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Lipid Profile Alterations in the Metabolic Syndrome the Latest Biochemical and Physiological Aspect

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Lipid Profile Alterations in the Metabolic Syndrome the Latest Biochemical and Physiological Aspect

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Abstract- **Cardiovascular and cerebrovacular complications form a major challenge in the management of the The Metabolic Syndrome. The risks of development are compounded by simultaneous occurrence of Type 2 diabetes mellitus (T2DM), dyslipid emias, hypertension and other medical conditions. The significant increase in morbidity, mortality along with premature death and disabilities resulting from these conditions in both developed and developing is a matter of great concern. The article makes a microanalysis of Biochemical alterations associated with dyslipidemias in cases of metabolic syndrome.**

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I. Text

The World Health Organization (WHO) developed a definition in 1998 stating that individual need to show evidence of insulin resistance and, at least 2 of 4 factors should be present namely hypertension, hyperlipidemia, obesity and microalbuminuria. In 2001, the National cholesterol Education program (NCEP) Adult Treatment panel (ATP III) suggested another definition, according to which at least 3 of 5 factors should be present for diagnosis of the Metabolic Syndrome and the five factors/components are the following: increased waist circumference, hypertriglyceriderma, low high density lipoprotein (HDL)-cholesterol, hvpertension (130/85mmHg) and fasting glucose of 110 mg/dl or high.

Obesity, insulin resistance, physical inactivity, advanced age and hormonal imbalance have been suggested as the underlying risk factors for the development of metabolic syndrome.

The metabolic syndrome is not a new syndrome. It was first described in the 1920 by Kylin, a Swedish physician, as the association of high blood pressure (hypertension), high blood glucose. (hyperglycemia) and gout. Advances in the 1970s and early 1980s expanded our understanding of the link of these to coronary heart disease, even in the absence of diabetes, and linked the metabolic risk factors to atherosclerosis.[1] In 1988, G.M. Reaven grouped several metabolic disorders together as syndrome X and proposed that insulin resistance was the underlying event explaining dyslipidemia, high blood pressure, and diabetes, and this characterization was further examined by DeFronzo and Ferranini in 1991. These factors were then observed to be influenced by both genetic and environmental factors.[2]Many other names were proposed for this syndrome, including the plurimetabolic syndrome (1988) , the deadly quartet (1989), syndrome X plus (1991), metabolic syndrome X, the metabolic syndrome, the insulin resistance syndrome (1991) In 2001, the National cholesterol EduScatoin program (NCEP) suggested another definition for the Metabolic syndrome, which requires at least 3 of 5 factors to be present for definition of the Metabolic syndrome[3]. This definition, is easier to use in clinical practice because glucose tolerance testing, insulin concentration measurement and microalbuminuria testing are not required. Today, the most common definitions are the (WHO version, revised) International Diabetes Federation definition of 2005 and the revised NCEP ATP definition of 2005.[4]

Table 1 : WHO Definition of metabolic syndrome

Hypertension	Raised arterial pressure(140/90 mmHg) or antihypertensive medication
Dyslipidemia	Raised plasma triglyceride(>1.7 mmol/L) or low HDL cholesterol(<0.9 mmol/L) in men and (<1.0mml/L) in women
Central or general obesity	Waist to hip ratio >0.90 in men: >0.85 in women or BMI>30Kg/m2
Microalbuminuria	Urinary albumin excretion rate >20ug/min or albumin: creatinine ratio>30 mg/g

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Table 2 : National Cholesterol education program (NCEP) Adult Treatment Panel III (ATPIII)

Risk factors	Defining levels*
Abdominal obesity (waist circumference) Men Women	 >102 cm(> 40 inch) >88cm (> 35 inches)
Triglycerides	>150 mg/dl
HDL Cholesterol Men Women	 <40mg/dl <50mg/dl
Blood Pressure	>130/85 mm Hg
Fasting Glucose	>110 mg/dl

Metabolic syndrome: diagnosis is established when >3 of these risk factors are present

II. Normal Physiology of Lipid Transport

a) Transport of dietry lipid (Exogenous pathway)

It is the transport of lipid from intestine to liver.Chylomicrons transport the dietry lipid from intestine to liver. In diet the major lipids are triglyceride and cholesterol.Cholesterol is absorbed as such in proximal small intestine and is esterified to cholesteryl ester (ChE). Triglycerides are hydrolysed by lipases to glycerol and fatty acids which are absorbed in intestine.Inside intestinal cells triglyceride is synthesized by fatty acids. Chylomicrons are synthesized in the small intestine that contain triglyceride, cholesteryl ester, cholesterol, phosphlipids, and apoprotein B-48 (apo B-48) and apo-A.These chylomicrons are secreted in the intestinal lymph and reach the systemic circulation via thoracic duct. In the circulation apo E and apo C are transfered to chylomicrons by HDL, so now chylomicrons contain apo A, apo B-48, apo- E, & apo-C.In the circulation, triglycerides of chylomicrons are hydrolysed by lipoprotein lipase (LPL) present on endothelial cells of vessels of skeletal muscles, adipose tissue and heart, but not in liver.The released fatty acids are utilized locally by these tissues.Adipose tissue uses these fatty acids to restore them as TGs and heart and skeletal muscle use them as source of energy.Thus, function of chylomicrons is to transport exogenous (dietry) triglyceride to adipose tissue (for storage), heart (for energy) and muscle (for energy).The chylomicron particle progressively shrinks in size by action of LPL and, cholesterol, phospholipids, apo-A and apo C are transferred to HDL, creating chylomicron remnants that contains more cholesterol, less triglycerides, apo-E & apo B-48.

b) Transport of Hepatic lipds (Endogenous pathway)

VLDL is synthesized in liver that contains high triglyceride, ChE, cholesterol, phospholipid and Apo B-100. (VLDL particles resemble chylomicrones in composition except that VLDL contains Apo B- 100 instead of Apo B-48).VLDL particles are secreted in the plasma and as with chylomicron, Apo E and Apo C are transferred from HDL to VLDL. Now VLDL contains Apo B-100, Apo E and Apo C.In plasma, triglycerides of VLDL are hydrolysed by same lipoprotein lipase and apo C is transferred to HDL and the remmants are called IDL.40-60% of IDL is removed by liver via LDL receptor mediated endocytosis, this process require Apo E which acts as ligand for LDL receptors.Remaining IDL is remodeled by hepatic lipase which hydrolyzes more triglyceride to form LDL that contains maximum cholesterol. 70% of LDL is removed by liver via LDL receptor and 30% is utilized by peripheral tissues as a source of cholesterol.

c) The Alterations in Metabolic Syndrome

The genetic and environmental factors play a major role in metabolic and cardiovascular of obesity. The way genetic factors modifying the effects of obsesity are largely unknown. Also there are the subjects who are defined as obese by various guidelines but do not have insulin resistance and conversely insulin resistance can be present in lean individuals. Abdominal obesity is related, to greater risk of cardiovascular events and T2DM. Initially waist: hip ratio was considered but the current clinical approach to Metabolic Syndrome uses sex specific waist circumference to define the body mass component contributing to increase in cardiovascular events, greater fasting insulin levels and increased insulin resistance. Waist-circumference is a general index of central fat mass and it reflects both abdominal subcutaneous adipose tissue (SAT) and abdominal visceral adipose tissue (VAT) and is major determinant of metabolic and cardiovascular complication of obesity[5]. Visceral obesity may partly be a marker of a dysmetabolic state and partly a cause of the metabolic syndrome. Although waist circumference is a better marker of abdominal fat accumulation than the body mass index, an elevated waistline alone is not sufficient to diagnose visceral obesity and have proposed that an elevated fasting triglyceride concentration could represent, when waist circumference is increased, a simple clinical marker of excess visceral/ectopic fat.[6] For the diagnosis of abdominal .obesity three simple measurements, namely height, weight and maximal abdominal girth should be made on all patients. The body mass index (BMI); 18.5-25 kg/rn^2 is normal, 25-30 kg/m-^{2} is overweight or >30 kg/m^2 is obese. According to the ATPIII criteria the waist circumference of >35 inches (88 cm) for women, >40 inches (102cm) for men] defines excess abdominal adiposity. The weight reduction diet is usually choice for the obese patient but the most common approach for overweight person who may have the Metabolic syndrome is a balanced calorie diet. Hypothyroidism is a major cause of secondary dyslipidernia, the cause of which resides in a decrease of cholesterol excretion and in a marked increase in apo

B lipoproteins because of a decreased catabolism and turnover by a reduced number of LDL receptors on the liver cell surface. LDL can be removed from plasma by receptors, which are regulated at mRNA level by thyroid hormone. Thus increased levels of total and LDL cholesterol are a common finding in hypothyroidism and may represent an increased risk factor for coronary heart disease.[7]Abdominal obesity, due to intra-abdominal adiposity, drives the progression of multiple cardiometabolic risk factors independently of body mass index. This occurs both through altered secretion of adipocyte-derived biologically active substances (adipokines), including free fatty acids, adiponectin. interleukin-6. tumour necrosis factor alpha. and plasminogen activator inhibitor- I, and through exacerbation of insulin resistance and associated cardiometabolic risk factors.[8] The prevalence of abdominal obesity is increasing in western populations, due to a combination of low physical activity and high-energy diets, and also in developing countries, where it is associated with the urbanization of populations. The measurement of waist circumference, together with an additional comorbidity, readily indentifies the presence of increased cardiometabolic risk associated with abdominal obesity. For example, 80% men with waist circumference 90 cm and triglycerides (TG) 2 mmo/L were found to have an atherogenic triad of elevated apolipoprotein B, fasting hyperinsulinaemia, and small, dense LDL, which had been strongly associated with adverse cardiovascular outcomes in a previous observational study.[9] Accordingly, measurement of waist circumference should become a standard component of cardiovascular risk evaluation in routine clinical practice. As a simple initial screening approach to distinguish viscerally obese from subcutaneously obese patients, has previously proposed that the simultaneous presence of fasting hypertiglyceridemia and of an increased waist circumference (hypertriglyceridemic waist) could represent a simple clinical phenotype to identify patients with an excess of visceral adipose tissue, with ectopic fat and with the related features of the metabolic syndrome.[10] Lifestyle modification remains the initial intervention of choice for this population, with pharmacological modulation of risk factors where this is insufficiently effective. Looking ahead, the initial results of randomized trials with rimonabant, the first CBI (cannabinoid) receptor blocker, indicate the potential of corrective overactivation of the endogenous endocannabinoid system for simultaneous improvement of multiple cardiometabolic risk factors.[11]

III. Increased Triglycerides

Dyslipidemia is widely established as an independent risk factor for CVD. Low HDL Cholesterol and hypertriglyceridimia have been found to be independent and significantly related to myocardial infarction and stroke in patient with Metabolic syndrome. The dyslipidemia in Metabolic syndrome patient may be caused by combination of overproduction of very low density lipoprotein (VLDL), apoB-100, decreased catabolism of apo B containing particle and increased catabolism of HDL apo-AI particle. In T2DM, insulin resistance and obesity combine to cause hypertriglyceridemia and low HDL-C, due to over production of VLDL. Plasma LDL-C levels are normal in Metabolic syndrome though LDL particles are smaller and denser than normal which may be associated with increased cardiovascular risk. The effects of low HDL-C and high triglyceride levels., are related to greater risk of coronary disease due to variety Of environmental and genetic factors. For instance lower HDL-C levels are formed in cigarette smokers, obese person, sedentary individuals, and androgen or progesterone users. The genetic variants of lipoprotein lipase, hepatic lipase, cholesterol ester transfer protein and peroxisome proliferator-activated receptors have effects on HDL-C and TG levels in population which contributes to the development of Metabolic syndrome.

The primary defect is probably focused in the inability to incorporate, the FFA to triglycerides (TGs) by the adipose tissue (inadequate esterification) [12]. This result is reduced fatty acid trapping and consequent retention by the adipose tissue. The insulin resistance also causes reduced retention of FFA by adipocytes. Both these abnormalities lead to the increased flux of FFA back in the liver. Adipose tissue is a prominent source of cholesteryl ester transfer protein.[13] Cholesteryl ester transfer protein is an important determinant of lipoprotein composition because of its capacity to mediate the transfer of cholesteryl esters from cholesteryl ester rich lipoproteins to TG rich lipoproteins in exchange for TGs.[14] In obese subjects, cholesteryl ester transfer protein activity and mass are increased.[15] Increased flux of FFA from periphery to the liver in increasing resistance state stimulates hepatic TG synthesis which in turn promotes the assembly & secretion of TG containing VLDL" as well as apo B production in liver. Under normolipidemic conditions in humans, VLDL secretion is affected by TG and cholesterol availability and recent studies suggest an-association between' cholesterol synthesis and. production of smaller-VLDL particles (VLDL2).[16]While insulin suppresses the formation, of large VLDL particles, VLDL receptors does not, have any impact on the production of the smaller VLDL2 fraction n When insulin resistance occurs, the high insulin values make the liver resistant to the inhibitory effects of insulin on VLDL secretion increasing insulin resistance is proposed to be the precursor for two events. in the presence of insulin resistance the visceral adipocytes is more sensitive to the metabolic effect of the lipolytic hormone glucocorticoids and catacholamines. The hormonal lipolytic activity produces an increased release of FFA

into portal system which serves as hepatic substrate to assemble TGs & TG rich VLDL. Secondly increasing JR leads to increased production of apo B as a consequent to increased synthesis & secretion of TG containing VLDL cholesterol particles. The fall off clearance rates is likely to reflect the-rates of lipolysis and could be attributable to a change in lipoprotein lipase activity (decreased in insulin resistance state) and other factors such as the apoC-II content or the apo-CII/CIII ratio (modulators of lipoprotein lipase activity) in VLDL.[17]

In the insulin resistance, LDL levels are usually within normal limit or only mildly raised, however LDL particle is often of abnormal composition (small dense LDL) Hypertriglyceridemia is responsible for abnormal composition.-It has been found that small dense LDL is not seen in hypothyroidism until plasma TG level exceeds 1.5 mmol/L. The elevation of TGs in hypothyroidism is caused by a reduced removal rate of TG from plasma due to a decrease in the activity of hepatic TG lipase. Under these condition large TG rich VLDL (VLDLT) molecules accumulates when VLDL is lyophilized by LPL a population of LDL particle with changed apo B conformation is produced. These particles fail to bind efficiently LDL receptor and so have a prolonged residence time in circulation. By the action of CETP, cholesterol esters are replaced by TG in LDL & HDL particle. TG rich LDL is a good substrate for hepatic lipase that finally generates small dense LDL which is associated with increased cardiovascular risk. Many studies have shown that small, dense LDL particles have proatherogenic properties such as: (a) reduced LDL receptor mediated clearance, (b) increased arterial wall retention,(c) increased susceptibility to oxidation.[19]

IV. Low HDL-Cholesterol

Low HDL-Cholesterol in patient with Metabolic syndrome is often considered as secondary to raised TG. Lipid exchange is taking place between LDL & LDL particles mediated by cholesterol ester transport protein (CETP). These TG rich but cholesterol depleted HDLC is more prone to be catabolized. They undergo hydrolysis of their TGs components and dissociation of their protein component apo-A (the main protein of HDL).[20] There is circumstantial evidence that low HDL-C contributes to increase risk of atherosclerosis in this Condition. There is also evidence that HDL-cholesterol regime-therapy may reduce the risk of atherosclerosis in Met yn.[21,22,23] The dyslipidemia contributing to diagnosis of Metabolic syndrome is defined by estimation of lipid levels after 12 hour fasting in usual healthy state. A low HDL-C level <40 mg/dl in men and <50 mg/dl in female and TG level >150 mg/dl in either sex are the components for the diagnostic of Metabolic syndrome. The complexity of HDL, in terms of both composition and metabolism is striking. It is clear, however, that low HDL-C levels are a very common characteristic of the dyslipidemia of IR and T2DM. In fact, it may be the most common finding; HDL-C.and apo A-I levels in plasma - can be low even when plasma TG levels are normal. Why are HDL-C and apo A-I levels reduced in individuals with JR and T2DM.

As was the case for LDL, the answer lies mainly, but not completely, with CETP. The reverse cholesterol transport system moves cholesterol from tissues to nascent, cholesterol-poor apo A-I phospholipid discs, where the cholesterol is esterified. Progressive accumulation of CE. (Cholesterol esters) leads to the maturation of the HDL into a spherical lipoprotein that delivers the CE and some of the unesterified cholesterol to the liver. Alternatively, HDL2 particles can participate in the CETP-mediated exchange of their CE for TG in VLDL, VLDL remnants, and chylomicron remnants. The impact of this exchange on reverse cholesterol transport is unclear If the TG rich lipoproteins that receive the CE from HDL are removed by the liver, there may be no effect on reverse cholesterol transport, assuming that delivery of CE via uptake of apo lipoproteins results in delivery of the lipid to the biliary tract with the same efficiency as does delivery via SRB 1. Unfortunately, increased CETP-mediated exchange of HDL CE for TGs is associated with lipolysis of HDL TG by HL, and this produces a small, lipid-depleted HDL that resembles nascent particles. Apo A-I binding to this HDL particle is diminished, causing apo A-I to dissociate from the particle and be cleared more rapidly from the plasma. Thus, fractional catabolism of apo A-I is increased in patients with T2DM, reducing the number of HDL particles n the circulation. Additionally, if the CE-enriched apo B-lipoproteins are not removed by the liver, but rather find their way into the artery wall, then reverse cholesterol transport will have been "short-circuited" and atherogenesis may be accelerated.

There are other metabolic pathways that can also generate low HDL in IR and Metabolic syndrome. IR is associated with increased HL (hormone lipase) activity, which can increase hydrolysis of HDL, TG and generate smaller HDL The potential roles of defective ABCA1-mediated efflux of cellular-free cholesterol, defective LCAT activity, or increased selective delivery of HDL cholesterol ester to hepatocytes as causes of the low HDL levels present in IR are under investigation However, the observation that low HDL-C and apo A-I are frequently present even when TG levels are relatively normal suggests that non-CETP mechanisms are clearly important in the pathogenesis of low HDL-C concentrations in IR.

V. Conclusion

Elevated triglyceride is the most prevalent (81%) component of metabolic syndrome in all thyroid patients of present study. Hence hypertriglyceridemia on routine

evaluation may warrants screening for other components of metabolic syndrome.

There is a significant correlation (p= 0.03) between waist circumference and triglyceride levels. It is the visceral fat which is responsible for hypertriglyceridemia. Hence it can be concluded that those having high TG levels and high waist circumference, have visceral adiposity. Therefore screening for other parameters of metabolic syndrome may be warranted as visceral adipose tissue causes the most metabolic derangements. All the results indicate that lipid prohile undergoes a change in metabolic syndrome and in clinical practice the fatal outcomes and complications are directly related to the severity of lipid abnormalities. Hence the change in Lipid Profile can be a prognostic factor for Metabolic Syndrome and the changes should be seriously taken care of and addressed at the earliest.

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