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Review Article

Type 2 Diabetes Mellitus: The Concerned Complications and Target Organs



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ABSTRACT

Diabetes has been considered as the most dreaded non-communicable disease consuming the mankind rapidly. WHO has predicted the number of diabetics to be approximately 366 millions by 2030. The disease is characterized by hyperglycemia and the basic symptoms are polyphagia, polydipsia and polyuria. The autoimmune type 1 diabetes represent almost 1% of the total diabetic population, the rest being that of type 2 diabetes (T2D). Type 2 diabetes has been linked to a variety of factors such as heredity, environmental factors, unhealthy eating habits, sedentary lifestyle, stress etc. The uncontrolled hyperglycemia has profound deleterious effects on almost all the organs and results in various cardiovascular disorders, retinopathy, neuropathy, and nephropathy. Recent studies have revealed an array of pulmonary dysfunctions related with T2D ranging from respiratory defects to tuberculosis. Diabetes also predisposes the person to hepatic dysfunctions like NAFLD and HCC and a range of infections at various sites which are difficult to manage. Post-surgical infections are of special interest for subjects with uncontrolled hyperglycemia prior to surgery. Scientists all over the world are revealing different pathways and associated therapies for type 2 diabetes in order to control the pathological effects covering almost whole body physiology.

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1. Introduction

Type 2 diabetes mellitus (T2DM) has been one of the most widely diagnosed non-communicable diseases in adults worldwide. The reason expands from genetic predisposition, environmental factors, obesity, sedentary lifestyle, polycystic ovary syndrome (PCOS), unhealthy eating habits etc. The number of diabetic patients, as predicted by WHO would approximately be 366 millions by the year 2030.¹ The type 2 diabetes patients experience unusual polyuria (frequent

urination mainly nocturia), polydipsia (thirst) and polyphagia (excess hunger) and weight loss as most general symptoms apart from the hyperglycemia.^{2,3} The uncontrolled high blood glucose leads to serious health complications and may even be fatal. Diabetes has been a major risk factor for cardiovascular disease and stroke and the diabetic adults have 2–4 times increased chance of such pathologies.⁴ Other major effects include retinopathy, nephropathy and neuropathy. The current most effective parameter for predicting diabetes is the measurement of glycated hemoglobin (HbA1c).⁴

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2. Pathophysiology of type 2 diabetes mellitus

The glucose obtained from food is either immediately utilized by the body or is converted to liver and muscle glycogen (storage polysaccharide) and adipose triglyceride (energy reservoir) by the action of insulin. Diabetes mellitus is the condition when the body is incapable of utilizing the glucose present in the blood for various cellular activities. According to the Williams Textbook of Endocrinology (10th edition), the pathophysiology of type 2 diabetes primarily demonstrates the following three abnormalities: (i) non-responsiveness of insulin receptors even though the body exhibits the physiological insulin level; (ii) the body is not manufacturing enough insulin; (iii) increased hepatic glucose production.

A decreased insulin secretion results from impairment in glucose response by insulin secreting β -cell of pancreas. A mutation in glucokinase gene, which plays an important role in glucose sensing mechanism of pancreatic beta cells, is also an important factor of impaired glucose tolerance in pancreas. Insulin resistance, on the other hand, is the condition when the insulin receptors become less responsive towards insulin even when the hormone is present in physiological amount. This condition is attributed to many factors major being the obesity which exerts its effect via free fatty acids and inflammatory cytokines (like $TNF-\alpha$) which downregulate the insulin receptor and insulin receptor substrate (IRS) protein^{5,6} (Fig. 1).

The diagnosis of diabetes depends on the conventional criteria of fasting plasma glucose (FPG) and 2 h post-prandial plasma glucose (2h-PG) where $FPG \leq 126 \text{ mg/dL}$ (7.0 mmol/L) and $2h-PG \leq 200 \text{ mg/dL}$ (11.1 mmol/L). The latest addition to the diabetes diagnosis has been the calculation of glycated hemoglobin (HbA1c) which has been treated as better criterion than the former two as it estimates an average hyperglycemia over several months with International Diabetes Federation (IDF) declared this in 2009 and American Diabetes Association (ADA) adopted in 2010. The cut-off for HbA1c has been 6.5%.⁷

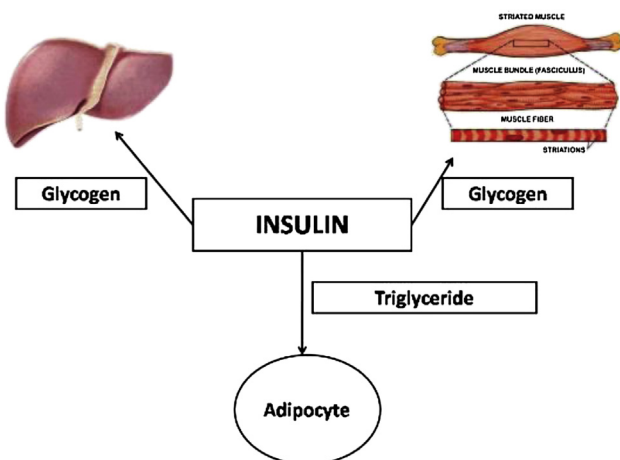


Fig. 1 – Physiological action of insulin on liver, muscles and adipocytes.

3. Diabetes related complications

According to the American Diabetes Association, a diabetes patient, as compared with the normal non-diabetic one, has approximately 7 year shorter life span resulting from various diabetic related complications.⁷ Some of the major complications include coronary artery disease, stroke, peripheral vascular disorders, nephropathy, neuropathy and diabetic retinopathy. People having diabetes have greater risk of acquiring cancer, cardiovascular complications and renal failure because of their susceptibility towards the diseases⁷ (Fig. 2).

3.1. Cardiovascular disorders

Uncontrolled hyperglycemia results in non-enzymatic glucose (aldose sugar) attachment (glycation) on the physiological proteins and lipids which disrupts their normal function and increases the related pathology. These altered products are known as advanced glycated end-products (AGEs) and the reaction involving the formation is known as Maillard reaction. The AGE receptors, known as RAGE belonging to immunoglobulin superfamily, have been shown to influence the cellular signaling on binding with AGEs. Cross-linking of AGEs with type I collagen and elastin in vessel wall leads to vasculature stiffness. Studies suggest that lipid AGEs like glycated LDL reduces the nitric oxide (NO) production which is a vasodilator and suppresses LDL receptor mediated LDL uptake by endothelial cells. The suppression of NO production from endothelial cells due to action of AGEs in diabetic patients can be an important factor promoting the atherosclerosis since NO show a range of anti-atherogenic actions like inhibition of platelet adhesion and aggregation, leukocyte adhesion to vessel walls etc.^{8,9}

The vascular conditions arising from AGEs namely arterial stiffness and platelets adhesion & aggregation can lead to stroke, myocardial infarction, cardiac failure and overall

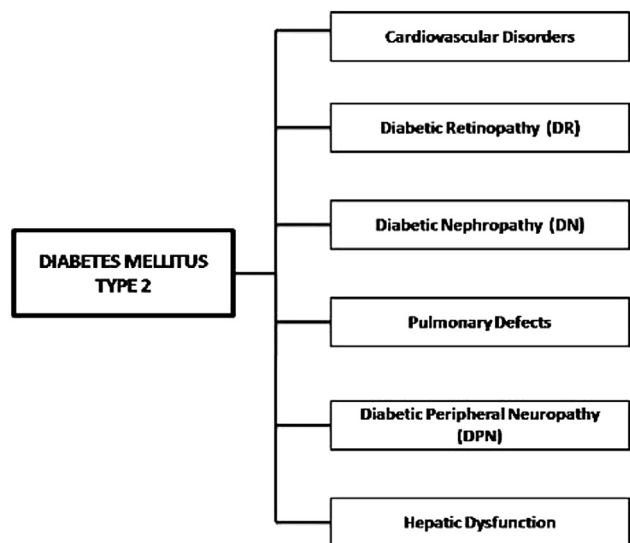


Fig. 2 – Major pathological conditions associated with diabetes type 2.

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