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ROLE OF FREE FATTY ACID AND ELEVATED VLDL IN TYPE II DIABETES MELLITUS - A REVIEW

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ABSTRACT

Diabetes is associated with abnormalities in plasma lipid and lipoproteins. Each of these dyslipidemia is associated with elevated Low density lipoprotein cholesterol(LDL-C) and impaired clearence of VLDL and reduced plasma HDL levels. Defects in insulin production and hyperglycemia causes change in plasma lipoproteins in patient with diabetes. obesity and insulin resistant also lead to lipid abnormalities. In diabetic ketoacidosis elevation in VLDL have been recognized in which insulin concentration are low. Increase in hepatic lipase activity also contribute to decreased HDL concentration.Thus changes in hepatic lipase and lipoprotein may result in decrease HDL. Although many factors play a role and there is evidence that abnormalities in serum lipids and lipid metabolism are risk factors for increased evidence of CHD in type 2 diabetes mellitus.

KEYWORDS: Diabetes, VLDL, Triglycerides, HDL, Lipoproteins.

INTRODUCTION

As of 2010 there were approximately 285 million people diagnosed with the disease compared to around 30 million in 1985.[1,2] Type 2 diabetes is basically a chronic disease associated with a ten-year-shorter life expectancy. Long-term complications from hyperglycemia can cause heart disease, strokes, diabetic retinopathy where eyesight is affected, kidney failure which may require dialysis, and poor blood flow in the limbs leading to amputations.Dyslipidemia is an abnormal amount of lipids (e.g. cholesterol and/or fat) in the blood. In developed countries, most dyslipidemias are hyperlipidemias; that is, an elevation of lipids in the blood. This is often due to diet and lifestyle. Prolonged elevation of insulin levels can also lead to dyslipidemia.

Diabetes is the most common endocrine disorder and by year 2025 it is estimated that 300 million people will be effected by this disease.the diagnostic criteria and classification was put up by world health organization (WHO) in 1965.WHO modified its recommendation in 1985.which is published by American Diabetics Association(ADA) in 1997and by WHO in 1999.

- Symptoms of diabetes (polyuria, polydipsia, unexplained weight loss, etc) and plasma glucose concentration =200mg/dl.
- Fasting plasma glucose = 70mmol/L (126mg/dl), with no calric intake for atleast 8 hrs.
- 2 hr plasma glucose 11.1mmol/L(126mg/dl).

Type 2 diabetes mellitus is caused by relatively impaired insulin secretion and peripheral insulin secretion.lack of insulin or low insulin level affect the metabolism of carbohydrate, protein ,fat, and electrolyte balance in diabetes[3-5] Cholesterol in the gut are reassembled to form triglycerides and cholesterol esters.Apo B-48 helps packaging and secretion of these newly formed chylomicrons.Apo C-II and Apo E, Apo CIII and esterified cholesterol from HDL.Apoc II activates lipoprotein lipase which hydrolyses triglycerides.[6] Lipid abnormalities in type 2 diabetes can be illustrate by reduced action of insuulin at tissue level.

Lipid Abnormalities in type 2 diabetes are described by -

- High triglycerides level (post prandial lipaemia)
- Low HDL-c concentrations.
- Increase in small dense LDL.

Recent data from several countries show that type 2 diabetes is increasingly becoming a problem among adolescents and even children.[7,8] In some countries, childhood diabetes type 2 is more common than type 1.[9] The disease is usually controlled through dietary therapy, exercise and hypoglycaemic agents.[10,11] Type 2 diabetes is characterized by increase in fasting and post prandial triglyceride and triglyceride rich lipoproteins (VLDL) and low HDL usually measured as HDL-c. High concentration of small dense LDL particles is arelated to three to seven fold increased risk of Heart Disease,although concentration of LDL is normal in type 2 diabetes ,its abnormal composition may be more atherogenic.In

both fasting and post prandial states decrease action of insulin on hepatic tissues result in decrease suppression of VLDL and is major triglyceride carrying lipoprotein particle in fasting state.

VLDL production is suppressed by high insulin circulation concentrations.decrease action of insulin at haptocyte results in increase VLDL production. Which results in hypertriglyceridemia , in fasting state. Most of the lipid abnormalities in type 2 diabetes can be explained by decreased action of Insulin at tissue level.LDL particle that are rich in triglyceride due to hypertriglyceridaemia and increased CETP activity are also converted by triglyceride lipase activity of hepatic lipase into smaller and denser particle.

In which large density LDL particle is removed by LDL receptor pathway where as small dense LDL particle is removed slowly .sd LDL is modified and oxidized easily due to glycation in type 2 diabetes mellitus and are more atherogenic.

Lipoproteins	Density	Lipid content
chylomicrons	0.95	Triglycerides
VLDL	0.95-1.006	Triglycerides
IDL	1.006-1.019	Triglycerides+phospholipid+cholesterol
LDL	1.019-1.063	Triglycerides+phospholipid+cholesterol
HDL	1.063-1.21	Triglycerides+phospholipid+cholesterol

LIPOPROTEIN ABNORMALITIES IN DAIBETES

Decrease	LPL(insulin dependent enzyme	Increase VLDL,reduced HDL
Glycation	Lipoproteins(LDL)	High LDL
Oxidation	LDL	High LDL

FUNCTIONS OF MAJOR APOPROTEINS

Apo A-1	HDL,CHYLOMICRONS	LCAT activator,component of HDL
Apo-B-48	CHYLOMICRONS	Formation,Packaging, and Release of chylomicrons
Apo-B-100	VLDL,IDL,LDL	Formation,Packaging and secretion of VLDL,LDL receptor ligand, Structural protein of VLDL,IDL,LDL
Apo-C-II	ALL	Activator of LPL
Apo-c-III	ALL	Inhibitor Of LPL
Apo-E	ALL	Ligand for LDL receptor binding proteins.

PATHOPHYSIOLOGY OF DIABETIC DYSLIPIDEMIA

Endogeneous triglycerides produced in hepatocytes VLDL also acquires APO-CII, and APO E, APO-CII like chylomicrons during circulation. Triglycerides present in VLDL are hydrolyzed by activation of LPL by APOC-II and phospholipids and apoprotein are transferred back to HDL.[12]

Type 2 diabetes is most common diabetes in India also known as non insulin dependent diabetes, maturiy onset,non -ketotic diabetes. Which causes overproduction of VLDL triglycerides.TG rich lipoprotein ApoB100 and small dense HDL increases in type 2 diabetes. Insulin resistance is associated with enhanced production of very low density lipoprotein and decrease in IDL and small dense LDL, increased production in HDL.

Adiels et al, overproduction of VLDL is the hallmark of dyslipidemia in the in the metabolic syndrome.[13]

In diabetic dyslipidemia resulting from insulin resistance along with dysfunction of the enzyme lipoprotein lipase(LPL)account for most of the abnormalities. Increase delivery of FFA to the liver along with hepatic insulin resisstance results in upregulation of apolipoprotein B (Apo-B). Therefore the liver produces and exports large amount of triglycerides(TG). LPL is enzyme which converts lipoprotein triglycerides into free fatty acids. In diabetic patient LPL activity is diminished which result in elevated VLDL-TG and low HDL and LDL. As a result of which plasma enzyme (CETP)cholesterol esteryl transferase protein abnormalities occurs and VLDL is elevated CETP functions in transfer of VLDL-TG move to HDL and then to LDL.hence ,diabetics with high plasma VLDL have low plasma HDL and LDL is enriched with TG which is converted by hepatic lipase .

Hepatic lipase synthesis occurs in hepatocytes is an enzyme which catalyzes phospholipid and triglycerides. This enzyme is reduce by insulin deficiency and effect of which causes decrease in clearence of remnant

lipoproteins.[14-16]

Poorly controlled type 2 diabetes are associated with increased plasma levels of VLDL.return of more fatty acid to lver due to increase action of hepatic lipase in adipose tissue and insulin action ob Apo B synthesis. These process prevent the degradation of newly synthsized Apo B and results in increased production of lipoprotein VLDL.In addition, low HDL and hypertriglyceridemia, an elevated Apo B level also causes of diabetic dyslipidemia. Interaction of LDL with its receptor can be rstricted by chemical modifications of lysine and arginine residue of apo B. Glucosylation of apo B containing lysine blocks the receptor mediated catabolism.glucosylated LDL also have altered interaction with endothelial cells. Activation of Renin Angiotensin aldosterone system (RAAS) can interfere with Insulin signalling, assist insulin ressistant in patient with type 2 diabetes. RAAS activation increase oxidative stress , decrease nitric oxide production , active protein kinase signalling pathway leading excess.[17-19]

The removal defect for VLDL in type 2 diabetes is most likely due to deficiency in lipoprotein lipase.LPL is an insulin dependent enzyme.Deficiency of lipoprotein lipase in type 2 diabetes is due to altered secretion of insulin.it is also recognize that abnormailities in LDL composition is a part of dyslipidemia .LDL is composed of several subfractions which varies in size and density. In LDL type A, large LDL buoyant LDL particle ,while in type B, smal dense LDL particle .LDL type B is associated with elevated triglycerides and loe HDL-c .whereas triglycerides concentration is seems to be the most important determinant of LDL subfraction profile.[20-22]

FREE FATTY ACID AND TEIR ROLE IN TYPE 2 DIABETES

Increased level of free atty acid and triglycerides are associated with type 2 diabetes.In obesity increased lipid induces both hyperinsulinemia and insulin resistant.Increase in fatty acid and TGs overload leads to impaired of Beta cell dysfunction and results in hyperglycemia.

There is increase in small dense LDL which is also atherogenic. In patient with poor glycemic control, level of TG rich lipoprotein increase. This occurs due to excess production of VLDL but also less peripheral clearence and lesser expression of ApoB 100 receptor on endothelial cell surface.[23,24]

ApoB functions in hepatic secretion of VLDL alteration caused both increased hepatic secretion and vitiate clearence of VLDL and intestinal chylomicrons.ApoB is susceptible to glycation in diabetes mellitus and impairs the interaction with hepatic LDL and slows clearence of LDL. Increase in ApoB levels are found in almost all diabetes mellitus patient which are associated with HDL cholesterol level.

Impairs clearence of VLDL results in increased production of small dense LDL particles and induce insulin resistance by impairing cell insulin action.Glucose has been shown to potentiate the lipolytic responsiveness of human adipocytes which leads to elevated free fatty acid flux to liver.[25] Defects in non insulin dependent are elevated serum triglycerides and reduced HDL cholesterol.

Insulin resistance is associated with increase in serum insulin and dysfunction of beta cell and result in lipoprotein abnormalities and glucose level.impairment in the ability of insulin to suppress hepatic production of large TG-VLDL.increase in influx of non esterified fatty acid in circulation occurs due to defective suppression of intracellular hydrolysis of TG into free fatty acid.[26-28]

High free fatty acid level effects insulin activity in peripheral blood. FFA increaes due to hydrolysis of triglycerides.therefore TG is considered as a surrogate marker for fatty acids.In insulin resisstant level of long chain fatty acid and their derivatives in type 2 diabetes mellitus invovles in interrupting the insulin signalling cascade and prevent with movement of glucose transporter 4(GLUT 4) from an intracellular compartment to muscle cell surface.[29] Insulin Ressistant is related to enhanced production of VLDL and reduction in catabolic rate of IDL and sd LDL lipoprotein. Overproduction of VLDL is hallmark of dyslipidemia in metabolic syndrome.[30] cholesterol ester transfer protein (CETP) facilitate the transport of triglyceride and esterified cholesterol between different lipoprotein particle, and between different particles within individual lipoprotein particles. Triglyceride levels are a major determinant of CETP activity. Therefore, in the presence of increased triglyceride-rich lipoproteins, CETP activity is increased so that all circulating lipoproteins become enriched in triglyceride, in particular HDL and LDL particles.Triglyceride-rich HDL particles are converted by the triglyceride lipase activity of hepatic lipase into smaller particles.In the insulin resistant hypertriglyceridaemic state, HDL particles therefore tend to be small and dense and so more likely to undergo catabolism, so that HDL particle numbers and HDL-c concentrations are reduced.In diabetic patients with poor glycemic control, triglycerides levels are increased not because of increase in VLDL but due to poor expression of ApoB 100 receptors on endothelial cell surface.and also in diabetic patient receptors recycling is slow.

CONCLUSION

Type 2 diabetes Mellitus had elevated levels of TG,TC with slightly elevated levels of HDL-c.serum, TC,HDL-c and LDL-c were significantly higher in diabetes Mellitus.All of the components of the

dyslipidemia, including higher triglycerides, decreased HDL levels, and increased small, dense LDL particles, have been shown to be atherogenic. Lifestyle modifications, weight loss and exercise, dietary fibers and with weight loss medications can improve this dyslipidemia. Insulin Ressistance plays a key role in the development of diabetic dyslipidemia. Hypertriglyceridemia (VLDL) is commonly associated with uncontrolled diabetes.Hyperlipidemia associated with alterations in VLDL metabolism contribute to risk of atherosclerosis and CHD in type 2 diabetes mellitus.

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