The diabetes mellitus and its Secondary complication

Abdur Rahim Abidi\textsuperscript{a}, Niamatullah Zaheer\textsuperscript{b}, Pranav Kumar Prabhakar\textsuperscript{c,*}

\textsuperscript{a}Department of Biochemistry, Faculty of Stomatology, Kunduz University, Afghanistan

\textsuperscript{b}Department of Internal Medicine, Faculty of Stomatology, Kunduz University, Afghanistan

\textsuperscript{c}Department of Medical Laboratory Sciences, Lovely Professional University, Panjab, India

Abstract

Diabetes mellitus and thyroid dysfunction are the two well-known endocrine disorders which are experienced in clinical practice. Different studies have evidenced that diabetes and thyroid disorders mutually influence each other and both disorders tend to co-exist. The unidentified thyroid disorders may adversely affect the metabolic control and increase the risk of secondary complications in diabetic patients. Insulin secretion and clearance is directly controlled by thyroid hormones. In hypothyroid condition, glucose-induced insulin secretion by β-cell is reduced. While in the hyperthyroid condition the resistance of insulin is increased. The prevalence of thyroid disorders is comparatively higher in diabetic patients than in general population. The association between diabetes and thyroid disorder was found to be significant. By considering this association and interdependence of these two conditions, evaluation of thyroid hormones level along with the diabetic profile in the early stage of diabetes is recommended. This will not only help in the management of diabetes but it will also delay and avoid the progression of the secondary complications in diabetic patients, particularly those with uncontrolled diabetes.

Keyword: Diabetes; thyroid; hypothyroidism; hyperthyroidism; complications; insulin

Diabetes: A Global Challenge

Diabetes mellitus was known to human being from the very beginning. Around 3000 years prior it was reported in the manuscript of Egyptian. The diabetes mellitus, one of the most common endocrine metabolic disease, is caused due is the decrease in insulin production of insulin action and is characterised by hyperglycemia. Symptoms of remarkable hyperglycemia include polyuria, polydipsia, polyphagia, sudden weight loss, blurry vision, sexual dysfunction and susceptibility to certain infections [1].
Diabetes mellitus has been defined as “a metabolic syndrome characterized by chronic hyperglycemia and disturbance of carbohydrate, fat and protein metabolism associated with an absolute or relative deficiency in insulin secretion or insulin action” [2]. The main causes of the epidemic are considered to be the aging population, economic development, urbanization, adaptation of sedentary lifestyle, dietary modification, ethnicity, genetic predisposition to the disease, overweight, obesity, and high blood pressure [3-5]. Various new factors such as depression, sleep disorder and use of antidepressant medication have been recognized to be freely related to the risk of Type 2 diabetes.

Worldwide diabetes and its complication constitute a noteworthy health problem. Based on the International Diabetes Federation (IDF) estimation, 415 million individuals had diabetes mellitus in 2015 and it is predicted that it will be 642 million by 2040. Most of them live in the developing countries. Asia has come out the significant zone with a rapidly developing type 2 diabetes mellitus: with the highest number in China and on the Indian subcontinent. In 2010 diabetes mellitus and its complication caused 3.96 million deaths, this number projected to 5.0 million during 2015 reported by IDF which is equal to one death every six seconds. In 2015, total expenditure was 673 billion US dollars, which is 12% of global health expenditure [6]. Moreover, globally about 193 million diabetics remain undiagnosed [7].

In India, in 2011 based on the national studies 77 million people had prediabetes and 62 million people had diabetes mellitus. As per the IDF report, in 2015 there were 69.2 million individuals with diabetes mellitus and it will be 123.5 million by 2040. In 2015 USA, was the third country with the highest number (29.3 million) of diabetes mellitus patients, and in 2008, 50% of the adults whose age was 65 or more had prediabetes [8]. In Latin American countries such as Mexico and Brazil, 25% of the health expenses contribution is on metabolic disorder and related complications [8].

The Middle East might be the next diabetes epicentre. Oman (with 9.5%) and Saudi Arabia (with 25.4%) are the two countries which have a high prevalence of diabetes mellitus among the adult population [9].

Current scenario of diabetes in India

India is one of the developing countries; people are economically making progress and tend to urbanization, carry a considerable increment in occurrence of DM and share a lot to global diabetes burden. Studies over the period 1990-2000 have shown a huge rise in the diabetics population in India from 5%- 15% in the urban population,
4.2% - 6.2% in semi-urban population and 2% - 5% among the rural population according to the WHO Standard or American Diabetes Association (ADA) criteria [1]. Recent studies conducted in different states of India have shown an increment in the prevalence of diabetes and prediabetes in both villages and cities populations. In the rural population, it is estimated approximately 10% while in urban populations 20%. There are several factors which contribute the rise in the prevalence of diabetes, and recognition of these contributors is considered to be important in the prevention of the disease burden. What are the factors which contribute to the prevalence of diabetes in India and making this problem so serious? Many factors are involved in the etiology of diabetes in India, such as genetic factors; along with others environmental factors like obesity due to a sedentary lifestyle, urbanization and lifestyle modifications.

Large community-based studies conducted by the ICMR (Indian Council of Medical Research) have shown that in Northern states of India like Jharkhand and Chandigarh comparatively less number of population is affected by diabetes mellitus than in Maharashtra and Tamil Nadu. This difference might be due to the reason that north Indians are vagrant Asian population while south Indians are the host populaces, however, this conveyable reason isn’t supported by other research studies [10].

**Classification of Diabetes Mellitus**

Diabetes can be generally categorized into the following four classes:

1. Type 1 diabetes mellitus (T1DM)
2. Type 2 diabetes mellitus (T2DM)
3. Gestational diabetes mellitus (Identifying during the second or third trimester of pregnancy)

(a) Type 1 diabetes mellitus (T1DM)

This is immune-mediated diabetes. Formerly it was known as “Insulin-dependent diabetes or juvenile-onset diabetes”. It constitutes 5-10% of diabetic cases. In Type 1 diabetes, due to the autoimmune destruction of the beta cells of the pancreas, there is insufficient amount insulin or no secretion of insulin [12]. This type of diabetes is usually characterized by the production of autoantibodies to insulin and glutamic acid decarboxylase (GAD), or islet cell autoantibodies, which recognize the autoimmune process and cause beta cells destruction [11]. The rate of the beta cell destruction varies in different individuals; in infant and children, it is rapid, while in adults it is slow. Youngsters and youths may have ketoacidosis as the early sign of the illness, while others may have mild
fasting hyperglycemia. In the presence of infection or other stress, it can be soon converted to severe hyperglycemia or ketoacidosis. For many years cells function efficiently to prevent ketoacidosis but such patients finally become insulin dependent for their survival, and they require insulin from the outside to maintain normoglycemia. These individual are at higher risk of developing ketoacidosis. The Insulin secretion decrease or diminished which is evident by the reduction or undetectable level of C-peptide in the plasma. Type 1 diabetes is generally occurring in the younger and adolescent but it can happen in the older persons at the age of 80-90 as well. T1DM patients are more prone for susceptible to other autoimmune diseases such as Hashimoto’s thyroiditis, Addison’s disease, Graves’ disease, vitiligo, myasthenia gravis etc.

(b) **Type 2 diabetes mellitus (T2DM)**

Formerly, known as “non-insulin dependent diabetes mellitus, or adult-onset diabetes”. This is the more common type (90-95% of all diabetic cases) of diabetes mellitus particularly in those women who have the history of Gestational diabetes. Both hereditary and environmental factors are engaged in the pathogenesis of T2DM [11]. People with type 2 diabetes have insulin resistance and insulin deficiency throughout their lifetime. Such individual doesn’t need to take insulin therapy for their survival. The two critically important factors which occur early manifestation in the pathogenesis of T2DM are resistance of insulin and the pancreatic beta cells dysfunction [12].

**Pathophysiology and major risk factors**

Insulin level in the blood is maintained by the feedback mechanism. In type 2 diabetes this feedback loop is abnormal which resulting in insulin resistance and β-cells dysfunction, due to this the metabolic process in the insulin specific tissue like muscles, liver and adipose tissues are affected, which cause an abnormal level of glucose in the blood. In addition, insulin resistance helps in increasing glucose synthesis in the hepatic tissues and reduces glucose uptake in the muscles and adipose tissue. Beta-cells dysfunction also supresses the insulin secretion, and ultimately the body glucose level rises [1].

Several risk factors are engaged in the development of T2DM such genetic, epigenetic and lifestyle factors. Modifiable risk factors such as obesity, sedentary lifestyle, smoking, high blood pressure, dyslipidemia, inflammation and intrauterine environment. Nonmodifiable hazard factors are age, gender, any kind of parental
history of diabetes, ethnicity and PCOS. A few other new factors have been recognized which are independently linked with the risk factor of T2DM like depression, sleep disorders, use of antidepressant drugs.

(c) Gestational diabetes

On the basis of operational classification, not a pathophysiologic condition, gestation diabetes is identifying in the women in the second or third trimester during gestation period. Women having undiagnosed T2DM without any symptoms or women who has developed T1DM during their gestation period categorized with Gestational diabetes. Disorder related to Gestational diabetes mellitus has started mostly in the 3\textsuperscript{rd} trimester of gestation period [11].

(d) Other specific type of diabetes (monogenic diabetes)

Apart from the above three major classes of diabetes, a number of other category of diabetes also exist with known etiologies which includes any kinds of hereditary defects in the pancreatic cell function, Monogenic syndrome such as MODY (maturity-onset diabetes in youth), persons with a disease of the exocrine pancreas (like cystic fibrosis), drug-induced diabetes (HIV/AIDS treatment), chemical induced diabetes and infections mediated diabetes (cytomegalovirus, adenovirus) [11].

Clinical Characteristics of Diabetes Mellitus

Both T1DM and T2DM have almost similar symptoms but differ in their degree and the symptoms are more common and develop more rapidly.

(a) Clinical conditions of T1DM: Some of the well studies symptoms of T1DM are frequent urination, always thirsty, always hungry, decrease in weight, constipation, cramps, tiredness, blurred vision, and fungal infection such as candidiasis. Chronic subjects with T1DM are prone to develop secondary complications. T2DM patients are more susceptible to develop secondary complications. Most cases are identified because of its complication or incidentally. Macrovascular complications are commonly related to high blood pressure, dyslipidemia, overweight, and obesity. Mortality in T2DM patients is mostly occurring due to cardiovascular disease and end-stage renal disease (Table 1) [11].

Table 1. Clinical characteristics of Type 1 and Type 2 diabetes in children and adolescents
Diabetic Secondary complications

The main problem in the case of diabetes is the its secondary complications. The important acute metabolic complications such as diabetic ketoacidosis, hyperglycemia, and nonketotic hyperosmolar coma. Chronic complications include injuries to blood vessels. Long-term abnormalities affect many different organs systems and lead to increase morbidity and mortality among diabetic persons. Chronic complications are classified into two major groups; microvascular complication and macrovascular complications. In addition, diabetes causes some other chronic complication like depression dementia and sexual dysfunction. Diabetes is often accompanied by hypertension. Chronic increased blood glucose level is associated with long-term damage and failure of different organ system such as eyes, kidney, nerve, and heart [7, 13].

DCCT and EDIC have demonstrated that in T1DM patients with regular clinical management the associate risk of major chronic secondary abnormalities like retinopathy (47%), chronic kidney disease (17%) and for cardiovascular disease (14%). Limited data are available for T2DM, and there is comparatively difference in the proportion of different severity in the Asian and Caucasian populations. Which shows that the Asian population has a comparatively reduced risk for the cardiovascular disorders than Caucasian and higher prevalence of nephropathy [1,13].

- **Diabetic microvascular complications**: Microvascular complications are retinopathy, nephropathy, and neuropathy. Till now the pathophysiology of these complications has not been fully understood, but many clinical investigations have demonstrated that hyperglycemia; a characteristic property of diabetes plays a crucial role in the pathogenesis of these complications [13]. Several other molecular mechanisms and pathways, which are engaged and may play an important role in the pathophysiology of these
microvascular diabetic complications such as Sorbitol pathway, glycated end product pathway, PKC pathways, hexosamine pathway and oxidative stress [6-7].

(i) **Diabetic retinopathy:** This is a disease of the retinal vasculature, the light-sensitive tissue that finally leads to blindness. A study conducted by Fong *et al* have shown that every year in the United States, diabetic retinopathy causes around 10000 new cases of blindness. The significant risk factors responsible for the development and progression of diabetic retinopathy are the duration of diabetes, the intensity of hyperglycemia as well as hypertension [14]. Several pathological mechanisms are engaged in the progression of diabetic retinopathy such as polyol pathway; in this pathway, the excess amount of glucose is changed to sorbitol by aldose reductase enzyme which deposits in the cells. Sorbitol has a hygroscopic property which retains water. Osmotic pressure caused by the accumulated sorbitol has been considered to be a fundamental mechanism in the progression of diabetic retinopathy. Nonenzymatic production of advanced glycosylated end products (AGEs), which is promoted by hyperglycemia has also been associated with the production of microaneurysms and pericyte loss. Oxidative stress is another important mechanism in the progression and development of diabetic retinopathy. Hyperglycemia stimulates the formation of free radical and reactive oxygen species (ROS) which causes cellular injury [14]. The investigation has demonstrated that vascular endothelial growth factor (VEGF) is a significant mediator in the pathogenesis of diabetic retinopathy. It enhances angiogenesis and is highly expressed in the retina of a patient with proliferative diabetic retinopathy. Hypertension worsens diabetic retinopathy by an alteration in the blood flow and VEGF dependent pathways. In hypertensive diabetic patient, the retinal blood flow is increased. Thickening of retinal capillary basement membrane causes reduces in contractility of retinal pericytes, which may result in impair retinal blood flow regulation. Hypertension increases the retinal expression of the VEGF receptors [6, 14].

(ii) **Diabetic neuropathy:** Diabetic neuropathy is the most widely recognized long-term complication of diabetes. The major risk factors for diabetic neuropathy are the duration of diabetes, levels of glycated hemoglobin, and hypertension. The molecular pathway engaged in the pathogenesis of diabetic neuropathy are polyol pathway, increase in the production AGEs due to chronic hyperglycemia. Decrease nerve oxygenation is another important factor recommended to be related to diabetic neuropathy. Neurovascular structural alterations like thickening of the basement membrane,
endothelial cell hyperplasia, degeneration of pericytes and arterial-venous shunt happen in diabetic neuropathy patients. These structural changes lead to ischemia in peripheral neurons, which induce peripheral neuronal injury by increasing oxygen reactive species [13].

(iii) **Diabetic nephropathy:** Diabetic nephropathy is the primary cause of kidney failure and associated with increased cardiovascular disease (CVD). It causes albuminuria and decrease in glomerular filtration rate. A moderate increase in microalbuminuria (30-299 mg/day) indicates the progression of diabetic kidney disease. The rate of albuminuria increase by 10-20% per year without proper treatment, resulting in a reduction of glomerular filtration rate (GFR) by 2-20 ml/1.7m²/year. When the amount of urine protein is more than 300 mg/day it is called overt nephropathy. The cause of diabetic kidney disease which leads to glomerular injury and proteinuria is increased level of blood glucose, increased glomerular pressure and increased glomerular filtration. Diabetic kidney disease causes pathological alteration to the kidney such as an increase in the glomerular basement membrane thickness, production of microaneurysm and formation of a mesangial nodule. The modifiable risk factors for diabetic nephropathy are hyperglycemia, dyslipidemia, hypertension, increased glomerular filtration, smoking and protein intake [13-14].

(a) **Macrovascular complications (Cardiovascular diseases):** Macrovascular complications are the main cause of death among diabetic individuals. Reports from 10 centers worldwide have shown 44% of death in Type 1 and 52% in Type 2 diabetic patients. Mainly atherosclerosis is engaged in the pathogenesis of macrovascular complication. It causes narrowing of arterial wall throughout the body. A study conducted by Framingham have shown that the occurrence of coronary artery disease in diabetic patients is 2-3 times higher as compared to nondiabetic subjects. There is a similar risk of myocardial infarction in a diabetic patient without prior myocardial infarction and nondiabetic individuals [12].

**Conclusion**

Worldwide diabetes is one of the main cause of morbidity and mortality. It is a global health burden and its incidences are increasing day by day. The metabolic disorder related to diabetes causes secondary pathophysiologic changes in multiple organ systems resulting in macrovascular and microvascular complications. Thyroid disorders are the second most well-known endocrine in the general population. Both the diseases tend to
coexist so it is common for an individual to be affected by both diabetes and thyroid diseases. Recent investigations have shown a very high prevalence of thyroid disorders in diabetic patients.

References


