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A REVIEW ON DIABETES MELLITUS

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ABSTRACT

Diabetes mellitus is a major and rapidly growing public health care problem. It is increasing in incidence, and brings with it long term complications. The global increase in the prevalence of diabetes mellitus is due to population growth, aging, urbanization and an increase of obesity and physical inactivity. The forgoing discussion explains the severity of the metabolic disorder and the complication arising there-of. Presently, whole world is in threat to suffer from these severe secondary complications. The disorder, albeit during treatment, may often precipitate certain medical emergencies, mainly due to the side-effect of ongoing therapy, requiring immediate medical attention. The emergencies and risk factors are described in the literature.

Keywords: Diabetes mellitus, diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, hyperlipidaemias, hyperosmolar hyperglycemic state, ketoacidosis

INTRODUCTION

Diabetes mellitus is a major and rapidly growing public health care problem. It is increasing in incidence, and brings with it long term complications. Presently more than 200 million people have diabetes mellitus; by 2030, it is estimated that approximately 366 million people will develop diabetes mellitus[1]. According to Diabetes Atlas-Fourth edition published by International Diabetes Federation (IDF), India alone had 50.8 million people with diabetes in 2010[2]. The global increase in the prevalence of diabetes mellitus is due to population growth, aging, urbanization and an increase of obesity and physical inactivity[3]. It has been estimated that global burden of Type 2 Diabetes Mellitus (Type 2 DM) for 2010 would be 285 million people which is projected to increase to 438 million in 2030; a

65 % increase. Similarly, for India this increase is estimated to be 58 %, from 51

million people in 2010 to 87 million in 2030 [4].

Figure 1: Prevalence of diabetes mellitus in Millions
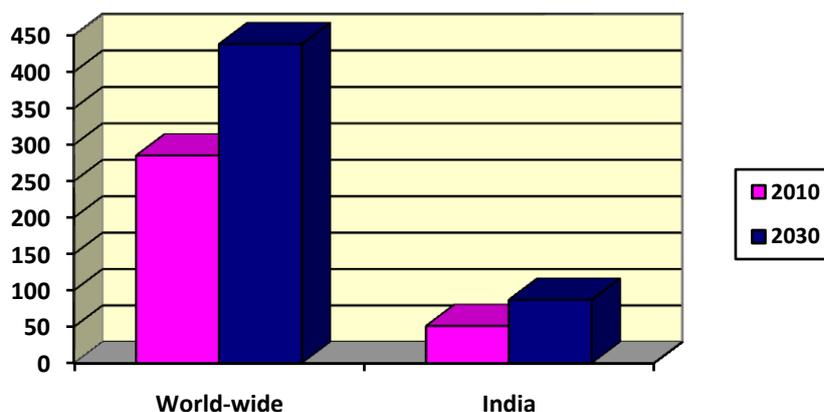
The ten countries estimated to have highest number of people with diabetes mellitus by 2030 are India, China, USA, Indonesia, Pakistan, Bangladesh, Japan, Philippines and Egypt. Healthcare expenditures on diabetes mellitus are expected to account for 11.6% of the total healthcare expenditure in the world in 2010. Estimated global healthcare expenditure to treat and prevent diabetes mellitus and its complications are expected to total at least 376 billion U. S. Dollars (USD) in 2010. By 2030, this number is projected to increase some USD490 billion.[3] India is the world most populated country with diabetic individuals. Results from national survey of 5516 diabetes individuals (both type 1 and type 2) in India showed that mean estimated annual direct costs of diabetes were Rs.4,727 (USD101.95) per individual including drug treatment, monitoring and check-ups, and Rs.2,343 (USD50.63) for hospitalization, indirect costs were Rs.12,756 (USD275.31) including measures of productivity and income loss

through illness in earning and non-earning family members and total costs were Rs.19,914 (USD429.74)[5].

Much of the mortality and morbidity seen in diabetic patients is the result of complications that develop with increasing duration of disease, particularly when glycemic control is poor[6]. Sustained exposure of vital organs to high levels of glucose is the predisposing reason for causing severe secondary complications of these organs. Few of those complications are described below.

Diabetic eye disease: Diabetic patients are more prone to cause blindness, usually in the form of diabetic retinopathy. Cataract generally requires surgical extraction, particular care being taken to avoid infections. Aggressive glycemic and blood pressure control are the main methods of prevention [6].

Diabetic nephropathy

Nephropathic changes associated with microvascular disease develop in upto 30

% of patients with type 1 diabetes and 40 % of those with type 2 diabetes; diabetic nephropathy, of which the first clinical sign in albuminuria, is one of the major causes of end stage renal disease. Diabetic nephropathy is a leading cause of chronic renal failure. It is characterized by thickening of the glomerular basement membrane, mesangial expansion, and glomerular sclerosis. [7].

Diabetic neuropathy

Peripheral neuropathies are common complications of diabetes mellitus. Diabetic neuropathy is the result of nerve ischemia from microvascular disease, direct effect of hyperglycemia on neurons, and intracellular metabolic changes that impair nerve function. The intensity and extent of neurological abnormalities are proportional to the degree and duration of hyperglycemia. Neuropathic symptoms include symmetrical sensory loss, particularly in the feet and lower limbs; features of autonomic neuropathy such as gastroparesis, orthostatic hypotension, erectile dysfunction and gustatory sweating; pain and cranial nerve palsy associated with mononeuropathies; and acute, painful, sensory neuropathy.

Microvascular disease

Large-vessel atherosclerosis is a result of the hyperinsulinemia, dyslipidemias, and hyperglycemia characteristics of diabetes mellitus. Manifestations are angina pectoris, transient ischemic attacks and strokes, and peripheral atrial disease. Treatment is rigorous control of atherosclerotic risk factors, including normalization of plasma glucose, lipids and blood pressure, combined with smoking cessation and daily intake of aspirin and ACE inhibitors.

Heart disease

Cardiovascular disease (heart failure, ischemic heart disease and stroke) is a major cause of morbidity and death in patients with diabetes. Conventional risk factors such as obesity, hypertension and hyperlipidaemias tend to be common in diabetic patients, but other factors including hyperglycemia itself (and particularly postprandial hyperglycemia) may play a role. Management of cardiovascular disease in diabetic patients is use of individual drug classes: β-blockers, aspirin (which may need to be given in higher than usual doses), and calcium-channel blockers.

Hyperlipidaemias

Insulin plays an important role in lipid metabolism and deficient insulin action means that diabetics are prone to hypertriglyceridaemia and have a blood-lipid profile associated with an increased risk of atherosclerosis, and hence of macrovascular complications. Where drug therapy is needed, statins, in at least moderate doses, are the lipid-lowering drugs of choice for both secondary and primary prevention of cardiovascular events in type 2 diabetes.

Hypertension

Hypertension is twice as common in the diabetics as in the non-diabetic population, and is associated with both macrovascular complications and microvascular diseases (especially diabetic neuropathy). It should be treated aggressively with a view to retarding development of complications, and the threshold for drug treatment and

treatment goal are lower than in non-diabetic patients. All of the main groups of antihypertensive drugs may be used although an ACE inhibitor, such as ramipril, or β-blocker may be effective in reducing complications.

Diarrhoea

Diabetic patients may develop intermittent bouts of watery diarrhoea, sometimes alternating with constipation; autonomic neuropathy and abnormalities of diagestion and bowel flora may play a role. Clonidine has been suggested for severe cases. A broad spectrum antibacterial (especially tetracycline) may also be effective.

Foot disease

Peripheral atrial disease, neuropathy, collagen changes, and increased susceptibility to infection may contribute to the foot lesions to which diabetics are prone. Management involves drainage and debridement of dead and infected tissue, and the use of antibacterials if necessary; broad spectrum cover should be given intravenously if there is severe infection, and adapted once the results of bacteriological culture are available.

Infections: Diabetics are prone to bacterial and fungal infections because of adverse effects of hyperglycemia on granulocyte and T-cell function. Most common are mucocutaneous fungal infections (*e. g.* oral and vaginal candidiasis) and bacterial foot infections (including osteomyelitis), which are typically exacerbated by lower extremity, vascular insufficiency, and diabetic neuropathy.

Depression: Diabetes doubles the likelihood of comorbid depression, which is present in approximately 30 % of patients with type 1 or type 2 diabetes. Mental depression represents a major public health problem worldwide. According to World Health Organization (WHO) estimates, 100 million people worldwide suffer from major depression at any given time. Depression is highly prevalent in diabetics and is associated with poor glucose regulation and increased risk of diabetic complications. Diabetes mellitus is accompanied by hormonal and neurochemical changes that can be associated with anxiety and depression.

Other complications: Diabetic foot complications (skin changes, ulceration, infection, gangrene) are common and are attributable to vascular disease neuropathy, and relative immunosuppression. Diabetics have an increased risk of developing some rheumatologic diseases, including muscle infarction [8-10].

Treatment of Diabetes Mellitus: Drug therapy of Type 2 Diabetes Mellitus should be considered when diet, patient's education, and increased physical activity have failed to achieve individual treatment goals. For type 2 diabetes it is clearly a priority to provide effective control of the hyperglycemia to reduce macrovascular and microvascular complications. The standard approach begins with dietary, exercise, and healthy-living advice, particularly designed to facilitate weight loss in the obese. These measures are ineffective in more than four-fifths of newly diagnosed type 2 diabetes patients, and the progressive nature of type 2 diabetes dictates that most patients require drug therapy. Oral agents, notably sulphonylureas, metformin, and acarbose, are instituted as monotherapy, and a new

class of TZDs (thiazolidinediones) has recently become available. If adequate glycemic control is not achieved with oral monotherapy, two different classes of oral drugs are used in combination. Insulin therapy sometimes is supplemented with an oral agent to further improve glycemic control and/or lower insulin dosage [10,11].

Table.1 Summary of common anti-diabetic drugs

Drug class	Example	Advantages	Disadvantages
Sulphonylureas	Gliclazide Glipizide	Long-term safety, low cost	Hypoglycemia, weight gain
Biguanide	Metformin	Low risk of hypoglycemia	Possible link to lactic acidosis
Meglitinides	Nateglinide Repaglinide	Rapid, short acting, suitable for prandial use	Weight gain, hypoglycemia
α-Glucosidase inhibitors	Acarbose Miglitol	Weight neutral	Gastrointestinal side-effects
Thiazolidinediones	Pioglitazone Rosiglitazone	Low risk of hypoglycemia	Risk of weight gain, heart failure
Glucagon-like peptide-1	Exenatide Liraglutide	Low risk of hypoglycemia	Gastrointestinal side-effects
Dipeptidyl peptidase-4 inhibitors	Sitagliptin Vildagliptin Saxaglitpin	Low risk of hypoglycemia	Unconfirmed association with pancreatitis
Amylin analogue	Pramlintide	Weight loss	Hypoglycemia
Insulin	Aspart Lispro Glulisine	More sustained Glycemic improvements	Weight gain, Hypoglycemia, fluid retention

Unique among drug withdrawals is the diabetes drug Phenformin, which was declared an imminent hazard by Secretary Califano and was removed from the market in 1977 because of lactic acidosis. The diabetic drug, Troglitazone was removed in 2000 because of liver failure and the lipid-lowering drug Baycol in 2001 because of rhabdomyolysis. Rosiglitazone and Pioglitazone were approved in 1999 and removed in 2007 because of liver failure and Congestive Heart Failure respectively.[12]

The forgoing discussion explains the severity of the metabolic disorder and the complication arising there-of. Presently, whole world is in threat to suffer from these severe secondary complications. The disorder, albeit during treatment, may often precipitate certain medical emergencies, mainly due to the side-effect of ongoing therapy, requiring immediate

medical attention. Those emergencies are described below.

Hypoglycemia: The most frequent complication of insulin therapy is hypoglycemia and patients taking insulin need to be educated about its cause, symptoms and treatment. Most patients recognize the early warning signs of hypoglycemia and by taking sugar immediately can prevent most serious symptoms developing.

Diabetic ketoacidosis: Diabetic ketoacidosis is caused by an absolute or relative lack of insulin and commonly occurs after noncompliance or failure to adjust insulin dosage in the presence of factors such as infection that increase insulin requirement. Diabetic ketoacidosis is a medical emergency and should be treated immediately with fluid replacement.

Hyperosmolar hyperglycemic state: Hyperosmolar hyperglycemic state or hyperosmolar hyperglycemic nonketotic coma (HONK) occurs mainly in elderly patients with Type 2 Diabetes and though much less common than diabetic ketoacidosis, it carries a higher mortality. Potassium requirements are lower and large amounts of fluid and less insulin may be required.

Although the disorder is linked to endocrine malfunction and interference in the hormone action, several predisposing factors have been identified as Diabetic risk factors. They are described as follows.

Obesity: Obesity is the most potent risk factor for developing Type 2 diabetes Mellitus. Overweight (Body Mass Index greater than $25Kg/m^2$) increase a person's

risk of developing type 2 diabetes mellitus [13-17]. **Genetic predisposition:** A first degree relative with diabetes, such as parent or grandparent, sister or brother.

Increasing age: Type 2 Diabetes Mellitus can develop at any stage. Typically, however, the prevalence of this disease increases with age and one reason why Type 2 Diabetes Mellitus is such a rapidly growing problem is aging population. Internationally, Type 2 Diabetes Mellitus is most common in the 40-59 age groups, but the incidence of the disease is increasing more rapidly in adolescents and young adults.

Clinical conditions: Other clinical conditions associated with insulin (*e. g.* acanthosis nigricans, polycystic ovary syndrome). **History:** Documented history of pre-diabetes, impaired fasting glucose or impaired glucose tolerance. For women, a previous history of gestational diabetes mellitus or delivery of a baby weighing more than 9 pounds at birth. **Ethnicity:** The prevalence of Type 2 Diabetes Mellitus around the world is heavily influenced by race/ethnicity. For example the incidence of Type 2 Diabetes Mellitus in White Europeans is relatively low compared with Asian/Pacific Islanders.

Lifestyle: A variety of lifestyle factors are known to influence the risk of Type 2 Diabetes Mellitus. Exercise has a definite effect on Type 2 Diabetes Mellitus. Studies have shown to reduce the risk of developing Type 2 Diabetes Mellitus even after adjusting for Body Mass Index. The relative risk of developing the disease in people exercising vigorously once a week, 2-4 times a week, and more than 5 times a week, is 0.77, 0.62 and 0.58, respectively.

Country of residence: As diabetes is an age related disorder, countries with elderly population have more diabetes than developing countries with younger populations. **Place of residence:** Diabetes is a disease proved to be a result of urbanization and several studies have found significantly higher prevalence rates in urban rather than rural environments within the same country. Comparisons of migrant populations living in rural and urban settings in the same country also show an excess of diabetes in urban communities. **Socio-economic status:** Socio-economic deprivation, which is associated with poor diet and other adverse lifestyle factors, is linked to high rates of diabetes.

The predisposing factors of the disorder and consequences of harbouring the dreaded ailment are quite clear. The alarming increase in the statistics of affected world-wide population urges to initiate concrete efforts by every individual to prevent, or at least prolong, the onset of diabetes mellitus, which is fortunately quite possible if initiated early.

Primary Prevention (to prevent people from developing diabetes): It includes action that encourage people to choose a diet rich in fruit and vegetables and low in fat and processed food, and to exercise and avoid tobacco and excessive alcohol. Thirty minutes of moderate physical activity a day, coupled with a 5-10 % reduction in the body weight, produce a 58 % reduction in diabetes.

Secondary prevention (to prevent people with diabetes from developing complications): It involves early diagnosis so that people can be treated early in the progress of diabetes. The

United Kingdom Prospective Diabetes Study (UKPDS) showed conclusively that effective treatment, with close monitoring and control of blood glucose levels, blood pressure, and blood lipids can greatly reduce diabetic complications. Improving glycemic control in people with HbA1c level of over 8 % has been shown to be cost-saving as avoidance of short-term and long-term complications. To achieve this type of glycemic control intensified treatment is often required, coupled with lifestyle interventions as follows.

Food planning: Effective management of Type 2 Diabetes cannot be achieved without proper attention to diet and nutrition. This extends to cardiovascular risk factors such as hypertension, dyslipidemia and obesity. Nutrition is an integral part of management of diabetes. The goals of nutritional management are to (1) achieve and maintain optimal blood glucose levels (2) reduce cardiovascular risk factors, including dyslipidemia and hypertension (3) provide a balanced, nutritional diet.

Weight control: A weight loss goals of 5-10 % of body weight over 3-6 months is recommended for people who are overweight. Long-term maintenance of achieved weight loss and prevention of weight gain are important. Reduced total energy intake is recommended by reducing portion sizes and avoiding excessive intake of fats and sugar.

Fat: Restricted saturated fat to less than 10 % of total energy intake is recommended. Avoiding the fatty meats, full cream dairy products, palm oil, coconut oil and processed foods are also few steps benefiting for reducing fat. **Carbohydrate:** Meals should contain

mostly carbohydrate with an emphasis on high-fiber foods such as vegetables, legumes, wholegrain, cereals, yams and fruit.

Protein: Good sources of protein are fish, seafood, lean meat, chicken, low fat dairy products, nuts and legumes, and these should be included as a part of daily diet.

Salt: Restrict salt intake to less than 6 g/day, particularly in patients with hypertension also helps in prolonging the onset of this disorder.

Alcohol: Total cut-off in all sorts of alcohol intake is strongly recommended in individuals showing risk of development of diabetes.

Physical activity: Physical activity improves insulin sensitivity, thus improving glycemic control, and may help with weight reduction. The common health goal should be achieved by at least 150 minutes of moderate-intensity physical activity each week.

CONCLUSION

The increasing prevalence, expensive cost for treating diabetes mellitus and developing complications poses major challenges in treating diabetes in developing countries. Serious efforts should be made available for treating diabetes mellitus. Hyperglycemia, acts in conjunction with other metabolic disturbances of the insulin-resistance syndrome to generate the characteristics chronic complications of type 2 diabetes mellitus. Insulin resistance, often in collision with hyper-insulinemia, has been identified as a link for the clustering together of obesity, impaired glucose tolerance, type 2 diabetes mellitus, and several other conditions that carry an increased risk of coronary heart disease, notably dyslipidemia, hypertension, atherosclerosis. Owing to the progressive nature of type 2 diabetes mellitus, currently available oral antidiabetic agents, even when used intensively, are often unable to control the hyperglycemia. Early intervention against insulin resistance should become a primary strategy for the future treatment of type 2 diabetes mellitus.

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