IJPSR (2020), Volume 11, Issue 3 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 16 June 2019; received in revised form, 29 November 2019; accepted, 20 February 2020; published 01 March 2020

A REVIEW ON IMPAIRMENT IN METABOLIC PATHWAYS DUE TO TYPE 2 DIABETES MELLITUS

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Keywords:

Micro and macrovascular complications, Reactive oxygen and Nitrogen species, Metabolic Pathways, Anti-oxidants, Oxidative stress

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ABSTRACT: Despite years of intensive research, impairment in metabolic pathways due to type 2 diabetes mellitus continues to be a daunting global challenge. It is equally challenging problem in this region as well. In recent years there is growing clinical and experimental evidence that oxidative stress plays an important role in induction and promotion of diabetes and its associated complications. Lipid peroxides are known to be essential consequence of biological processes of excessive oxidative cellular damage can be a cause of consequences of numerous diseases, micro and macro complications of type 2 diabetes mellitus. There have been reports of elevated lipid peroxide levels in type 2 diabetes. To defend themselves against these free radical attacks, cell has developed different antioxidant systems. There are low molecular weight antioxidant molecules like uric acid, ascorbic acid, *etc*. and antioxidant enzymes superoxide dismutase, catalase and glutathione peroxidases. Under physiological conditions, these defense mechanisms maintain a low steady-state concentration of free radicals in the cell and their activities are very precisely regulated. The levels of these parameters are altered during the development of diabetes.

INTRODUCTION: "All the diseases are the result of a collection of waste materials, the latter being initiated by many causes to produce symptoms; wastes collect due to in correct dieting and living".

– Atharva-Veda

Impairment in metabolic pathways due to type 2 diabetes mellitus, are main causes of morbidity, mortality and third leading cause of death in many developed countries. Diabetic dyslipoproteinemia is the main cause of heart attacks in diabetic patients. Diabetes is one of the major causes of blindness, renal failure, stroke, and nephritis, *etc*.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(3).1089-97

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(3).1089-97

Diabetes is as old as mankind and its incidence is considered to be high all over the world (Picup and Williams [1]. In ancient India, diabetes was also known as "Madhumeha" [2]. The worldwide prevalence of diabetes mellitus has risen dramatically over the past two decades. It is projected that the number of individuals with diabetes mellitus will continue to increase in the future as the prevalence of diabetes mellitus among adults in the United States increased from 12.3% to 13% between 1994 to 2000 [3-6].

The prevalence of diabetes in our country is 2.4% in rural and 8.2% in urban areas and the rate of prevalence increases per year. It has been reported that in February 2005 approximately 60 million people in India are suffering from this disease [7-15]. Clinically diabetes mellitus is a heterogeneous disease with a common phenotype of impaired glucose tolerance.

More than fifty genes have been identified in the regulation of lipoprotein metabolism, giving rise to a novel molecular pathophysiological basis for dyslipoproteinemia and other disorders related to liver homeostasis [16-20]. The most common abnormalities of lipid metabolism in diabetes are hypertriglyceridemia and hypercholesterolemia. Not only hyperglycemia, but dyslipoproteinemia is also responsible for death in diabetic patients [21-28].

Diabetes mellitus can be divided in type-I, Insulin-dependent diabetes mellitus (IDDM) and type-II Non-insulin dependent diabetes mellitus (NIDDM), type-I diabetes mainly occurs in childhood and puberty and is characterized by absolute insulin deficiency. Type-II diabetes usually develops in adults over age 40 and is characterized by insulin resistance [29-30]. In the pathogenesis of some forms of diabetes, it is observed that malnutrition is also one of the causes of this disease. Financially weak communities in tropical developing countries are highly prone to malnutrition-related diabetes mellitus, MRDM. Moreover, it has been suggested that the deficiency of antioxidant and trace elements such as Zn, Cu, Cr, Ni, Mn may also play a role in diabetes mellitus with dyslipoproteinemia. Endothelial function is abnormal in both the macro and microcirculation in subjects with type-I and type-II diabetes mellitus [31-38]. Furthermore, endothelial functions are impaired in healthy subjects who are at risk of developing type-II diabetes by virtue of having one or both parents with type-II diabetes, with or without impaired glucose tolerance. Previous studies in children have highlighted the concern for type-II diabetes and pre-diabetes or impaired glucose tolerance [39-40]. This significant clinical issue is greater for overweight children and especially among certain ethnic groups. Insulin resistance in type-II diabetes is developed due to increased levels of plasma free fatty acid.

These free fatty acids promote diabetic dyslipoproteinemia through increasing VLDL synthesis in the liver which generates atherogenic lipoprotein-profile and facilitates the development of atherosclerosis and increases the risk of cardiovascular disease, the most common cause of death in diabetes type-II, patients. High-density lipoprotein and apolipoprotein A^{-1} may prevent the origin and development of obstructive disease [41-52].

The excess release of fatty acids, lipid and fat deposition in various tissues are root causes of atherosclerosis and coronary artery disease. Hemorrhagic abnormalities are also responsible for atherosclerotic processes. Abnormalities in insulin and glucose do not seem to entirely account for the high frequency of cardiovascular disease in patients with type-II diabetes mellitus. An important additional factor may be hyper-triglyceridemic hyper apo-B, an atherogenic dys-lipoproteinemia that is common in these patients. The major feature of hypertriglyceridemic hyper apo-B is hypertriglyceridemia, low levels of high-density lipoprotein cholesterol and increased number of small dense low-density lipoprotein particles [53].

Serum lipoproteins are known to play a key role in the transport and metabolism of lipids. In normal animals, the concentration and distribution of various lipoproteins have definite range. The incidence of hypercholesterolemia and cardio-vascular disease is directly related to the increased lipid contents of lipoproteins. The apolipoproteins have an affinity to bind with phospholipids, triglycerides, cholesterol and form three major types of lipoproteins *i.e.*, low-density lipoprotein, very low-density lipoprotein, and high-density lipoprotein. In recent years series of studies on high-density lipoprotein has drawn much attention due to their significant role in the regulation of lipid metabolism. Apart from the role of high-density lipoprotein to regulate the lipid metabolism in the body it also possesses the property of biological antioxidant [54-61].

Qualitative or quantitative abnormalities of plasma lipoprotein metabolism are known as dyslipo-proteinemia. Five types of dyslipoproteinemia were identified by scientists. Type-I dyslipoproteinemia occurs in childhood with abdominal pain and pancreatitis. Type-II dyslipoproteinemia or familial hyper cholestrolemia manifests itself clinically by xanthomata, corneal arcus, and premature athero-sclerotic disease. Type-III dyslipoproteinemia manifests clinically by accelerated atherosclerosis of the coronary and peripheral arteries and by characteristic tuberoeruptive and planar xanthomas. Type IV dyslipoproteinemia is characterized by an increased level of plasma triglycerides and very low density lipoprotein.

Type-V dyslipoproteinemia or hyper lipo-proteinemia is characterized by elevated levels of both VLDL and chylomicrons, retinalis, eruptive xanthoma and pancreatitis [62-79]. Free oxygen radicals and oxidative stress is responsible for diabetic dyslipoproteinemia and other secondary complications in diabetes mellitus. Severe hyperglycemia cause generation of reactive oxygen species which are involved in peroxidative degradation of lipid. Increased lipid peroxides have been noted in diabetic patients and experimental animals. Oxidative modification in low-density lipoprotein (LDL) is atherogenic.

Retinal oxidative stress is increased in diabetic patients and rats due to downregulation of antioxidant defense enzymes like glutathione reductase (GSH) [80-83]. Prevention of diabetes still lies in the realm of future on until then tens of millions will continue to suffer from this disease.

Etiology: Diabetes mellitus is characterized by essential biochemical changes like lowered glucose tolerance, hyperglycemia, and glycosuria. The basic defect is an absolute or relative lack of insulin, either due to its antagonism by excessive secretion of other hormones having an opposite action or due to insulin antibodies or due to some other reasons the insulin is not able to act on the target cell which leads to abnormalities not only of carbohydrate but also of fat and protein metabolism. The failure of glucose utilization through the normal pathways for the production of energy in the deficiency of insulin results in fat mobilization from the adipose tissue leading to elevated levels of cholesterol, triglyceride (TG), free fatty acids (FFA), lipoproteins and ketone bodies [84-95].

Carbohydrate Metabolism: One of the most important actions of insulin is to promote the entry of glucose into the cell from extra cellular fluids. It increases its conversion into glycogen by increasing the activity of glycogen synthetase and thus promotes glycogenesis. It also promotes utilization of glucose in the cell for the production of energy both through Embden Meyerhof pathway, acting on enzyme glucokinase, phosphofructokinase and pyruvate kinase and through HMP shunt by increasing the availability of glucose for glucose 6-phosphate and NADPH (co-factor) in the cell.

It also inhibits gluconeogenesis by inhibiting the enzyme pyruvate carboxylase, phosphoenol pyruvate carboxylase, fructose, 1, 6 bisphosphatase and glucose 6-phosphatase. Due to the above action, it reduces blood sugar level and its deficiency leads to hyperglycemia glycosuria and increased glycosylation of hemoglobin leading to an increased level of HbA_1C in blood [90-96].

Glycosylated Haemoglobin: The evaluation of glycosylated Hb in diabetes began in 1958 when Allen showed chromatography heterogeneity of hemoglobin [97]. Tehran first demonstrated elevation of minor hemoglobin in diabetes mellitus introduced the column method of separating out the fast hemoglobin, pointed out that HbA_1C is related to control of diabetes. The advantages of Gly Hb estimation are those of a simple procedure, lack of any need for dietary preparation or for fasting, elimination of the variability usually found an oral glucose tolerance tests as well as an accurate reflection of overall chronic hyperglycemia [98-101].

Reaction Leading to the Formation of HbA_1C:

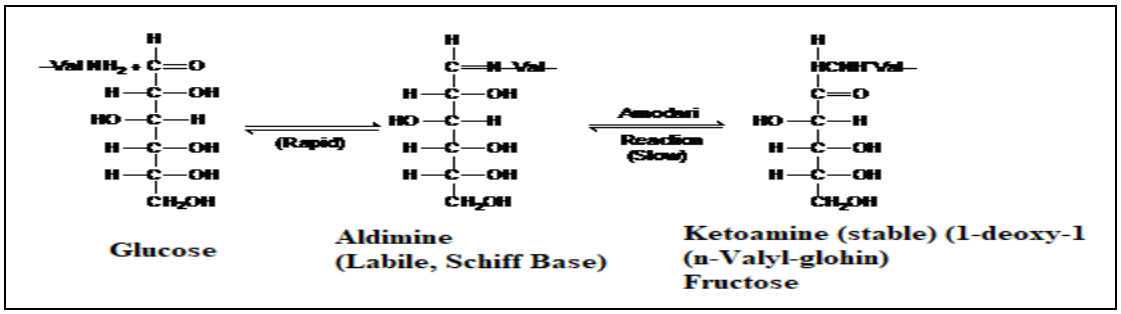

FIG. 1: GLYCOSYLATED HAEMOGLOBINS ARE THE RESULT OF SIMPLE CHEMICAL REACTION BETWEEN HAEMOGLOBIN AND SUGARS AFTER SYNTHESIS OF HAEMOGLOBIN IS COMPLETE *i.e.* POST TRANSLATIONAL MODIFICATIONS

Lipid Metabolism: Insulin promotes the entry of fatty acids from the extracellular fluid into the cell, increases the availability of NADPH from HMP shunt, D-glycerophosphate through glycolysis and acetyl COA from pyruvate, which is derived mainly from carbohydrate and also protein. Thus it promotes fatty acid synthesis in tissues that possess an active HMP shunt. These tissues are specialized in active lipogenesis, *e.g.*, liver, adipose tissue, and lactating mammary glands. Insulin inhibits the mobilization of triglyceride in the form of fatty acids from adipose tissue, inhibiting the activity of hormone-sensitive lipase. In diabetes mellitus, lack of insulin make adipose tissue more sensitive to mobilize an increased amount of free fatty acids in plasma. Plasma concentration of cholesterol and phospholipids undergo very little change in comparison to the other group of neutral lipids. The increased level of plasma cholesterol may also be due to reduced activity of HMGCOA reductase in diabetes. The liver is a major site of synthesis of endogenous triglyceride and the greatest portion of circulating prebeta lipoproteins (VLDL).

An important source of triglyceride synthesis in plasma free fatty acids, the quantity of which is increased primarily by any factor that increases lipolysis or decreases glycerol esterification in adipose tissue. In diabetes, the fasting hyper-lipidemia and hyperlipoproteinnemia occur. Due to increased level of VLDL and triglycerides, an elevated level of cholesterol is usually visible.

It has been reported that the levels of high-density lipoprotein cholesterol (HDL-TC) are decreased or remains unchanged. An elevated level of VLDL triglyceride has been found in all major classes of diabetic patients usually associated with inadequate salinization. In untreated juvenile-onset diabetics, there is little evidence of increased VLDL triglyceride production. The deficiency of insulin appears to result in altered low and high-density lipoprotein composition.

The mechanism for changes in the HDL is unknown but in the light of present knowledge the presence of triglyceride enriched low-density lipoprotein could mean that a less dense moiety of LDL may be accumulating in diabetic plasma and this could be due to altered rates of turnover of Apo-B containing lipoproteins [102-112].

Lipoprotein Profile: Incubation of LDL cholesterol with glucose, at concentrations observed in diabetic condition, increased susceptibility of LDL to oxidation as measured by TBARS and conjugated diene formation, electrophoretic mobility and degradation by macrophages. LDL and RBC membranes isolated from type-I and type-II DM patients were much more susceptible to oxidation than LDL from normal subjects. Furthermore, the susceptibility of LDL to oxidation was strongly correlated with the degree of LDL glycosylation. Plasma TRAP (total peroxyl radical trapping potential) was lower and susceptibility of LDL to oxidation as measured by the lay phase of conjugated diene formation after initiation of LDL oxidation by the addition of copper was greater in the poorly controlled type-I diabetic subject than in normal subjects.

In contrast, there was no difference between type-I diabetic patients and non-diabetic subjects in the susceptibility of LDL and VLDL cholesterol to oxidation in a number of studies. Although, there was no difference between the groups for LDL vitamin E content, LDL fatty acid composition in cholesterol esters or triglycerides, LDL glycation was elevated in the type-I DM subjects. Dyslipoproteinemia is involved in the origin of arteriosclerosis by changing the architecture of the coronary artery wall and therefore represents an important factor in the development of coronary artery disease (CAD). High-density lipoprotein (HDL) and apolipoprotein-A1 (Apo-A1) serves a projection against the origin and development of the coronary obstructive disease.

Abnormalities in insulin and glucose metabolism do not seem to entirely account for the high frequency of cardiovascular disease in patients with type-2 diabetes mellitus. An important additional factor may be hypertriglyceridemic hyper apo B and atherogenic dyslipoproteinemia that is common in these patients. Coronary artery disease is becoming more prevalent in developing countries, particularly in urban areas. More than 75% of patients with diabetes mellitus die from acute ischemic events, *e.g.* myocardial infarction or stroke. Diabetic dyslipoproteinemia characterized by hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol and often elevated low-density lipoprotein (LDL) cholesterol with

predominance of small, dense LDL is a strong risk factor for atherosclerosis. Dyslipoproteinemia is probably the principal cause of endothelial dysfunction of conduit arteries in patients with nephrosis and the basis for their increased risk of cardiovascular disease. The strong association between coronary heart disease and dyslipo-proteinemia has often overshadowed the effects of the non- lipid risk factors-smoking, hypertension, obesity and diabetes, and impaired glucose tolerance and even led to questioning the importance of these risk factors in the presence of a favourable lipoprotein profile. Elevated levels of plasminogen activator inhibitor-1 (PAI-I) with and without reduction of tissue plasminogen frequently found in patients with diabetes mellitus.

Coronary events have a close association with a low HDL/hypertriglyceridemia (LHDL/HTG) phenotype. As enzymes that hydrolyze triglyceride-rich lipoproteins are associated with modulation of both HDL cholesterol and triglycerides, the mutation in the gene encoding lipoprotein lipase (LPL) or hepatic lipase (HTGL) may contribute to the formation of coronary atherosclerosis and thus, of coronary heart disease (CHD). A primary cause of abnormal lipids and lipoproteins is genetic. There are also a number of secondary causes of lipid and lipoprotein abnormalities. These secondary causes include endocrine problems, metabolic syndrome, certain pharmacologic agents and infection [113].

In mediating the transfer of cholesterol esterase from anti-atherogenic HDL to proatherogenic apolipoprotein (apo-B) containing lipoprotein particles (including VLDL, IDL, LDL, the cholesterol ester (CE) transfer protein (CETP) plays a critical role not only in the reverse cholesterol transport (RCT) pathway but also in the intravascular remodeling and recycling of HDL particles. Catabolism of circulating triglyceride-rich lipoproteins requires their interaction with lipolytic enzymes available to the plasma space.

As a result of this process, chylomicrons are converted to smaller remnant particles before their uptake by the liver. VLDL is degraded to IDL and then to LDL. This stepwise catabolism of chylomicrons and VLDL may be mediated by more than one enzyme.

Two lipolytic enzymes known to be present on the luminal surface of the endothelial cells are lipoprotein lipase and hepatic triglyceride lipase. The function of (LPL) has been studied extensively over the past 25 years and it now seems clear that this enzyme is primarily responsible for the hydrolysis of most circulating triglyceride. By contrast, the physiologic function of the hepatic triglyceride lipase is not established [114-124].

Protein Metabolism: Insulin stimulates protein synthesis and amino acid uptake especially in muscle and inhibits protein catabolism and output of amino-acids from muscle. Insulin deficient muscle takes up and incorporates less amino acids into protein resulting in decreased protein synthesis and release more amino acids into the bloodstream. Increased catabolism of protein leads to an increase in the level of urea in the blood. The elevation of especially branched-chain amino-acids in the blood is reported by. Most of the chronic complications of diabetes involve protein changes, particularly in the blood vessel walls. The basement membrane is often altered. Early studies reporting elevated plasma levels of several amino-acids in obese subjects already suggested a link between this hyper amino-acidemia and decreased insulin sensitivity. The amino-acids usually elevated are valine, leucine, isoleucine, phenylalanine, and tyrosine [125-130].

Lipoprotein Metabolism: Lipoprotein lipase (LPL) hydrolyzes the core of triglyceride-rich lipoproteins into free fatty acids and mono-acylglycerol, facilitating the removal of triglyceride-rich lipoproteins from the bloodstream. Patients with diabetes, especially insulin-deficient diabetes, often manifest a decrease in adipose tissue LPL activity and this is accompanied by an increase in plasma triglyceride. With insulin treatment, there is an improvement in both LPL activity and triglycerides. The regulation of lipoprotein lipase activity is closely linked to insulin levels and nutritional state, as demonstrated by the changes in LPL during cycles of feeding and fasting. Both in rat models of diabetes and human diabetes, the use of drugs to improve diabetes control resulted in increased adipose tissue LPL activity. However, recent studies demonstrated that the treatment of diabetes resulted in increase in LPL protein and LPL synthesis with no change in

LPL on RNA levels, suggesting posttranscriptional regulation, possibly at the level of LPL translation. The translational regulation has been identified as an important mechanism for the regulations of LPL in response to catecholamines and thyroid hormone. Lipoprotein lipase is a central enzyme in lipid metabolism, and adipose tissue enzyme is important in the regulation of plasma triglyceride levels and in the accumulation of adipose tissue lipid stores [131-135].

CONCLUSION: Impairment in metabolic path-ways due to type 2 diabetes mellitus is the root cause of micro and macrovascular complications of type 2 diabetes mellitus. This review article will be very helpful in the study of understanding the causes of type 2 diabetic complications. This review article will be also helpful in the sequencing of pre-existing knowledge, regarding learning with an understanding of micro and macrovascular complications of type 2 diabetes mellitus. Review articles would facilitate in the study of the promotion of knowledge regarding the regulation of different types of diabetic-dys-lipoproteinemias.

Studies on diabetic-dys-lipoproteinemia and oxidative stress would further contribute to a better understanding of the progression of diabetic complications. All over the world millions of people are suffering from microvascular (nephritis, retinopathy, blindness, and macrovascular (atherosclerosis) complications of diabetes mellitus, and these complications are mainly responsible for mortality in diabetes. This review article will be of great national and international importance due to its significant content regarding metabolic pathways to understand the process of micro and macrovascular complications in type 2 diabetes mellitus.

ACKNOWLEDGEMENT: One of us (Dr Vishnu Kumar) is grateful to the Director, Central Drug Research Institute (CDRI), Lucknow and Principal, ASMC, Shahjahanpur for moral support

CONFLICTS OF INTEREST: The authors declare that they have no conflict of interest.

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How to cite this article:
Kumar V, Deepak AD, Giri VP and Kumar A: A review on impairment in metabolic pathways due to type 2 diabetes mellitus. Int J Pharm Sci & Res 2020; 11(3): 1089-97. doi: 10.13040/IJPSR.0975-8232.11(3).1089-97.