Diabetes mellitus: The Silent Killer disease A Review

Neeraj Gupta

Department of Zoology, D.A.V College, Amritsar, Punjab, India

ABSTRACT: Diabetes Mellitus is a globally recognized chronic multifactorial progressive disease marked by elevated levels of sugar in the blood. It affects approximately 8.5% of the adult population in the world. Metabolic and hereditary factors along with ageing and obesity are the driving forces behind it. The actual prevalence of diabetes is relatively high because more than 50% diabetics are not diagnosed until ten years after onset of the disease. This review focuses on the causes, types, complications along with its management and treatment.

Index Terms: Blood glucose, Diabetes mellitus, Insulin, Pancreas

1) INTRODUCTION

Historically, Egyptians firstly recognized diabetes mellitus with the usual symptoms of weight loss with frequent urination reflexes. The word "diabetes" is derived from a Greek term for passing through, a reference to increased urination a common symptom of the disease. "Mellitus" is the Latin word for honey, a reference to glucose noted in the urine of diabetic patients. Diabetes Mellitus manifests as a chronic global epidemic disease as evident from recent WHO reports indicating more than 1.6 million deaths annually due to diabetes. 7% of deaths among men aged 20–69 and 8% among women aged 20–69 occur due to diabetes at global level. The estimated number of people with diabetes has jumped from 108 million in 1980 to 422 million in 2014. Its global prevalence expected to increase from 4.7% in 1980 to 8.5% by the year 2014 as predicted by recent surveys. The actual prevalence of diabetes is relatively high because more than 50% diabetics remain undiagnosed. Its prevalence has increased rapidly in low and middle income countries in last three decades (WHO. Global reports on diabetes, 2016).

Diabetic patients are prone to both short- term and long-term complications facilitating chronic health problems and premature deaths, nearly 1 death every 10 seconds (Kaul, 2012).The root causes of diabetes mellitus are unhealthy lifestyle factors such as overeating, physical inactivity, obesity or uncontrollable risk factors including genetics, family history and age. Diabetes not only affects humans but also other mammals like dogs, cats and other animals (Riaz, 2009).

2) PATHOPHYSIOLOGY OF DIABETES MELLITUS

A healthy physiological state in the human body is maintained by the differential and effective functioning of all the organ systems. Any deviation from their normal functioning led to the development of disorder or pathological state. Diabetes mellitus is one of the pathological condition in which body fails to maintain normal glucose level in the blood stream due to inability of the body to make or use insulin hormone. Insulin is needed for glucose transport into the cells so they can metabolize. The common symptoms of diabetes mellitus are hyperglycemia, polydipsia, polyuria, dehydration, polyphagia, ketoacidosis, impaired vision, increased susceptibility to infections, delayed healing of sores, fatigue, lethargy or dizziness.

2.1. BLOOD GLUCOSE REGULATION MECHANISM

Being the primary respiratory substrate, Glucose is normally found in the blood**.** When its concentration in the blood exceeds beyond 126 mg/dl of the blood volume (abbreviated as FBS/FPG, Fasting blood sugar/Fasting plasma glucose) before a meal or 200 mg/dl of the blood volume after a meal (abbreviated as RBS, Random blood sugar), the person is said to be hyperglycemic or diabetic. There are two major hormones namely insulin and glucagon which act antagonistically in order to maintain normal blood glucose level. An increase in the blood glucose level stimulates the β cells of islets of langerhans of pancreas to secrete insulin

hormone which in turn causes the transport of glucose into the liver cells where glucose get converted into the glycogen, the reserve food molecule.

Insulin is a 51 amino acid containing polypeptide hormone consisting of two chains A and B which are connected by disulphide bonds. It is firstly secreted in an inactive form pro-insulin having three chains- A, B and C and thereafter it is converted into active form by the enzymes convertases and carboxypeptidase. The insulin is the carried by the blood to the liver cell where it binds to the tyrosine kinase insulin receptor which is made up of two α subunits (extracellular) and two β subunits (intramembrane) linked by disulfide bonds. It results into autophosphorylation of the β subunit which is then followed by conversion of excess glucose to glycogen for storage (Pessin and Saltiel, 2000).

Adipose and skeletal muscle cells also get stimulated to uptake more glucose by the translocation of glucose transporter (GLUT4) to the cell surface. This control mechanism normalizes blood glucose concentration. At low blood glucose level, α cells of pancreas are stimulated to release glucagon. Glucagon signals the liver cells to convert stored glycogen into glucose which is then released into the blood to achieve homeostasis. In diabetes mellitus, there is a defect either in the synthesis or secretion of insulin as seen in type 1 diabetes mellitus (T1DM) or the development of resistance to insulin as in the case of type 2 diabetes (T2DM).

2.2 TYPES OF DIABETES MELLITUS

There are different variants of Diabetes Mellitus available in the population like type 1 diabetes mellitus (T1DM) type 2 diabetes mellitus (T2DM), Gestational diabetes (GD) Maturity onset diabetes of the young (MODY) and Latent autoimmune diabetes in adults (LADA).

2.2.1TYPE 1 DIABETES MELLITUS

T1DM previously known as insulin-dependent, juvenile or childhood-onset diabetes usually occurs in childhood and early adulthood (<35 years). It may be due to genetic and environmental factors. HLA gene present on chromosome 6 code for HLA proteins on the cell surfaces. These proteins are responsible for recognition of self or nonself by immune system. Any defect in the HLA gene results into encoding of defective HLA proteins that triggers autoimmune response of the immune cells against the β cells of pancreas. Activated CD^{4+} and CD^{8+} T cells and macrophages infiltrating the pancreatic islets attacks on β cells of pancreas and destroy them. In African and Asian populations another rare form of T1DM, called idiopathic diabetes that does not involve autoimmunity is found due to the less insulin production (Harris and Flegal,1998).Regular Administration of insulin becomes mandatory in this case to maintain glucose balance in the body for survival. In some cases, Type 1 diabetic patients develop insulin resistance due to genetic reasons or weight gain leading to development of double diabetes condition. Polyuria, polyphagia and increased thirst, loss of weight, weakness and fatigue are the common symptoms of type 1 diabetes.

2.2.2 TYPE 2 DIABETES MELLITUS: It is the most common type of diabetes worldwide accounting for 90% of diabetic cases, as per reports of NIH, USA. It has been reported that type 2 diabetes in obese persons develops resistance to endogenous insulin due to changes in the cell receptors associated with the deposition of abdominal fat whereas in non-obese persons, insulin inefficiency has been seen at the post receptor levels in addition to a deficiency in insulin production and release. Overweight and obesity are the strongest risk factors for type 2 diabetes. Physical inactivity along with a diet that is high in calories, processed carbohydrates and saturated fats and insufficient in fibre rich whole foods are promoters of type 2 diabetes. Common symptoms of type 2 diabetes are blurred vision, slow healing of sores, irritability, tingling in hands or feet and frequent infections of bladder, vagina and skin (Mehta and Wolfsdorf, 2010).

2.2.3 GESTATIONAL DIABETES

During pregnancy period, females show great deal of glucose fluctuation and often experience accelerated starvation. It raises the glucose concentration in the blood of mother leading to gestational diabetes. In majority of cases, it terminates with the termination of gestation but it increases the risk of type 2 diabetes later in life for the mother and the child.

It is associated with secretion of insulin by the placenta and a decrease in insulin sensitivity by the end of the first trimester, results in a transient state of insulin resistance. But it may prove fatal to both mother and foetus resulting into neuropathy, intrauterine growth retardation, premature delivery, neonatal jaundice; breathing difficulties in the infant and even still birth due to its potential teratogenicity (Maria, 2011). According to the American Diabetes Association about 4% of pregnant women develop gestational diabetes (American Diabetes Association, 2007).

2.2.4 MATURITY ONSET DIABETES OF THE YOUNG

It is a rare monogenic type of diabetes caused due to mutation in any one of the genes namely hepatocyte nuclear factor 4α (HNF-4α), glucokinase gene (HNF-1α), insulin promoter factor-1 (IPF-1), HNF-1β and NEUROD1 [2]. 70% cases of this kind of diabetes are associated with mutation in HNF-1 α gene. It is characterized by major defect in insulin secretion (Fajans et al., 2001). It may be caused due to secondary factors like pancreatitis, Cushing's syndrome, Klinefelter's syndrome and hyperthyroidism.

2.2.5 LATENT AUTOIMMUNE DIABETES IN ADULTS: Latent Autoimmune Diabetes in Adults (LADA) is a form of autoimmune (type 1 diabetes) which is diagnosed in individuals who are older than the usual age of onset of type 1 diabetes (with age more than 25 years). Alternate terms that have been used for "LADA" include Late-onset Autoimmune Diabetes of Adulthood, "Slow Onset Type 1" diabetes, and sometimes also "Type 1.5 diabetes". Often, patients with LADA are mistakenly thought to have type 2 diabetes, based on their age at the time of diagnosis.

3) RISK FACTORS AND CAUSES OF DIABETES

Diabetes is a chronic multifactorial disorder depending on genetics, habits and environment of a person. According to study reports of the American Diabetes Association, there is 10 to 25% chance and 50% chance of inheritance of type 2 diabetes [3, 9]. The leading factors for type 2 diabetes are lack of regular exercise, weight gain and central obesity that involves accumulation of fat around the abdomen promoting insulin resistance. Consumption of simple carbohydrates, fibre free diet and excessive intake of soft drinks pose risk to type 2 diabetes. Hypertension, hypercholesterolemia, asthma and polycystic ovarian syndrome are also linked to it. Hormonal disturbances particularly glucocorticoids, anabolic steroids and injected contraceptives may change blood glucose levels. Mumps, rubella and coxsackie virus infection may result into type 1 diabetes.

4) DIAGNOSTIC CRITERIA

Clinical diagnosis of Diabetes Mellitus involves following tests (Diabetes care, 2004):

1. Random plasma glucose ≥ 200 mg/dl
2. Fasting plasma glucose ≥ 126 mg/dl
3. Oral glucose tolerance test for gestational diabetes (measure of plasma glucose levels 2 hr after glucose is given orally >200 mg/dl)
4. Hb A1C glycohemoglobin tests (for assessing long-term control of glucose)

Another test called C-peptide test can distinguish different types of diabetes. Type 2 diabetes patients have C-peptide, which is a byproduct of insulin production, but people with Type 1 diabetes do not or have a very low level.

5) MANAGEMENT AND TREATMENT OF DIABETES MELLITUS

Diabetes can be managed by diet control and exercise, oral hypoglycemic therapy and insulin therapy. Diet is a basic part of management in every case. Treatment cannot be effective unless adequate attention is given to ensuring appropriate nutrition. Diabetic patient's diet should not contain more than 10% saturated fats or more than 300 mg Cholesterol (Zarogoulidis and as N, Kouliatsis, 2011). There should be minimum intake of 20 g dietry fibres through regular consumption of wholegrain cereals, legumes, fruits and vegetables. Excessive salt intake is to be avoided.

It should be particularly restricted in people with hypertension and those with nephropathy. Dietary treatment should aim at weight control, providing nutritional requirements, allowing good glycaemic control with blood glucose levels as close to normal as possible, correcting any associated blood lipid abnormalities. Regular monitoring of blood glucose concentration must be done by using glucometer to prevent diabetes associated complications. Type 1 diabetes patients are treated with insulin which can be administered in injectable, oral or possibly as inhaled forms, or with novel delivery systems based on nanotechnology (Chaillous et al., 2000 and Card and Magnuson, 2011).

Type 2 diabetes patients who do not follow above stated management of diabetes show increased levels of glucose concentration with glycated haemoglobin (HbA1C of >6.0). In such cases use of anti- diabetic drugs become a necessity (TNCCFC, 2008). Type 2 diabetes is generally treated by antidiabetic drugs like Alpha-glucosidase inhibitors, DPP-4 inhibitors, Biguanides, Meglitinides, Sulfonylureas and Thiazolidinediones. These anti-diabetic drugs are broadly classified into four types [2]:

a) Biguanides which reduce gluconeogenesis in the liver and include Metformin
b) Insulin secretagogues which stimulate the pancreas to secrete insulin and include drugs such as sulfonylureas
c) Insulin sensitizers which improve sensitivity of peripheral tissues to insulin and include thialzolidinediones
d) Insulin/Insulin analogues which provide insulin exogenously in the form of recombinant insulin

Certain antihypertensive like ACE inhibitors and angiotensin- II receptor blockers and antichloestrol drugs are also recommended along with these drugs to prevent diabetic nephropathy. Synthetic amylin is employed top treat type 1 diabetes. Glucagon kit can be used in cases of severe hypoglycemia or insulin shock. Research as well as technology developments in the field of diabetes with respect to its pathophysiology and management led to the development of more effective drugs that work upon incretin system and include injectable glucagon-like peptide-1 agonists (potentially stimulate insulin secretion) and oral dipeptidylpeptidase-4 (DPP-4) inhibitors (like Linagliptin, Saxagliptin, Sitagliptin, Vildagliptin inhibit the DPP-4 enzyme, and increase the circulating incretin hormone GLP-1) (Gallwitz , 2010 and Riedel and Kieffer, 2010).

In addition, sodium-glucose transport protein-2 (SGLT-2) inhibitors aiming to block renal glucose re-absorption via the SGLT-2 transporter are also being developed (Washburn, 2009). Type 1 diabetes can be treated by transplantation of whole pancreas or pancreatic islets from suitable donor but transplantation therapy is challenged by organ rejection reaction even in the presence of immunosuppressant (Vardanyan, 2010). Furthermore, researches are being carried out to develop the stem cell that can generate insulin producing β-cells (Kroon, 2008). General precautionary measures like dietary management, exercise, foot and skin care, regular monitoring of blood glucose and cholesterol may prove helpful in the avoidance of diabetes.

6) COMPLICATIONS OF DIABETES MELLITUS

Diabetes is commonly referred as silent killer disease as it attacks on multiple organs like heart, kidney, muscles, eyes and immune system leading to their malfunctioning or failure. It may involve damage to the small blood vessels (diabetic angiopathy) and contribute to diabetic neuropathy, nephropathy and retinopathy. Diabetic patients have 2 to 4 fold increased risk of developing coronary heart disease, atherosclerosis and stroke. T2DM patients generally show hypertension, hypercholesterolemia and hyperinsulinemia. 15% of diabetics develop foot ulcers and 5-15% of patients with foot ulcers need amputations.16% of diabetics are suffering from kidney failures. Diabetic retinopathy caused 1.9% of moderate or severe visual impairment globally and 2.6% of blindness in 2010. It is the second leading cause of blindness and renal disease worldwide resulting into glaucoma and cataracts (Boyle,2007 and Ceriello,2010).

However, retinopathy rates are higher among: people with type 1 diabetes; people with longer duration of diabetes; Caucasian populations; and possibly among people of lower socioeconomic status (Yau, 2010). The most commonly occurring long term complication of diabetes is neuropathy which affects more than 60% of diabetic patients resulting into loss of hearing/visual sensation, pain, weakness and even limb amputations (Casellini and Vinik, 2007 and Edwards et al., 2008). Peripheral neuropathy often causes pain or numbness in the limbs and autonomic neuropathy can impede digestion and contribute to sexual dysfunction and incontinence. Diabetics show more risk of memory loss, dementia, Alzheimer's disease and other cognitive deficits. Diabetic nephropathy is the leading cause of end stage renal failure and marked by progressive rise of albumin in urine, increase in the glomerular blood pressure as well as urinary tract infections (Selby, 1990). It requires treatment with dialysis or a kidney transplant.

7) CONCLUSION

The prevalence of diabetes is increasing at a very fast rate as indicated by world diabetes statistics that number of people living with diabetes has jumped from 108 million in 1980 to 422 million in 2014. In order to have check on the global spread of diabetes, there is urgent need to develop new strategies involving establishment of mechanisms for resource allocation effective leadership and advocacy for an integrated non-communicable diseases programme, with specific attention to diabetes. In addition to this, there is need for production of antidiabetic drugs having more efficacies along with effective developments in pancreas or pancreatic islet transplantation, β-cell regeneration and stem cell therapy.

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