Review Article

AN OVERVIEW OF DIABETES MELLITUS WITH EMPHASIS ON BIOCHEMICAL AND CLINICAL MANAGEMENT

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ABSTRACT

Type 2 diabetes (previously called "adult onset diabetes") is the most common form of diabetes accounting for about 90 to 95 percent of all diabetes cases. Diabetes can have a significant impact on quality of life by increasing risk for a variety of complications. The countries with the largest number of diabetic subjects are, and will be India, China and U.S. and in the former two countries diabetes occurs mostly in the age range of 45-64yrs, in contrast with an age of >65 in the developed countries. Diabetic nephropathy is one of the most serious complications of diabetes and the most common cause of end stage renal disease.

Keywords: Diabetes mellitus, Type 2 diabetes, nephropathy.

DIABETES MELLITUS

It compromises of a group of common metabolic disorders that share the phenotype of hyperglycemia. It is characterized by absolute insulin deficiency, decreased glucose usage, increased glucose production or insulin resistance.

Diabetes is typically classified according to three main types

Type 1 diabetes, type 2 diabetes including a related condition called pre-diabetes and gestational diabetes.

Type 1 diabetes (previously called "juvenile diabetes") is an autoimmune disorder in which the insulin producing beta cells are destroyed by the body's immune system. As a result the body is unable to produce insulin. Without insulin, the body is unable to use glucose (sugar) as energy for everyday activities. Children and adolescents are most often diagnosed with type 1 diabetes although a significant portion of those with type 1 diabetes are diagnosed as adults.

Type 2 diabetes (previously called "adult onset diabetes") is the most common form of diabetes accounting for about 90 to 95 percent of all diabetes cases. In this type of diabetes, the body does not produce enough insulin and/or the body's cells become resistant to insulin. Insulin resistance occurs when the body's muscle, fat, and liver cells do not respond to insulin. The pancreas tries to keep up with the demand for insulin by producing more. Since insulin helps to mobilize glucose from the blood stream into cells, excess glucose builds up in the blood stream. Many people with insulin resistance have high levels of blood glucose and high levels of insulin circulating in their blood at the same time indicating that the cells are not responding properly to insulin.

A related condition, called *pre-diabetes*, occurs when a person's blood sugar levels are higher than normal, but not high enough for a diagnosis of diabetes. People with pre-diabetes have impaired fasting glucose (fasting blood sugar level is 70 to 110 mg/dl) or impaired glucose tolerance (blood sugar level is 140 to 199 mg/dl after a 2-hour oral glucose tolerance test)[1]. People with pre-diabetes and type 2 diabetes often do not show symptoms and they do not know that they have the condition. People with pre-diabetes can prevent or delay the development of type 2 diabetes through lifestyle changes that include eating a low-calorie, low-fat diet to lose weight and getting 150 minutes of physical activity a week[2].

Gestational diabetes is a form of diabetes that occurs in some women who have high blood glucose levels during pregnancy but have never had diabetes before. This type of diabetes may disappear after the pregnancy ends, but women who have had gestational diabetes have a 20 to 50 percent chance of developing type 2 diabetes in the next 5 to 10 years[3].

HEALTH PROBLEMS RELATED TO DIABETES

Diabetes can have a significant impact on quality of life by increasing risk for a variety of complications. These include:

Blindness: Diabetes is the leading cause of new cases of blindness among adults aged 20 to 74 years, with the greatest number in adults 65 years and older. Retinopathy causes 12,000 to 24,000 new cases of blindness each year in people with diabetes[3].

Kidney Disease: Diabetes is the leading cause of end stage kidney disease, accounting for 43 percent of new

cases each year[2]. In 2001, nearly 43,000 people with diabetes began treatment for end stage kidney disease and approximately 143,000 people with end stage kidney disease were living on chronic dialysis or with a kidney transplant due to diabetes[2].

High Blood Pressure: About 73 percent of adults with diabetes have blood pressure greater than or equal to 140/90 mm Hg or use prescription medications for hypertension[4].

Heart Disease and Stroke: About 65 percent of deaths among people with diabetes are due to heart disease and stroke[2]. Adults with diabetes have heart disease death rates about two to four times higher than adults without diabetes. It is projected that in the year 2025, twenty-nine percent of all heart disease deaths will be due to diabetes. The risk for stroke is two to four times higher among people with diabetes.

Nervous System Disease: About 60 to 70 percent of people with diabetes have mild to severe forms of nervous system damage including impaired sensation or pain in the feet or hands, carpal tunnel syndrome, slowed digestion of food in the stomach, and other nerve problems[2]. Severe forms of nerve disease are a major contributing cause of lower-extremity amputations for people with diabetes.

Amputations: More than 60 percent of non-traumatic lower limb amputations occur among people with diabetes[2]. In 2000– 2001, about 82,000 non-traumatic lower limb amputations were performed annually among people with diabetes[2].

Pregnancy Complications: Poorly controlled diabetes before conception and during the first trimester of pregnancy can cause major birth defects in 5 to 10 percent of pregnancies and spontaneous abortions in 15 percent to 20 percent of pregnancies[4]. Poorly controlled diabetes during the second and third trimesters of pregnancy can result in very large babies, posing a risk to the mother and the child during delivery.

Other Complications: People with diabetes are more susceptible to many other illnesses and often have worse outcomes. For example, people with diabetes are more likely to die from pneumonia or the flu than people who do not have diabetes.

SOCIO-ECONOMIC BURDEN OF DIABETES IN INDIA

Type 2 diabetes is the commonest form of diabetes constituting 90% of the diabetic population in any country. The global prevalence of diabetes is estimated to increase from 4% in 1995 to 5.4% by the year 2025[5]. The countries with the largest number of diabetic subjects are, and will be India, China and U.S. and in the former two countries diabetes occurs mostly in the age range of 45-64yrs, in contrast with an age of >65 in the developed countries. Epidemiological studies conducted in India showed that not only was the prevalence high in urban India but it was also increasing[6-8].

The period between 1989-95 showed a 40% rise in the prevalence and subsequently a further increase of 16.4% was seen in the next 5 years. A national survey of diabetes conducted in six major cities in India in year 2000 showed that the prevalence of diabetes in urban adults was 12.1%.

Prevalence of impaired glucose tolerance (IGT) was also high (14.0%)[8]. A younger age at onset of diabetes had been noted in Asian Indians in several studies[8,9].

In the national study, onset of diabetes occurred before the age of 50 years in 54.1% of cases, implying that these subjects developed diabetes in the most productive years of their life and had a greater chance of developing the chronic complications of diabetes.

Long standing diabetes mellitus is associated with an increased prevalence of microvascular and macrovascular diseases. With the rising prevalence of diabetes, the number suffering from the vascular complications of diabetes will also increase.

Table 1 shows the prevalences of the vascular complications observed in a study by the Diabetes Research Centre[10].

Table 1: Prevalence (%) of vascular complications in type 2 diabetes

Microvascular		Macrovascular	
Retinopathy	23.7	Cardiovascular disease	11.4
Background	20.0	Peripheral vascular disease	4.0
Proliferative	3.7	Cerebrovascular accidents	0.9
Nephropathy	5.5	Hypertension	38.0
Peri-neuropathy	27.5		

Prevalence of retinopathy is high among the Indian type 2 diabetic subjects. Another study done in 1996 in South India showed a prevalence of 34.1% of retinopathy[11]. The prevalence of nephropathy in India was less (8.9% in Vellore)[12]. 5.5% in Chennai[10] when compared with the prevalence of 22.3% in Asian Indians in the UK in the study by Samanta *et al* in 1991[13].

DIABETIC NEPHROPATHY

Natural history of diabetic nephropathy

- Diabetic nephropathy is a spectrum of progressive renal lesions secondary to diabetes mellitus ranging from renal hyper-filtration to end stage kidney disease.

- The earliest clinical evidence of nephropathy is the presence of microalbuminuria (Table 3). It occurs in 30% of type 1 diabetics 5 to 15 years after diagnosis but may be present at diagnosis in type 2 diabetics as the time of onset of type 2 diabetes is often unknown.

- Microalbuminuria progresses to overt proteinuria over the next 7 to 10 years.

- Once overt proteinuria develops, renal function progressively declines and end stage renal disease is reached after about 10 years.

Diabetic nephropathy is one of the most serious complications of diabetes and the most common cause of end stage renal disease. It is characterized by specific renal morphological and functional alterations. Features of early diabetic changes are glomerular hyperfiltration, glomerular and renal hypertrophy, increased urinary albumin excretion (UAER), increased basement membrane thickness (BMT) and mesangial expansion with the accumulation of extracellular matrix (ECM) proteins such as collagen, fibronectin and laminin.

Advanced diabetic nephropathy is characterized by proteinuria, a decline in renal function, decreasing creatinine clearance, glomerulosclerosis and interstitial fibrosis.

Magnitude of the problem

Mani M.K, had shown the prevalence of diabetic nephropathy among 4837 patents with chronic renal failure to be 30.3%, chronic interstitial nephritis to be 23% and chronic glomerulonephritis to be 17.7% respectively[14]. In India, only less than 5% of patients with end stage renal diasease (ESRD) receive renal transplantation, because only a few centres have the facilities for renal transplantation. Cadaveric kidney transplantation is yet to pick up and there is non-availability of related donors.

The patients with longer duration of diabetes, poor glycemic control and raised blood pressure, have a major risk of developing diabetic nephropathy. Therefore, it is important to screen these high risk patients and intervene at the microalbuminuria stage to prevent ESRD.

Factors involved in development of diabetic nephropathy

Metabolic factors

- Advanced glycation end products (AGEs)
- Aldose reductase (AR)/ Polyol pathway

Hemodynamic factors

- Angiotensin 2 / renin – angiotension system (RAS)
- Endothelin
- Nitric oxide

Intracellular factors

- Diacyglycerol (DAG) – protien kinase C (PKC) pathway

Growth factors and cytokines

- Transforming growth factor β (TGF-β)
- Growth hormone (GH) and insulin –like growth factors

- (IGFs)
- Vascular endothelial growth factor (VEGF)
- Platelet-derived growth factor (PDGF)

Table 2: Evolution of diabetic renal disease

Stage 1	- Glomerular hypertension and hyperfiltration - Normoalbuminuria: urinary albumin excretion rate (AER) <20 μg/min - Raised GFR, normal serum creatinine
Stage 2	"Silent phase" (structural changes on biopsy but no clinical manifestations) - Normoalbuminuria
Stage 3	- Microalbuminuria: AER 20 – 200μg/min - Normal serum creatinine - Increased blood pressure
Stage 4	- Overt "dipstick positive" proteinuria (macroalbuminuria) : AER > 200μg/min - Hypertension - Serum creatinine may be normal - Increase in serum creatinine with progression of nephropathy
Stage 5	- End stage renal failure - Requiring dialysis or transplant to maintain life

Adapted from SIGN Guidelines[15]

MANAGEMENT OF DIABETES MELLITUS[16]

The following guidelines provide recommendations for the management of type 1 and type 2 diabetes mellitus.

DIAGNOSIS

New criteria for diagnosing diabetes in adults	Normal plasma glucose values for adults		
One or more of the following must be present: 1. Fasting plasma glucose level of > 126 mg/dL on at least two separate occasions. 2. Random plasma glucose level of > 200 mg/dL with signs and symptoms of diabetes. 3. Fasting plasma glucose level < 126 mg/dL but 2 hour glucose concentration of > 200 mg/dL during a 75-gram oral glucose tolerance test.	Fasting After 75g oral glucose load	Time Zero 30 min 60 min 90 min 120 min	< 115 mg/dL (6.4 mM) < 200 mg/dL (11.1 mM) < 200 mg/dL (11.1 mM) < 200 mg/dL (11.1 mM) < 140 mg/dL (7.8 mM)

FREQUENCY OF VISITS AND LABORATORY TESTING

The recommended frequency of follow-up is 3-6 months for patients with type 1 diabetes and type 2 diabetes, depending on the stability of the patient.

EVERY 3 - 6 MONTHS	YEARLY
• Glycosylated hemoglobin • Electrolytes, BUN and creatinine • Physical examination including foot examination by filament testing (Carville approach)	• TSH • U/A or urine for microalbumin • complete chemistry panel (lipids, LFT, electrolytes, BUN & creatinine) • Ophthalmology examination • Podiatry and nutrition

The frequency of laboratory assessment is subject to flexibility, based on clinical judgement, patients' current control of diabetes, and past laboratory values.

Podiatry if any evidence of neuropathy or breakdown of skin integrity, and nutrition, if dietary non-compliance is suspected.

Microalbumin testing

Type 1: Annual screening for type 1 diabetes should begin at puberty and for those patients who have had the disease for 5 years.

Type 2: Initial testing at diagnosis and annual screening thereafter.

Note: *Microalbuminuria is urinary albumin excretion between 30-300 mg per day without an alternative explanation (e.g. urinary tract infection, heart failure, exercise in past 48 hours and blood glucose > 200 mg/dL). If no protein is found in a urine analysis, then a 24 hour urine collection for microalbumin or a spot urine albumin-creatinine ratio may be used (abnormal if > 30 mg albumin/ g creatinine) for screening.*

Retinopathy screening

Baseline Screening

- For patients with type 1 diabetes who are 13 years of age or older and who have had the disease for 5 years, a baseline screening examination is recommended, and yearly thereafter.

- For patients with type 2 diabetes, a baseline screening examination is recommended at the time of diagnosis and yearly thereafter.

Diabetic retinopathy is the leading cause of legal blindness among Americans, aged 20-74. It is highly correlated with patient age and duration of diabetes. Visual loss secondary to diabetic retinopathy is largely preventable if screening is universal and appropriate treatment follows screening.

Vaccines

- Pneumovaz every five years.

- Influenza vaccine annually.

ACE inhibitors

Recommendations

- All patients who demonstrate microalbuminuria should be prescribed ACE inhibitors to slow the progression of nephropathy whether they are hypertensive or normotensive.

- Patients with type 1 who are hypertensive and do not demonstrate microalbuminuria should be prescribed ACE inhibitors. Such patients usually develop microalbuminuria in concert with hypertension and are best served by controlling blood pressure initially with ACE inhibitors.

- ACE inhibitors should not be used in pregnant women due to the risk of fetal morbidity and mortality.

NOTE: ACE inhibitors should be titrated as high as the patient tolerates without orthostatic symptoms, hyperkalemia and /or increasing renal insufficiency.

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