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Review Article

DIABETES MELLITUS: AN EMPHASIS ON DYSLIPIDEMIA AND ASSOCIATED COMPLICATIONS

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ABSTRACT

Cardiovascular disease is the most common cause of morbidity and mortality in patients with diabetes and the major source of cost in the care of diabetes. Dyslipidemia is a common risk factor and a strong predictor of CVD in T2D patients. Diabetic dyslipidemia is characterized by elevated fasting and postprandial triglycerides, low HDL-cholesterol, elevated LDL-cholesterol and the predominance of small dense LDL particles. These lipid changes represent the major link between diabetes and the increased cardiovascular risk of diabetic patients. The underlying pathophysiology is only partially understood. Alterations of insulin sensitive pathways, increased concentrations of free fatty acids and low grade inflammation all play a role and result in an overproduction and decreased catabolism of triglyceride rich lipoproteins of intestinal and hepatic origin. The observed changes in HDL and LDL are mostly sequence to this. Lifestyle modification, pharmaceutical interventions and glucose control may improve the lipid profile. This article reviews overviews diabetic dyslipidemia, its complications and its relationship to cardiovascular diseases, with an overview on Management approaches.

Key words: Diabetes mellitus, Diabetic dyslipidemia, Cardiovascular complications, Type 2 diabetes mellitus, Hyperlipidemia.

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INTRODUCTION

Diabetes Mellitus (DM) is a disease known to humankind since a very long time. The disease has been mentioned in 3500 years old literature. The etymology of the name diabetes mellitus states its meaning as "the sweet flow or siphon." In spite of being such an ancient disease a complete cure for DM is not available till date (Patlak *et al*., 2002). Millions of people all over the world are suffering from this disease; the incidence of DM is increasing year by year due to several reasons (Patlak *et al*., 2002). In India, 40.9 million people were suffering from DM in 2007. The number is expected to rise up to 69.9 million by 2025 (Mohan *et al*., 2007).

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The common symptoms of this disease are hyperglycemia, frequent urination, polyuria, polydipsia, and unexplained weight loss. Diabetic patients often show abnormalities termed altogether as "metabolic syndrome." The indicative signs of this syndrome are high blood levels of triglycerides and low blood levels of high density lipoprotein (HDL) cholesterol which increase the risk of developing heart diseases in human (Patlak *et al*., 2002, Olokoba *et al*., 2012). Diabetes often leads to several complications such as stroke, myocardial infarction, loss of vision, renal failure and neuropathies. There are major two types of DM, Type 1 and Type 2. Type 1 Diabetes Mellitus (T1DM) is an autoimmune disease caused due to disturbance in T-cell mediated immune response of β cells of pancreas; whereas Type 2 Diabetes Mellitus (T2DM) is caused due to insulin resistance due to failure of β cell function. However, exact mechanism of insulin resistance is not yet known and further study in this area is needed. DM patients show impaired glucose tolerance, which is mainly caused by impaired insulin action and insulin secretory malfunction (Inzucchi *et al*., 2002, El-Badri *et*

al., 2013). The predisposing factors are genetic susceptibility, environmental factors and lifestyle. The facets of modern lifestyle such as physical inactivity, sedentary habits, overly rich nutrition, cigarette smoking, consumption of alcohol and obesity have led to increase in spread of diabetes (Marble *et al*., 2005, Zimmet *et al*., 2001).

Diabetes mellitus type 2 is a multicomponent disease and in most cases accompanied by dyslipidemia, which is a risk factor for cardiovascular disease (Knowler *et al*., 1981). The combination of dyslipidemia and diabetes mellitus type 2 is accompanied by a significant increase in the risk of complications such as stroke, coronary artery disease (CAD), congestive heart failure and atherosclerosis, that worsen the prognosis and quality of life of patients and is one of the main causes of mortality.

This article provides a review of the current literature on diabetic dyslipidemia and address the potential role of dyslipidemia in causing type-2 diabetes with an overview on management of dyslipidemia among patients with type 2 diabetes that achieve good glycaemic and lipidaemic control that could potentially reduce the morbidity and mortality associated with type 2 diabetes.

MECHANISMS INVOLVED IN DIABETIC DYSLIPIDEMIA:

Diabetic dyslipidemia using World Health Organization (WHO) criteria (WHO, 2003, WHO, 1999) is characterized by serum triglyceride levels are 150-400 mg / dL (1.7 to 4.5 mmol / L), total cholesterol (TC) > 200 mg / dL (> 5.2 mmol / L), low density lipoprotein cholesterol (LDL-C) > 135 mg / dl (> 3.5 mmol / L), high density lipoprotein cholesterol (HDL-C) <35 mg / dL (< 0.9 mmol / L) in men or < 40 mg / dl (< 1.0 mmol / L) in women, and a ratio of total cholesterol: HDL-cholesterol > 5.

Dyslipidemia as a metabolic abnormality is frequently associated with diabetes mellitus. Its prevalence is variable, depending on the type and severity of diabetes, glycaemic control, nutritional status, age and other factors. Some studies indicated a strong clustering risk factor for coronary artery disease in diabetic subjects (Elinasri *et al*., 2008). Over 70% of patients with type 2 diabetes mellitus had one or more types of dyslipidemia.

In type 2 diabetes, there is often an associated dyslipidemia, the major abnormalities being elevated triglycerides and low HDL cholesterol. Abnormalities in lipid handling are not traditionally associated with type 1 diabetes, except in some subjects as an elevation in HDL cholesterol (Oresic *et al*., 2008)

Broadly, hyperlipidemia can result in increased uptake of free fatty acids by cells, both by passive diffusion and through protein-mediated pathways. The most common proteins that mediate fatty acid uptake into tissues are CD36 and members of the fatty acid binding protein (FABP) family. Changes in the expression of CD36 within the diabetic kidney have been previously reported (Susztak *et al*., 2005). In addition, circulating soluble CD36 (sCD36) concentrations (Bernal-Lopez *et al*., 2011) and monocyte expression of sCD36 are higher in diabetic patients (Sampson *et al*., 2003).

The lipid abnormalities in diabetic dyslipidaemia are prevalent in diabetes mellitus because insulin resistance or deficiency affects key enzymes and pathways in lipid metabolism. In particular, the following processes are affected: apoprotein production, regulation of lipoprotein lipase, action of cholesteryl ester, transfer proteins and hepatic and peripheral actions of insulin (Elinasri *et al*., 2008). Even more, it has been proposed that the composition of lipid particles in diabetic dyslipidaemia is more atherogenic than other types of dyslipidaemia. This means that even normal lipid concentrations might be more atherogenic in diabetic than in nondiabetic people (Elinasri *et al*., 2008, Wagenknecht *et al*.,, 2003, Taskinen *et al*., 2002).

Reduced HDLC is likely a powerful predicator for premature coronary heart diseases (Packard *et al*., 2002). Hyperglycemia progressively increases the transfer of cholesterol esters from HDL-C to VLDL-C particles, hence, denser LDL particles acquire a large proportion of these HDL esters, further diminishing the HDL-C level (Goldberg *et al*., 2001). In addition, HDL-C is a ready substrate for hepatic lipase which converts it into smaller particles, which are readily cleared from the plasma (Elinasri *et al*., 2008, Mooradian *et al*., 2009).

As with the triglycerides, improvement in glycaemic control leads to an increase in the levels of HDL-C, and suggest the evidence for a role for poor glycaemia in decreasing the level of this lipoproteins. Poor insulinization results in increased lipolysis in adipocytes. The resulting increase in fatty acid transport to the liver, which is a common abnormality in type 2 diabetes, may cause an increase in VLDL-C. Insulin directly degrades the apo B (which is the major protein of VLDL particles) and thus insulin may increase secretion of apo B (and then VLDL) (Sparks *et al*., 1990).

In diabetes many factors may affect blood lipid levels, because of interrelationship between carbohydrates and lipid metabolism. Therefore, any disorder in carbohydrate metabolism leads to disorder in lipid metabolism and vice versa (Chatterjee *et al*., 2005). Insulin resistance is a primary defects in the majority of individuals with type-2 diabetes. In non diabetic individuals insulin resistance in combination with hyperinsulinemia has a strong predictive value for future development for type-2 diabetes (Haffner *et al*., 2000). Several studies showed that insulin affects the liver apolipoprotein production and regulates the enzymatic activity of lipoprotein lipase and cholesterol ester transport protein, which causes dyslipidemia in diabetes mellitus. Moreover, insulin deficiency reduces the activity of

hepatic lipase and several steps in the production of biologically active lipoprotein lipase (Elinasri *et al*., 2008, Mooradian *et al*., 2009, Smith *et al*., 2008)

COMPLICATIONS ASSOCIATED WITH T2DM

The complications associated with T2DM intensify the state of morbidity and mortality of the patients. Diabetes complications are of two types- microvascular, which are caused due to damage to small blood vessels and macrovascular, which are caused due to damage to larger blood vessels. Microvascular complications include retinopathy leading to blindness, nephropathy leading to renal failure and neuropathy leading to impotence and diabetic foot disorders including severe infections, which may even lead to amputation. Macrovascular complications include cardiovascular diseases like heart attacks, strokes and deficiency of blood flow to legs (Hoogwerf *et al*., 2005).

Cardiovascular Complications:

Atherosclerotic cardiovascular disease (ASCVD) defined as acute coronary syndromes (ACSs), a history of myocardial infarction (MI), stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin is the leading cause of morbidity and mortality for individuals with diabetes and is the largest contributor to the direct and indirect costs of diabetes. The common conditions coexisting with type 2 diabetes (e.g., hypertension and dyslipidemia) are clear risk factors for ASCVD, and diabetes itself confers independent risk. Numerous studies have shown the efficacy of controlling individual cardiovascular risk factors in preventing or slowing ASCVD in people with diabetes. Large benefits are seen when multiple risk factors are addressed simultaneously. There is evidence that measures of 10-year coronary heart disease (CHD) risk among U.S. adults with diabetes have improved significantly over the past decade and that ASCVD morbidity and mortality have decreased (Smith *et al*., 2004).

In all patients with diabetes, cardiovascular risk factors should be systematically assessed at least annually. These risk factors include hypertension, dyslipidemia, smoking, a family history of premature coronary disease, and the presence of albuminuria.

Hypercholesterolemia is a significant coronary heart disease risk factor, and with the advent of statins, it is relatively straightforward to treat. However, despite this ease of treatment, recent data indicate that only a minority of diabetic patients are being optimally treated, even in those diabetic patients with coexistent coronary heart disease (Gaede *et al*., 2003).

Although the traditional treatment focus for diabetic patients has been in the area of glycemic control, there is growing evidence that improvements in lipid levels provide greater reductions in coronary heart disease risk.(Ansquer *et al*., 2005)

Lifestyle, Obesity and T2DM:

Many life style habits are responsible for prevalence of T2DM such as overweight, obesity, lack of physical activity, family history, Vitamin A deficiency, use of cholesterol lowering drugs, etc. (Imamura *et al*., 2015). We know diabetes and obesity interrelation from the earliest descriptions of the disease. The modern lifestyle and foodstuffs have resulted in an increase in obesity and thus diabetes cases. Most of the patients who are above 50 years age and overweight are suffering from T2DM. Obesity is an important factor linked to DM however, exact relation and mechanism is inadequately understood. Ozcan et al. (Ozcan *et al*., 2008) has worked to show that obesity leads to endoplasmic reticulum stress, which plays an important role in peripheral insulin resistance and hence in occurrence of T2DM at the molecular, cellular, and organismal levels. Fiber and fat content of the diet, alcohol consumption, smoking habit and sedentary lifestyle play a significant role in prevalence of DM. A higher incidence of DM is linked to Body Mass Index higher (BMI) than 25 kg/m^2. The results are similar worldwide as reported in studies from all over. The association between BMI and DM occurrence is found to be stronger among younger, than among older individuals (Boffetta *et al*., 2011, Yoon *et al*., 2006, Willi *et al*., 2007). A research on Pima Indians reveals that incidence of DM and obesity has increased in this century. This is possibly due to the changes in lifestyle and diet of the people who are already genetically susceptible to diabetes. The risk is higher when one of the parents is diabetic and even higher when both the parents are diabetic (Knowler *et al*., 1981).

The current therapies like insulin, diet, exercise, behaviour modification, and oral agents, fail to return patients to long-term euglycemia. Gastric bypass seems to be a promising option to restore and maintain normal levels of glucose, insulin, and HbA1c. It also reduces considerable amount of body fat. The possible reasons for the success of gastric bypass could be- total caloric intake is limited, proportion of carbohydrates in the diet is reduced, food is excluded from the hormonally active parts of the digestive system i.e. antrum, duodenum, and proximal jejunum, transit time from the stomach to the small intestine is delayed due to the small gastric outlet. This operative procedure can also prove to reverse other related complications like cardiopulmonary function, cure sleep apnea and snoring, control asthma, clear peptic reflux, improve physical activity of patients suffering from arthritis, and restore fertility (Pories *et al*., 1995). Lifestyle changes along with proper medications can prove to control morbidity and mortality of diabetes and related metabolic syndromes.

DIABETIC DYSLIPIDEMIA – CARDIOVASCULAR RISK:

The combination of dyslipidemia and diabetes mellitus type 2 is accompanied by a significant increase in the risk of complications such as stroke, coronary artery disease (CAD), congestive heart failure and atherosclerosis, that worsen the prognosis and quality of life of patients and is one of the main causes of mortality. Atherosclerosis in diabetes mellitus type 2 is characterized by early development, widespread nature of vascular lesions and crueler course. Accelerated atheroma formation in diabetes mellitus type 2 is associated with contributing factors such as dyslipidemia and insulin resistance (Bali *et al*., 2016, CTT Collaborators *et al*., 2012, Cryer *et al*., 2016).

The relationship between hyperlipidemia and vascular complication of diabetes has long been of interest because both tend to occur with greater frequency in Type 2 DM. Insulin resistance and obesity combine to cause dyslipidemia and hyperglycemia, hyperlipidemia have additive cardiovascular risk (haturvedi *et al*., 2001, Mazzone *et al*., 2000, Ginsberg *et al*., 2001).

In diabetes the associated hyperglycemia, obesity and insulin changes highly accelerate the progression to atherosclerosis (Bornfeldt *et al*., 2011, Nesto *et al*., 2004). Atherosclerosis accounts for up to 80% of deaths in diabetic patients due to coronary heart disease (CHD) and cerebrovascular or peripheral vascular disease (Elinasri *et al*., 2008, Tagoe *et al*., 2013).

It is recommended that patients with DM should be treated as if they already have coronary artery disease. Hence identification, critical evaluation, and follow-up of serum lipid profile in Type 2 DM continue to be important (Harvey *et al*., 2002).

OTHER COMPLICATIONS OF DIABETIC DYSLIPIDEMIA:

Dyslipidemia has been reported to be particularly important for the development of neuropathy (Davis *et al*., 2008). In type 1 diabetes, dyslipidemia develops later in the disease and is often seen to coincide with the delayed onset of diabetic neuropathy (Vincent *et al*., 2009). In type 2 diabetes, a high number of cases of peripheral neuropathy (as many as 10–20% of patients) present at the time of diagnosis of diabetes (Charles *et al*., 2011). This is likely exacerbated by serum lipids and increases in body mass index which are independently associated with the risk of developing diabetic neuropathy (Tesfaye *et al*., 2005).

Dyslipidemia is also thought to be a comorbidity influencing the progression of diabetic kidney disease (American Diabetes Association, 2017).

MANAGEMENT OF DIABETIC DYSLIPIDEMIA:

Managing diabetic dyslipidemia requires a multifaceted approach. Dietary modification and pharmacotherapy are integral components of management (Bell *et al*., 2011, Chehade *et al*., 2013). Because obesity and insulin resistance are closely linked, weight loss is an important treatment goal. Moderate weight loss (5% of body weight) is associated with improvements in insulin sensitivity, glycemic control and lipid profile (Klein *et al*., 2004). Weight reduction raises HDL and decreases triglyceride levels (Wing *et al*., 2011). However, the observed improvements in metabolic parameters through weight loss may not translate directly into an improvement in cardiovascular outcomes. The Look AHEAD (Action For Health in Diabetes) trial showed that longterm weight loss achieved through intensive lifestyle intervention did not decrease the rate of cardiovascular events despite an improvement in all cardiovascular risk factors, except for LDL (Look *et al*., 2013). Lifestyle intervention alone is often insufficient to achieve the strict lipid goals. In such cases, pharmacotherapy should be initiated concomitantly.

CONCLUSIONS:

Diabetic dyslipidemia is a widespread condition, in which insulin resistance is considered the driving force behind the characteristic lipid abnormalities. This combined dyslipidemia, put them to increased risk of cardiovascular, cerebrovascular and peripheral arterial diseases morbidity and mortality. Efforts should therefore intensified in the area of glycemic control, lipid lowering and lifestyle modifications among others to reduce the risk of morbidity and mortality in diabetic patients. Indeed the very high prevalence of dyslipidemia among diabetic subjects irrespective of duration of DM makes a case for early commencement of lipid lowering therapy even in the absence of biochemically proven dyslipidemia.

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