/litre. In such a situation 0.45% NaCI solution may be used.

Usually K+ is instituted at the start of therapy at the rate of 20-30 mEq/hr and the dose is changed as per serial measurements. Phosphate salt of K+ is preferred to chloride salt as it helps in restoring the PO4 deficit too.

Phosphate deficiency occurs in DKA due to increased tissue catabolism, impaired glucose utilization and cellular phosphorus uptake and increased renal excretion due to metabolic acidosis. But only about 11 % have low serum PO_4 at the time of diagnosis. Serious disturbances in tissue oxygenation occurs when plasma PO_4 is less 0.1 m Eq/dl. PO_4 can be given orally or intravenously as potassium salts. Routine use of PO_4 is controversial as regards the final outcome of DKA therapy and is deferred because of the danger of inducing serious hypocalcemia.

Routine use of bicarbonate in the treatment of DKA is contraindicated. Rapid restoration of blood pH by institution of I.V. HCO_3 can be hazardous. There may be occurrence of paradoxical CNS acidosis, as CO_2 crosses the blood-brain barrier freely when compared to HCO_3. It is recommended only if pH is less than 6.9 and plasma HCO_3 levels are less than 7.0 m Eq/L or there is associated lactic acidemia which is very difficult to ascertain in the presence of DKA. The correction of acidosis is done up to pH of 7.l only. The occurrence of rebound alkalosis in such cases is significantly higher.

1. Correction of Hyperglycemia

High dose insulin therapy is no longer practised because of its drawbacks like hypokalemia, late hypoglycaemia osmotic disequilibrium, hyperlactatemia, hypophosphatemia and hypomagnesemia.

Maximal rates of fall in blood glucose concentration and transport into the isolated forearm in normal and diabetic subjects is obtained with plasma IRI levels between 20-200 micro unit/ml, which can be achieved with infusion of insulin of 1.3-10.8 units/hr.

Route of Administration of Insulin

Presently, the widely practised regimen of intraveous insulin therapy is 4-5 units/hr in adults and when blood glucose falls below 250 mg/dl, the infusate is changed over to 5% dextrose and the rate of insulin infusion is decreased to 2 units/hr. If there is no significant fall in blood glucose after one hour of treatment, the amount of insulin per hour to be infused is doubled.

Sexual Dysfunctions in Diabetes Mellitus

Brig. Y. Sachdev. Deputy Director of Medical Sciences. Head Qrs. 16 Corps. 56 APO.

Diabetes mellitus is probably the most common organic cause of sexual dysfunction in male patients. The sexuality of women is much less affected and they are less likely to have sexual problems.

In male diabetics, the sexual problems caused by diabetes mellitus may be divided into two main groups:

a) Non-specific dysfunctions which are due to metabolic disorder and are attributed to lethargy, fatigue etc associated with hyperglycaemia.

b) Specific, organically determined sexual dyfunetions which may be sub-divided into :

1. Erectile failure
2. Ejaculatory dysfunctions
3. Disturbed spermatogenesis
4. Decreased libido

Etiopathogenesis of these disorders is still debated. Vascular, neurological, endocrine, and other physical factors are considered to be responsible. However, psychogenic factors also contribute to a varying degree.

Besides improving metabolic control of diabetes, general nutrition of the patient, review of the drug therapy, avoidence of alcohol, daily regular exercises and sex education, the role of implantation of synthetic penile prostheses and other surgical interventions may prove useful. In cases of ejaculatory infertility, artificial insemination may have to be resorted to with due precautions:

In females, proper diabetic control, attention to contributory physical and psychological factors, variations in sex postures and sex education may be enough to improve their sexual function.

Problems of Pregnant Diabetic

Lt. Col. M.M. Gupta. Command Hospital. Pune.

In normal pregnancy, metabolic and endocrinal changes take place in the mother in order to supply adequate nutrients to the growing foetus. Aminoacids and glucose cross the placental barrier to reach the foetus but maternal insulin fails to cross the placental barrier. Due to increase in the secretion of human placental lactogen and cortisol during pregnancy, the glucose tolerance is slightly impaired in pregnant women but this is met with secretion of extra insulin which is within the reserve capacity of the normal beta cells of the pancreas.

Effect of Diabetes on Pregnancy

a) Maternal complications : These include urinary tract infection, preclampsia and hydramnios.

   1. Urinary tract infection is usually due to E. Coli and this infection must be treated promptly.

   2. Pre-Eclampsia (defined as albuminuria & hypertension) is 5-l0 times more common in diabetics than nondiabetics. It contributes to perinatal mortality. The incidence is much less in well controlled diabetics than poorly controlled diabetics.

   3. Hydramnios is found in 5-20% cases of diabetic pregnancy. The incidence is higher in uncontrolled diabetics. Foetal anomaly is often associated with hydramnios. Ultra-sonography should be undertaken in such cases as it helps in defining foetal malformations.

b) Foetal Complications :

   1. Unexplained intra-uterine feotal death remains the main problem in pregnant diabetics. The incidence is high if the patient develops diabetic ketoacidosis or pre-eclampsia. Hyperinsulinemia in foetus and placental insufficiency have been incriminated in its pathogenesis.

   2. Macrosomia may indicate poor diabetic control resulting in foetal hyper-insulinaemia due to over stimulation of B-cell of pancreas by hyperglycaemia.

Hyperinsulinaemia in turn stimulates the release of growth hormone from foetal pituitary gland. Rarely, macrosomia may occur despite adequate diabetic control.

c) Neonatal complications :

Perinatal mortality and morbidity are considerably increased in new borns of diabetic mothers. Jaundice, respiratory distress syndrome and birth trauma due to macrosomia are not infrequent, Jaundice can be managed with phototherapy. Respiratory distress syndrome is related to the immaturity of lungs. Delivery at full term almost eliminates this life-threatening syndrome. Hypoglycaemia, hypocalcaemia, and acidosis are other biochemical abnormalities frequently seen in such cases.

Glucose Intolerance in Pregnancy

V. Seshiah. Professor of Diabetology. Madras Medical College. Madras.

Carbohydrate metabolism in the feto placental maternal unit is discussed under the following heads :

1. Fuel metabolism in normal pregnant state.
2. Pathogenesis of glucose intolerance developing during pregnancy.
3. Implications of the changes in fuel metabolism during pregnancy.

(1) *Fuel metabolism in normal pregnant state :* The metabolism is altered during pregnancy and the changes brought about by the conceptus are as follows:

a) Placental enzymes like insulinase break down the maternal insulin

b) placenta is an endocrine organ albeit temporarily elaborating contra insulin hormones (Oestrogen, progesterone, human placental lactogen) that blunt insulin action.

c) maternal fuel utilisation by the foetus is persistant, irrespective of maternal meal eating.

a) Fuel metabolism during the fed state : the levels of insulin as well as glucose following an oral glucose load during the 3rd trimester of pregnancy are higher and more prolonged than during immediate postnatal period and glucagon levels are suppressed by facilitating anabolism.

b) Fuel metabolism during fasted state : In the fasted state there is a lowering of plasma glucose in the mother due to the continual removal of glucose by the foetus. It is also attributed to substrate deficiency syndrome i.e. the inability of the glucogenic precursors to maintain the plasma glucose at nonpregnant level.

This results in rapid diversion of maternal metabolism to ketogenesis leading on to a state of accelerated starvation.

Therefore, facilitated anabolism in the fed state and accelerated starvation in the fasted state characterise the maternal fuel adaptive changes during pregnancy.

The hormonal and metabolic milieu of the first half of pregnancy is characterised by facilitated anabolism under insulin action.

(2) *Pathogenesis of glucose intolerance developing during pregnancy*: Genetic factors: The relative importance of genetic factors have not yet been established. Increasing maternal age and obesity have been identified as significant contributing and complicating factors :

Gestational factors :

a) Islet secretion : As a group, gestational diabetics manifest a sluggish early insulin release during 100 g OGTT even when integrated 3hr insulin areas are normal.

b) Insulin resistance and hormones of gestation : In about 20% of gestational diabetics sluggish early insulin secretion cannot be demonstrated. It is tempting to speculate that in these individuals atleast there is an increased elaboration of and/or heightened sensitivity to one or more of the gestational hormones leading to resistance to insulin action. Indirect evidence of resistance to insulin action are available. Further when gestational diabetics who had reverted to normal glucose tolerance postpartum and normal pregnant women were pretreated with prednisolone or HPL in the postpartum period, the former failed to increase plasma insulin levels above those in the latter despite greater hyperglycaemia. Thus the subjects had limited ability to secrete insulin which, is responsible for the development of glucose intolerance during pregnancy.

Implications of the changes in fuel metabolism during pregnancy : If hyperglyceamia is present during the first trimester of pregnancy when organogenesis takes place congenital malformations occur. If they are to be avoided, the control of metabolic fuels should commence before conception.

In gestational diabetics macrosomia results if maternal hyperglycaemia is not controlled during the 3rd trimester of pregnancy. As the foetal pancreas responds to glucose stimuli only by 32nd week, hyperglycaemia induced hyperinsulinism results in foetal macrosomia if tight glycaemic control is hot maintained at that time.

Management of Diabetes Mellitus in Pregnancy

Col. M. C. Srivastava. Consultant Diabetologist. MCR Hospital. New Delhi

Pregnancy complicated by diabetes mellitus is a challenge to the diabetologist, the obstetrician and the neonatologist.

Glucose crosses placenta by facilitated diffusion i.e. certain amount of glucose will cross the placental barrier irrespective of maternal blood glucose levels. Insulin however does not cross the placenta. Fetus receives a constant supply of maternal glucose but not maternal insulin. In normal pregnancy maternal blood glucose levels rarely exceed 100 mg% except during a short period after meals. Fasting blood glucose levels range from 60 to 80 mg%. In a diabetic pregnancy, since the maternal blood glucose levels are higher, fetus also remains hyperglycemic. Specially in the later stages of pregnancy when fetal islets become responsive to hyperglycemia both hyperglycemia and hyperinsulinemia result in macrosomia of fetus, although other functional maturity greatly lags behind:

Diagnosis and early Detection of Diabetes

Since 90% of diabetes in pregnancy is of the gestational type, more emphasis should be laid on early detection of diabetes in pregnant women. In those having family history of diabetes, history of unexplained still birth, malformed infants; birth weight over 4 kg. various screening tests have been advocated. Patients must be tested for blood glucose after 1 hour of ingestion of 50g glucose at the first antenatal check up and at 28 weeks: If the levels are more than 130mg%, a GTT should be done. The recommended blood glucose values of oral GTT are : F 90; 1 hr 195; 2 hr 145, 3 hr 125mg percent. If any two values are abnormal, diagnosis of diabetes should be considered.

Management of Pregnant Insulin Dependant Diabetic Patient

Certain special considerations have to be followed in managing the pregnant insulin dependant diabetic patient. The mother needs extra diet both calorie and nutrients to account for the needs of fetus. To avoid wider fluctuations of blood glucose levels, the food intake should be split and given more frequently. It is judged by regular weight gain and adequate development of fetus. Normoglycemia round the clock throughout the pregnancy can be achieved with multiple doses of regular or regular+ NPH insulin according to individual needs. In the first trimester the insulin requirements may increase, settle down in the mid 2nd trimester but definitely increase in third trimester: A more frequent self monitoring of blood glucose and minor adjustment of insuiin dose-by the patient herself significantly improves the outcome. During labor and delivery maternal hyperglycemia may add the risk of fetal hypoglycemic complications hence more vigourous efforts are required to maintain normoglycemia.

Assessment of Fetal well-being and Maturation

This is important for deciding the time of delivery. Fetal surveillance is important in third trimester, more intensively around 34 weeks. The Lecithin/Sphingomyelin ratio of amniotic fluid has been proven to be the most useful tool in assessing the production of surfactant by the fetal lung. Elective delivery should be planned for those women with diabetes complicated with vascular disease, patient in poor control, in patients with hypertension or history of still birth. Intensive care of neonate is essential for any emergency.

Diabetic Polyneuropathy

Upinder K. Dhand, Asst. Prof. Neurology, PGIMER, Chandigarh

Incidence & Definition

Incidence of neuropathy in diabetic patients has been variably reported from 0 to 93% probably because of lack of uniform diagnostic criteria. It is now generally agreed that the term diabetic neuropathy should be restricted to those patients who have to seek medical advice on account of signs and symptoms referable to peripheral nervous system. In a recent analysis of 570 patients with peripheral neuropathy 60% of the cases were due to diabetic neuropathy.

Classification

1. Distal symmetrical polyneuropathy

a. mixed neuropathy b. predominantly sensory neuropathy i) predominantly large fibre ii) mixed large & small fibre iii) predominantly small fibre Predominantly motor neuropathy

Predominantly autonomic neuropathy

2. Symmetrical proximal motor neuropathy

3. Focal and multifocal neuropathies

a) Asymmetrical proximal motor neuropathy

b) Cranial neuropathy

c) Intercostal and other neuropathies

d) Entrapment neuropathy

Pathology

Axonal damage seems to be the primary lesion in most of the cases, segmental demyelination is not secondary to axonal atrophy but is attributed to primary Schwann cell disorder. Causal relationship of microangiopathy with neuropathy is not established. It may be of importance in multifocal neuropathy.

Electrodiagnosis

Reduced nerve conduction is atributted to loss of large myelinated fibres, segmental demyelination and sometimes to metabolic disturbances.

Pathophysiology

Neuropathy, like other long term complications seems to result from multiple factors, of which chronic hyperglycemia is the most important. Inhibition of sodium dependent myo-inositol uptake and increased polyol pathway activity alter nerve phosphoinosilot metabolism and impair sodium-potassium ATPase. Other membrane defects and nonenzymatic glycosylation of nerve proteins may be associated. These result in slowed nerve conduction, impaired axonal transport and eventually structural damage to peripheral nerves.

Therapy

The management includes control of blood glucose, symptomatic treatment with dilantin, amitryptaline, skin care and other supportive measures.

Bone dynamics underlying Osteopenia and bone mineral loss in diabetes mellitus

S.B.S. Teotia. Head. Deptt. Human Metabolism. LLRM Medical College, Meerut.

Observations in five patients of diabetes mellitus and suspected metabolic bone disease have been made including the measurements of CAMP, IPTH, 24, 25 (OH) 2D, 25-OHD and 1,25 (OH) 2D and the pertinent investigations to exclude associated renal dysfunction, intestinal malabsorption and dietary deficiencies. Quantitative bone histostatic and dynamic measurements were performed on undecalcified sections of double tetracycline labeled iliac crest trephine biospsies and included structural measurements, formation indices, resorption indices and bone dynamics.

Bone mineral loss, osteopenia and osteoporosis occurred in untreated insulin dependant diabetics and bone morphometric and histomorphometric measurements were variable and there was over-lap of observations seen in normals and in patients with metabolic bone disease.