

Global Epidemic of Diabetes Mellitus - An Overview

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Diabetes Mellitus is defined as a clinical syndrome characterized by persistent hyperglycemia due to relative or absolute deficiency of insulin. Uncontrolled diabetes can lead to dreadful complications that cause physical, emotional and economical burden on the individual as well as on the society. In 1995, more than 135 million people (4.0%) had diabetes mellitus worldwide, in 2000 it increased to 146 million, in 2015 it will rise to 215 million which is predicted to rise to almost 300 million (5.4%) by 2025.¹ It is estimated that there will be about 42% increase in developed countries but it will be up to 170% increase in developing countries, which is a menace to face in the future.² It is therefore right to say that diabetes mellitus is the most common non-infectious disease occurring globally. In Pakistan, 5.54 million people had diabetes with a prevalence of 4.19% in 1995 but in 2000 about 6.99 million people had diabetes with a prevalence of 4.66 %, however it is estimated that in 2025, it will be 14.5 million with a prevalence of 6.76%. Pakistan will be the fourth country in the world with diabetes by 2025 after India, China and the USA respectively.³ Therefore, diabetes has emerged as a major health problem in Asia indicating the urgent need for planning prevention programs for it.

In Pakistan, in all the four provinces, prevalence of diabetes mellitus and impaired glucose tolerance (IGT) is more in urban population than rural.⁴ The overall prevalence of type-2 diabetes is 11.52% and of IGT is 9.25% respectively, which is very alarming.⁵ The type-1 diabetes constitutes about 2-4% of total diabetics and the rest of 96-98% are type-2 diabetics. There are almost as many as patients with IGT as there are diabetics.⁴ Studies show that there is higher prevalence of diabetes among the Indo Pak migrants as compared to indigenous population in Europe. Although a number of studies have been done in the indigenous population in the Indian subcontinent, they are not very reliable, as very few have used the WHO criteria for diagnosis of diabetes mellitus. The

hospital data is also limited as these studies were done on small scale and therefore were non-representative. The Diabetic Association of Pakistan (DAP) initiated a national diabetes prevalence survey in collaboration with the World Health Organization (WHO) in 1994, which was completed in 1998. It showed that type-2 diabetes occur at relatively young age in our population as compared to the Western world. In our set up, 15-20% of people get type-2 diabetes under the age 40. However, the prevalence rate increases with advancing age in both sexes and reaches a peak at the age 55-64 in men and 65-74 age brackets in women. Type-1 diabetes continues to be rare.⁶ A study done in children in Karachi showed that the incidence of type-1 in Karachi per 100,000 population per year was 1.01 for males and 1.04 for females and the peak incidence was at the age 10-12.⁷

The implications of all this discussion is important as Pakistan has a population of approximately 145 million and presuming the prevalence of diabetes is around 12%, the estimated number of diabetics will be 7 million for those above the age of 25 years. There are an estimated number of 6 million people with IGT and 50% of this group will become diabetic over the next 5 years if they do not observe proper eating habits and reduce weight. It is therefore mandatory to plan a strategy to deal with this menace and there is a need for planning treatment and preventive programmes for diabetes. In 1995, the Government of Pakistan developed a National Action Plan in collaboration with the Eastern Mediterranean Region Office (EMRO) of WHO for the prevention and control of diabetes. This included primary prevention of diabetes and to improve diabetes management in people with diabetes and to achieve favourable changes in dietary patterns, smoking and physical activities and last but not the least to reduce the new cases of diabetic complications.

As far as risk factors for diabetes mellitus are concerned a strong family history, obesity especially

central obesity, gestational diabetes, increasing age, physical inactivity and of course impaired glucose tolerance are all of paramount significance.⁸ In Pakistan, about 44% type-2 diabetics have a strong family history of diabetes. There is a strong relation between IGT and high waist to hip ratio (WHR) than IGT and high body mass index (BMI). This is consistent with the earlier studies that people with central obesity are at higher risk of developing type-2 diabetes than peripheral obesity irrespective of BMI. Central obesity is also associated with hypertension and majority of type-2 diabetics are also hypertensive.⁹ National Health Survey of Pakistan (1990-1994) showed that there is increased prevalence of obesity in urban than rural areas and that it is directly related to socio-economic status irrespective of residential area and that social and environmental changes are occurring in rapidly increasing urbanization, change in life style, higher energy density of diets and diets with less fibre and decreased physical activity all leading to higher prevalence and incidence of hypertension and diabetes.¹⁰ In a study it was shown that 53% of type-2 diabetics were hypertensive as compared to 12% who were not diabetic.

As the time has passed along, the terminology and diagnostic criteria has changed accordingly and currently WHO has classified diabetes as type-1 (juvenile, insulin dependent diabetes mellitus or IDDM) and type-2 (maturity onset, non-insulin dependent diabetes mellitus or NIDDM).

Type-1 has an association with HLA-DR3 or HLA-DR4, however HLA-DQ is more specific. Type-2 diabetes has no association with any HLA. Type-1 diabetes may exist as an asymptomatic, autoimmune state for months to years (e.g., up to 35 years) before the onset of symptoms.¹¹

As regards diagnostic criteria, Diabetes Expert Committee criteria are used. A fasting glucose of ≥ 126 mg/dl or a random glucose of ≥ 200 mg/dl will label a person diabetic, where as a fasting glucose between 110-125 mg/dl is called impaired fasting glucose (IFG) or 2 hours post glucose load between 140-199 mg/dl indicates an impaired glucose tolerance (IGT). See Table 1.

Gestational diabetes is diagnosed as hyperglycemia during pregnancy which itself is diabetogenic. According to the 4th International

Workshop-Conference on Gestational Diabetes, gestational diabetes is present if two or more of the following serum glucose values are exceeded. See Table 2.

Table 1: Diabetes Expert Committee criteria for evaluating the standard oral glucose tolerance test.

Oral glucose tolerance test (mg/dl)	Normal glucose tolerance	Impaired glucose tolerance (IFG)	Diabetes mellitus
Fasting plasma glucose	<110	110-125	≥ 126
Two hours after glucose load	<140	> 140 but <200	≥ 200

Table 2: Diagnostic criteria for gestational diabetes. Fourth International Workshop-Conference on Gestational Diabetes.

Serum glucose concentration	
Fasting	> 95 mg/dl (5.3 mmol/L)
One hour	> 180 mg/dl (10 mmol/L)
Two hour	> 155 mg/dl (8.6 mmol/L)
Three hour	> 140 mg/dl (7.8 mmol/L)

In pregnancy, euglycaemia is considered to be 60-80mg/dl while fasting and 30-45 minute before meals, and between 80-120mg/dl two hours after meals. Screening of women for glucose intolerance has been recommended between the 24th and 28th weeks of pregnancy. Patients with gestational diabetes should be evaluated 6-8 weeks postpartum by a 2-hour oral glucose tolerance test with 75g glucose load¹².

Maturity onset diabetes of the young (MODY) is < 1% and is of 5 types (1 to 5). It is similar to type-2 diabetes but with a genetic etiology (Mendelian dominant transmission) and is generally diagnosed before age 25. All except MODY-2 involve mutation of a nuclear transcription factor that regulates gene expression.¹³

Another modality is Latent Autoimmune Diabetes in Adults (LADA) in which antibodies are directed against an enzyme called glutamic acid decarboxylase (GAD) and is proposed as an early

differentiating marker of type-1 diabetes in those subjects who are questioned whether they have type-1 or type-2 diabetes mellitus. A correlation has been found between individuals originally classified as type-2 requiring insulin and anti-GAD antibodies.¹⁴

The most important question is, what is the acceptable level of glycaemic control? The aim should be normal glycaemic excursions with out causing severe or frequent hypoglycaemia. Acceptable control includes glucose levels of 90-130 mg/dl before meals and levels not higher than 180 mg/dl after 1 hour and 150 mg/dl 2 hours after meals. HbA1c level should not be higher than 1% above upper limit of normal range for any particular laboratory.

It is also well known that adequate control of diabetes can avert a number of complications and various trials have been done in the past and the facts have been well documented. Self monitoring of blood glucose (SMBG) is advocated and it is recommended that the preprandial glucose should be between 80-120 mg/dl (ideally <110mg/dl), post prandial glucose should be < 160 mg/dl (ideally <140), bed time glucose should be 100-140 mg/dl (ideally < 120mg/dl) and glycosylated haemoglobin HbA1c should be on average < 7.0%.¹⁵ The significance of HbA1c is getting more importance as it indicates overall control of diabetes. If it is less than 7% (few studies recommend < 6.2%) the control is good, if between 7-10%, control is poor and if it is > 10%, then the control is bad. A large study called UKPDS done in type-2 diabetics showed that an intensive glucose control with HbA1c of 7% vs HbA1c of 7.9% reduced the risk of any diabetes related complications end point by 12%, micro vascular endpoints by 25% and myocardial infarction by 16%.¹⁶ where as DCCT done in type-1 diabetics showed that by tight control of DM with a HbA1c of <7% the retinopathy is reduced by 63%, nephropathy by 54%, neuropathy by 60% and macro vascular disease by 41%. DCCT also showed that previous poor prognosis for as many as 40% type-1 diabetics are markedly improved by optimal care. These benefits were observed with an average HbA1c of 7.2% in intensively treated groups of patients compared with 9% in conventionally treated groups of patients.¹⁷

UKPDS documented that for type-2 diabetics there is a significant reduction in microvascular complications by tight control but not in obese patients. Cardiovascular outcome did not improve but hypertensive diabetics with adequate control of blood pressure resulted in reduced mortality. It also showed that aggressive control of blood pressure consistent with American Diabetes Association recommendations, significantly reduced strokes, diabetes related deaths, heart failure, microvascular complications and visual loss. It is also documented that management of obesity improves prognosis for type-2 diabetics and high risk for cardiovascular problems also improve considerably.¹⁸

It also showed that if intensive glucose control lowered HbA1c of 1.0% at 10 years, it significantly reduced complications. However, glycaemic control deteriorated over time regardless of therapy and other measures. Fifty percent of newly diagnosed patients already have signs of diabetes related vascular tissue damage.¹⁹

UKPDS also concluded that metformin may be preferred in overweight patients as it also helps reducing HbA1c and lowered risk of cardiovascular diseases including myocardial infarction and it is thought that the benefit is related to treatment of insulin resistance indirectly.²⁰

In reference to obesity and weight gain and its relation with diabetes, another important study by DAP-WHO collaboration to check chronic complications of diabetes and associated factors in type-2 DM in 500 patients revealed that 44.6% were overweight (BMI 25-26.9) and 17% were obese (BMI > 27). It was also found that waist to hip ratio (WHR) was normal (<0.95 for males and <0.85 for females) in 12% and was abnormal in 88% of the subjects recruited. If BMI is < 23 the relative risk of developing DM is 1.0 where as if it is > 35, the relative risk rises up to 93.2. Relative risk of diabetes mellitus in South East Asians is about 12.5 in age 55-64 as compared to the European in the same age bracket, which is 4.0.

Other trials for type-2 diabetes include Kumamoto study and Veterans Administration Co-operative study, which highlight significance of good diabetic control.²¹

Diabetes Prevention Program is to evaluate safety and efficacy of interventions that may delay

or prevent the development of diabetes in people at increased risk for type-2 diabetes. It was clearly concluded from DCCT and EDIC (Epidemiology of Diabetes Intervention and Complications) that any lowering of blood glucose is important since there is a continuous relationship between glucose lowering and reduction in the risk of complications. However, benefits of intensive glycaemic control outweighs the risk of hypoglycaemia.²²

Diabetes Prevention Programme (DPP) was conducted by US National Institutes of Health in 27 countries and measured progression from IGT to established Type-2 diabetes. It was intended to follow up for 3-6 years to be ended in 2002 but terminated in August 2001 as it had answered all the questions.

The results of Diabetes Prevention Program (DPP) have shown to be very encouraging. It was performed on obese subjects age 25-85 years with IGT. It has shown that low fat diet, 150 minutes of moderate exercise (equivalent to brisk walking) per week will reduce the risk of progression to type-2 diabetes by 58% as compared to matched controls in patients with IGT. Use of 850 mg of metformin twice daily reduces the risk of developing diabetes type-2 by 31%. This is relatively ineffective in less obese and older patients.^{23,24}

One more exciting trial in context with prevention of diabetes besides DPP is Diabetes Prevention Trial-1 in which low dose insulin administered up to 8 years in 1st degree relatives of type-1 diabetics having circulating antibodies failed to affect the onset of type-1 diabetes. Another trial included administering low dose oral insulin in first-degree relatives having islet cell antibodies and proven diabetes is under way.

IGT is a risk factor for developing type-2 diabetes. Eleven percent of American aged 24-74 years have IGT and about 10 million are therefore at risk of developing diabetes in the USA. IGT itself is a risk factor for developing cardiovascular diseases. This is why the term "Impaired Glucose Tolerance" is changing over to the term "Prediabetes" which can stimulate better understanding for the patients, thus leading to exercise and healthier dietary habits.

Having documented the significance of tight control of diabetes to avoid life threatening or crippling complications leading to significant

morbidity and mortality, the question arises what current therapeutic interventions are available for adequate management of diabetes. The various modalities available include diet, exercise, and diet and exercise combined, oral hypoglycaemic agents, insulins (various types with different modes of delivery), insulin sensitizers (glitazones) and pancreatic and islet cell transplants. In Pakistan, it was documented by DAP-WHO survey that approximately 81% of type-2 diabetics use oral hypoglycaemic agents, 15% are treated with diet alone and 2% use insulin and 2% take no treatment. People show reluctance to use insulin and have various beliefs about it.

It has been observed that sticking to food plan alone or performing exercise on regular basis can lower blood glucose by up to 100 mg/dl. Oral agents alone or in combination lower blood glucose greater than 80-100 mg/dl but food plan and exercise combined with oral agents will lower blood glucose by up to 200 mg/dl. However, there is no limit to the blood glucose lowering action of insulin. The early introduction of insulin in type-2 diabetics should be encouraged.²⁵ The potential for diabetic control (HbA1c reduction) is on average 1-2 % with oral hypoglycaemic agents but potential for insulin is unlimited. This has been confirmed by various published studies.²⁵

As far as diet plan is concerned, one has to be very careful about choosing the type of diet and its contents i.e. carbohydrates, proteins and fats. One has to be very careful about calories. It is advised to take small meals but more frequently in type-2 diabetes but for type-1 diabetes; strict dietary restriction may lead to extreme weight loss. Fluctuation in glucose levels is dealt with adjustment of insulin.²⁶

Traditional sulphonylureas are well known, (first, second and third generation i.e. tolbutamide, glibenclamide, glimepride or gliclazide respectively). Also drugs like metformin from biguanides group, acarbose from alpha glucosidase inhibitors help controlling postprandial hyperglycaemia. Lipase inhibitors e.g. xenical (orlistat) also help in controlling diabetes and helps weight reduction. Repaglinide when given with each meal also helps reducing postprandial rise in blood glucose.²⁵

Recently, thiazolidinediones, known as glitazones or insulin sensitizers have revolutionized diabetic control by increasing insulin sensitivity at receptor level with a convenient single daily dose combined with sulphonylureas or insulins. The common examples are pioglitazone and rosiglitazone. One of the earlier glitazones i.e. troglitazone was taken off from the market due to its serious hepatotoxicity.

As far as insulins are concerned, there are five types of insulins namely ultra short acting, short acting, intermediate acting, long acting and ultra long acting, depending upon onset of action, peak levels and duration of action.²⁷ They can be given alone or in combination with other insulins (except insulin glargine which cannot be combined with ultra or short acting insulin due to its structure and pH) as with oral hypoglycaemic agents. Recently developed insulin is insulin lispro also called executive insulin as it is ultra short acting and reduces post-prandial increase in glucose very quickly to desired levels. Insulin glargine is ultra long acting insulin and is given at bed time with daily supplements of ultra short acting or short acting insulins for appropriate control of diabetes. The change in duration of action is due to mainly change in the sequence of amino acids in either A or B chain of insulin by recombinant technology.²⁸ These newer insulin are expensive and availability in our set up is not so convenient either. Recently, oral insulin in the form of a tablet or capsule and inhaled insulins (Exubera) have been formulated and tried but results are not encouraging. Insulin glulisine and AVE – 0277 are other new products. Pancreatic and islet cell transplantations have proved to be quite promising and might solve problems in controlling diabetes mellitus in difficult cases.

It is also stressed that one should seek new knowledge and technologies and enhance diabetic care through rapid implementation. This also includes practicing guidelines and clinical pathways that meet international standards of care. A process should be designed for consensus building and it should be locally customized to reflect the community needs and resources. This process should continuously improve quality designed to measure clinical outcome. The ultimate goal is to

establish an international set of standards that would guarantee that the individual with diabetes would survive free of complications with the help of good quality care.

To conclude, it is suggested that any newly diagnosed or suspected patient should have a comprehensive medical history including family, medical and social history. One should also review risk factors for diabetes and other associated disorders and evaluate the old monitored records if any. A complete general physical and systemic examination should be performed including cardiovascular, respiratory, abdominal and neurological examination. Thyroid gland should always be examined to rule out concurrent presence of its pathology, which is a common observation.

Laboratory estimation of glucose, HbA1c, lipid profile, creatinine, urea and urine analysis with other special investigations should be performed. Management plan should be clearly narrated including metabolic control and surveillance of complications and treatment. It is very important to assess educational needs of the patient and provide him necessary advice in this context. These patients should be reviewed at regular intervals and treatment goals should be assessed. Assessment of the complications is also important and their prompt management is very essential.

As there is no cure of this disease and only control is possible with the current therapeutic strategies, it is utmost important to focus on primary care prevention if possible and a systematic approach should be adopted e.g. a multidisciplinary approach is desired. One should also focus on people at higher risk for developing diabetes. If diagnosed, these patients should be referred to specialists and/or to organized diabetic clinics with all facilities of referral to specialists. An increasing number of such clinics should be established either at government levels or by NGO's and other beneficiaries. By adopting these steps one can control the disease appropriately, avoid a number of complications and therefore decreasing morbidity and mortality, resulting in a healthier society. These measures will ultimately result in reducing the menace of this global epidemic, which may prove to be a time bomb. Proper education of the patient in this regard is very important, so that he should

report any difficulty in controlling diabetes and any complications can be picked up as early as possible.

It is time for all health professionals to understand that diabetes needs to be treated aggressively. It is also the time for patients to understand that they should take their diabetes with utmost seriousness and the health care system to provide the necessary resources for both to be successful. Compromise or acceptance of a disadvantageous and dangerous status quo in patients with diabetes mellitus should not be acceptable any longer.

To end the discussion, there are yet poorly understood genetic factors relating to difference in individual susceptibility to development of long-term complications of persistent hyperglycaemia. It is clear that in both types of diabetes the patient's intelligence, motivation and awareness of the potential complications of the disease contribute to the ultimate outcome.

International Diabetes Federation (IDF) is absolutely right to say that diabetes will be one of the most challenging public health problems of the 21st century. The situation is particularly worrying in developing countries (Pakistan and other in this region) where detection of diabetes in the community is poor; insulin is not always and easily available, frequent problems are faced in the form of unavailability of proper care and difficulties in access to the organizations providing care. Therefore, IDF must focus on the developing world and become a more effective advocate for people with diabetes mellitus in every corner of the world if this menace had to be controlled.

It is very alarming as well to know that the global population of the world is around 6 billion, which is growing rapidly. It is also estimated that every 6th person is diabetic at present, which will be every 3rd person in 2025.²⁹ This is certainly a cause of great concern and scare but is also food for thought to control the menace of diabetes mellitus on a global level which is spreading like an epidemic.

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