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Atherogenic Dyslipidemia: An Important Risk Factor for Cardiovascular Disease in Metabolic Syndrome and Type 2 Diabetes Mellitus Patients

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Review Article

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Abstract

Both metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM) are increased risk of cardiovascular disease (CVD) and coronary heart events. Lipid abnormalities in MetS and T2DM patients are the major role in atherogenesis development. These lipid disorders include both quantitative and qualitative abnormalities of lipoproteins the potentially atherogenic. Hypertriglyceridemia is the main quantitative abnormalities, correlated with hepatic VLDL over production and the reduction of both VLDL and IDL catabolism in circulation, and accelerated HDL catabolism to cause decreased HDL-Cholesterol levels. Increased triglyceride content in VLDL particles cause VLDL1 (large VLDL) and also increase in triglyceride content of LDL and HDL particle, small dense LDL particles, easy to cause LDL oxidation and apolipoproteins glycation. Although the LDL-cholesterol level in circulation is usually normal in MetS and T2DM patients, but these types of LDL particles show easy oxidized and reduced turn-over, which is potentially harmful. However, insulin resistance and the insulin deficiency are occurred in MetS and T2DM patients, may play the important role of dyslipidemia. Insulin has the important function and regulation in lipid metabolism. In addition with adipokine, both in the pro-inflammatory and anti-pro-inflammatory adipokines, it could play the important role in the pathophysiology of dyslipidemia.

Keywords: Atherogenic dyslipidemia; Lipoprotein; Insulin resistance; Metabolic syndrome; Type 2 diabetes mellitus

Introduction

The International Diabetes Federation (IDF) reported estimation of 246 million adults worldwide had type 2diabetes mellitus (T2DM) in 2008 and provided the expectation of the prevalence to reach 380 million by 2025 [1]. Estimation of the prevalence of T2DM in the USA was from 21.9 million to 30.3 (11.2%) by the year 2025 [2,3]. This increase in T2DM results from increase of the incidence or rise in new patients of T2DM, which is a consequence of obesity particularly in abdominal obesity, ageing and lack of exercise population. The World Health Organization (WHO) has estimated that over 1 billion persons are overweight and more than 300 million of obese worldwide [4]. In the United States, adults more than 60% are overweight and/or obese, and also increased in the number of both obese children and adolescents [5]. In the Lower Northern Region (seven provinces) of Thailand, adults aged ≥40 years of abdominal obesity (AO) men and women were 37% and 41.8% [6]. Obesity is now become an important health problem worldwide. Clinical evidence proved that AO is an effect or of cardiovascular disease (CVD) and risk of T2DM [7,8]. The development of AO promotes insulin resistance and inflammation, and/or altered hemostasis as risk factors for CVD [9]. The increasing prevalence of obesity and abdominal obesity is considered as the pandemic levels. This has been attributed to increase the adoption of energy-dense diets, physical inactivity and sedentary lifestyles as the consequence of economic globalization and urbanization [4]. Most health care systems are concerned or based on the drug treatment diseases which caused by the specific organism or agents after diseases merge. However, what is really needed for the pandemic of obesity.

Metabolic syndrome (MetS) is defined as the cluster of cardio metabolic disorders that individuals are increase risk of T2DM, coronary heart disease (CHD), and cardiovascular disease (CVD). The major components of MetS are abdominal obesity, glucose intolerance or diabetes, pre-hypertension (HT) or HT and dyslipidemia characterized by hypertriglyceridemia and low levels of high-density lipoprotein cholesterol (HDL-C). The definition of MetS is varies slightly different between each guidelines from the expert groups such as the World Health Organization (WHO), the European Group for the Study of Insulin Resistance, the National Cholesterol Education Program Third Adult Treatment Panel (NCEP ATP III), the International Diabetes Federation (IDF) and the American Heart Association/National Heart, Lung, and Blood Institute. However, all definitions include AO, as a major risk factor, with in the IDF guidelines AO as a prerequisite (Table 1). The guidelines of NCEP ATP III define MetS as the presence of ≥3 of the following abnormalities: waist circumference (WC) ≥102 cm (~40 in) in men or ≥88 cm (~35 in) in women, elevated blood pressure (BP) (systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg), triglycerides (TG) ≥150 mg/dL, HDL-C <40 mg/dL in men and <50 mg/dL in women, and fasting blood glucose ≥110 mg/dL. By the American Diabetes Association (ADA) criteria modified the threshold for fasting glucose ≥100 mg/dL for impaired fasting glucose. International Diabetes Federation (IDF) also modified the threshold for WC to ≥90 cm. in men and ≥80 cm. in women for Asian population. When using the NCEP ATP III definition, the prevalence of MetS in US adults is estimated 22% [10] to 34% [11], 39% as the IDF definition [11]. The IDF definition also identify a greater prevalence of MetS than, (approximately 80% increase) the NCEP ATP III definition do in many countries [12,13]. Increasing of the obesity especially AO consequence glowing the MetS and T2DM will correspond increase the incidence of CVD. There is the urgent need to improve the therapeutic strategies for CVD management in MetS and/or T2DM patients. The prevention of MetS and T2DM is based on the changes in lifestyle. However, neither private companies nor governments have provided any funds for these approaches. Obesity especially AO is an established risk factor for HT and T2DM, and as the major component of MetS. Not surprisingly, about the increasing prevalence of obesity is paralleled with the increasing of the number of HT and T2DM and/or MetS patients.

Central obesity(defined as **waist circumference*** with ethnicity specificvalues); plus any two of these following factors:		
Elevated TG levels	≥50 mg/dL (1.7 mmol/L)	
	or specific medication for lipid abnormality	
Reduced HDL-C levels	<40 mg/dL (1.03 mmol/L) in males	
	<50 mg/dL (1.29 mmol/L) in females	
	or specific medication for lipid abnormality	
Elevated Blood Pressure (BP)	systolic BP ≥130 or diastolic BP ≥85 mm Hg	
	or medication for hypertension	
Elevated fasting plasma glucose(FPG)	≥100 mg/dL (5.6 mmol/L),	
	or diagnosed and treated with type 2 diabetes mellitus	
	If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended.	
Country/Ethnic group	**waist circumference**	
Europids*In the USA, the ATP III values(102 cm male; 88 cm female)are likely to continue to be used for clinical purposes	Male	≥94 cm
	Female	≥80 cm
South Asians: Chinese based, Malay and Asian-Indian population	Male	≥90 cm
	Female	≥80 cm
Chinese	Male	≥90 cm
	Female	≥80 cm
Japanese	Male	≥90 cm
	Female	≥80 cm

Table 1: The International Diabetes Federation (IDF) definition for the persons having the metabolic syndrome.

Cardiovascular Disease Risk in MetS and/or T2DM Patients

There are many clinical research evidences demonstrated that patients with MetS and/orT2DM are at the state of increased CVD risk [11,14-19]. In MetS definition is useful for the physicians to identify patients at high risk for CVD. In population-based cohort study of Finnish men (aged 42-60 years) without CVD or T2DM at baseline, the risk of death from CHD or CVD (≥12-yrs follow-up period) was significantly higher in participants with MetS [14]. In the epidemiologic studies in the United States have identified individuals with MetS also elevated risk of CVD [11,17-19]. The incidence of cardiovascular mortality was 12.0% in patients with MetS and 2.2% in individuals without MS (P<.001) [15]. Many epidemiologic studies and clinical trials have demonstrated that T2DMpatients are at increased risk for CVD [20-23]. In the Multiple Risk Factor Intervention Trial, a cohort study of a large population (aged 35-57 yrs) without T2DM and with T2DM (same ages), the incidence of the >12 yrs follow-up for cardiovascular mortality was 11.7% in T2DM patients and 2.6% in non-T2DM individuals [21]. In the generally accepted that T2DM increases the CVD risk by 2- to 4-fold.Generally, we known that the elevated CVD risk in MetS and T2DM patients is multi factorial, one of the risk factor in particular-atherogenic dyslipidemia. The excess CVD risk in patients with MetS and/or T2DM is due to several risk factors including both un-modifiable risk factors (age, gender and genetics) and traditional risk factors (HT, dyslipidemia, hyperglycemia and smoking). The overall cardio-metabolic risk is modified by the disorders of these lipoproteins complex and demonstrated the same components of the MetS and T2DM. The characteristics of atherogenic dyslipidemia which consists of elevated triglyceride-rich lipoproteins (TRLs), small dense low-density lipoprotein (sdLDL) and low high-density lipoprotein (HDL) cholesterol concentrations in plasma in both fasting and postprandial. This review aims to summarize our understanding of the pathophysiology of dyslipidemia and abnormalities of lipid metabolism in MetS and/or T2DM are the major risk factors of the CVD [20,24].Cardiovascular disease risk in T2DM patients is 2 - 4 greater than in non-diabetic subjects [20,25-27], CVD in T2DM patients is the major cause of morbidity and mortality. Insulin resistance plays the major role in the pathophysiology of lipid abnormalities in MetS and T2DM. Addition with adipokines (leptin, and adiponectine) could

be associated in the development of lipid abnormalities in these patients.

Brief Normal Human Lipoprotein Metabolism

Lipid is transported as lipoproteins, the biochemical complex for all hydrophobic lipids molecules transportation in the circulation. They have a single layer on the surface as monolayer of phospholipids, free cholesterol and apolipoproteins as the hydrophilic portions oriented outward surrounding by the water. The central inner is lipophilic portions, the non-water soluble cholesterol esters and triglycerides (TG) as spherical particles composed of a central core of each molecule oriented inwards the lipids molecules within the lipoprotein particles in the circulations. General, lipoproteins are classified according to their density following as: (i) chylomicron, (ii) very low density lipoprotein (VLDL), (iii) intermediate density lipoprotein (IDL), (iv) low density lipoprotein (LDL) and (v) high density lipoprotein (HDL). The brief schematic of normal lipoprotein metabolism is shown in (Figure 1).

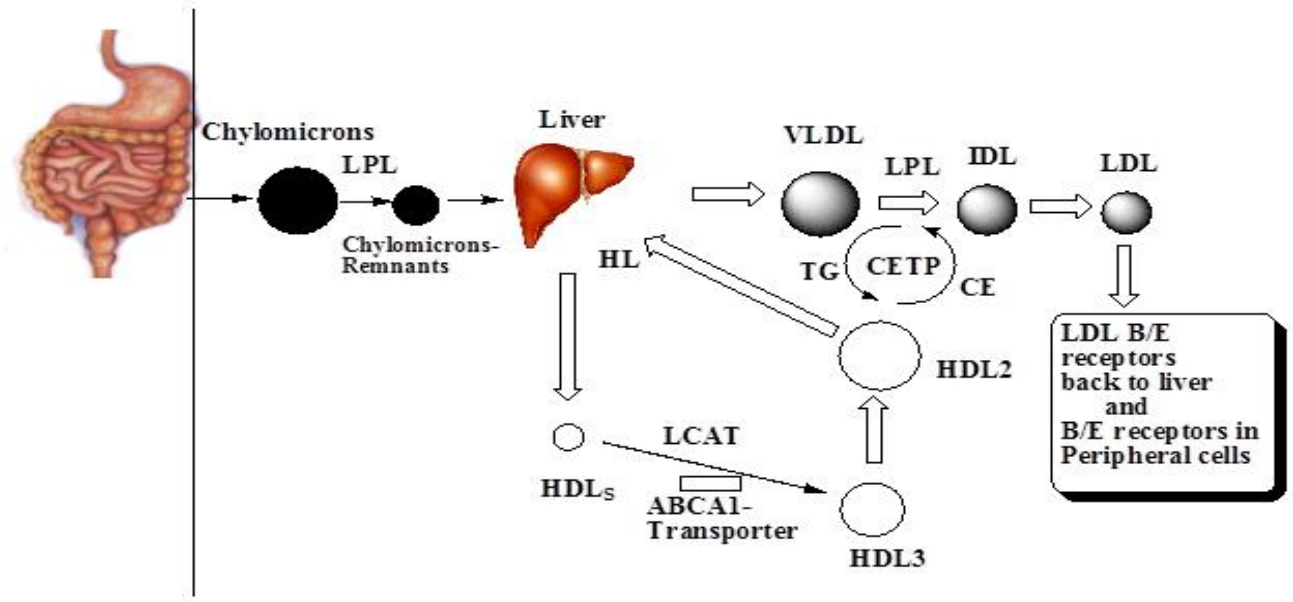

Figure 1: Briefs chematic of normal human lipoprotein metabolism: LPL; lipoprotein lipase, HL; hepatic lipase, VLDL; very low density lipoprotein, IDL; intermediate density lipoprotein, LDL; low density lipoprotein, TG; triglycerides, CETP; cholesteryl ester transfer protein, CE; cholesteryl ester, HDL; high density lipoprotein, LCAT; lecithin-cholesterol acyl transferase, ABCA1; ATP binding cassette A1 transporter.

Chylomicrons

Chylomicrons are the largest lipoprotein particles. The major purpose is responsible for the dietary triglycerides and cholesterol transportation in the circulation. Chylomicrons are composed with cholesterol esters, TG (85%-90%), phospholipids and apolipoproteins (apoB48, apoA-I, apoA-IV). Chylomicrons are synthesized in the enterocytes, and the processing of the lipid components (TG, cholesterol esters, phospholipids) and apoB48 association is performed by the microsomal transfer protein (MTP). Chylomicrons are secreted into the lymphatic circulation before entering the circulation. In circulation, TG in chylomicrons is hydrolyzed by LPL releasing FFA for energy production or for re-esterification or storage in adipose tissues. This chylomicron depleted TG leading to form chylomicron-remnants, the smaller, TG-poorer particles. Chylomicron-remnants are cleared by the liver via LDL B/E receptor or LDL-receptor related protein (LRP) and do not accumulated in the circulation.

VLDLs and IDLs

VLDL particles are the first lipoprotein particles that are synthesized and secreted by the liver. VLDL particles are composed endogenous cholesterol, TG (55% to 65%), phospholipids and apolipoproteins (apoB100, apoC and

apoE). The synthesis of VLDL in the hepatocyte occurs in two major steps as follow: (i) pre-VLDL formation, is takes place in the rough endoplasmic reticulum. ApoB is co-translational and post-translational lipid mediated by the MTP. MTP transfers lipids (majorin TG but also cholesterol esters, phospholipids) to apoB [28]. (ii) This step is the conversion step of pre-VLDL to VLDL in the smooth membrane compartment by the ADP ribosylation factor-1 (ARF-1) and phospholipase deactivation [28]. Triglycerides, the major component of VLDLs are hydrolyzed by lipoprotein lipase in circulation. Triglycerides in VLDLs are become progressively reduced, while phospholipids and apolipoprotein C and E on the surface are transferred to HDLs. This metabolic process causes the IDL particles formation, which are cleared by the liver (via LDL B/E receptors) or further metabolized to form LDLs particles. For this metabolic process of LDL particles formation from IDLs is cause by hepatic lipase enzyme, consist with triglyceride lipase and phospholipase activities.

LDLs

LDL particles are the main cholesterol-carrying lipoprotein in circulation. LDL particles are the final production of the VLDL-IDL-LDL process. In each LDL particle contains one molecule of apoB100, which plays the major role in the LDL metabolism. LDL particles are cleared in the plasma mediated via the LDL B/E receptor. LDL B/E receptors are located on hepatic cells (70%) and the other cells of the body (30%).These cells can take up LDL-C from circulation. All cells of extra-hepatic tissues cannot be process these cholesterol which may accumulate in these cells.

HDLs

HDL particles are secreted as the small lipid-poor lipoproteins by the hepatocyte, a major lipoprotein containing is apoA-I, which receive in the circulation, and the others are apoC, apoE and phospholipids from chylomicrons and VLDLs. The original HDL lipoprotein particles (nascent or lipid-poor HDLs) are synthesized by the liver as the complexes of apolipoproteins and phospholipid, which form with cholesterol-free flattened spherical particles. These complexes are capable to pick up cholesterol from the cells cytoplasm by interaction with the ATP-binding cassette transporter A1 (ABCA1) [42]. Lecithin-cholesterol acyltransferase (LCAT) enzyme in circulation converts the free cholesterol into cholesteryl ester (a more hydrophobic form of cholesterol), which is sequestered into the core of the HDL lipoprotein leading to the formation of HDL3 particles. The fusion of 2 HDL3 particles formed a one larger size HDL2 particle that is promoted by phospho lipid transfer protein (PLTP). These HDL2 lipoproteins, cholesteryl ester rich, are degraded by hepatic lipase and endothelial lipase to form HDL remnant particles that are cleared by the liver via recognition of scavenger receptor class B type 1(SR-B1) receptor as direct pathway. HDL particles increase in size by more cholesterol and phospholipid molecules incorporation from cells and other lipoproteins, as they circulate through the circulation. Liver and the steroidogenic organs (adrenals, ovary, and testes) are the sites that HDL transports cholesterol to degrade by both direct and indirect pathways. In humans, cholesteryl ester transfer protein (CETP), the one indirect pathway exchanges TG of VLDL against cholesteryl esters of HDL. After that VLDLs are hydrolyzed to LDL and removed from the circulation via the LDL receptor. Triglycerides in HDL are not stable and degraded by hepatic lipase to generate small HDL particles and restart to uptake cholesterol from the cells. The HDL cholesterol delivery to other organs (adrenals, ovaries, and testes) is important for steroid hormones synthesis. The delivered cholesterol in the liver is excreted into the bile and intestine after conversion into bile acids. The importance step of the HDL metabolism may participate in the cholesterol transportation from the foam cells (lipid-laden macrophages of atherosclerotic arteries) to the liver for secretion into the bile. This step has been termed reverse cholesterol transport as the protective function of HDL for atherosclerosis.

There are two major lipid transfer proteins (CETP and PLTP) involved in lipoprotein metabolism. Among of these, CETP facilitates the transfer of TG from VLDL (TG-rich lipoproteins) to HDL and LDL particles, and also transfer cholesteryl esters from HDL and LDL to VLDL particles. While, PLTP will facilitates the transfer of phospholipids and α-tocopherol between the lipoproteins particles and also involved in the HDL2 particles formation from HDL3 particles. Any modification from CETP or PLTP activities will promote the qualitative abnormalities of lipoproteins particles.

Role of Insulin on Lipid Metabolism

Insulin plays the regulation role of the lipid metabolism. Figure 2 demonstrated the main sites of insulin action in lipoprotein metabolism. Insulin inhibits hormone-sensitive lipase in adipose tissue as the anti-lipolytic action and promotes TG storage in the adipocytes and reduces the secretion of free fatty acids from adipose tissue into the circulation. Insulin also inhibits VLDL

synthesis from the liver. It has been demonstrated that insulin decreased the VLDL-TG synthesis (by 67%) and decreased of VLDL-apoB synthesis (by 52%) in normal subjects [30,31]. Insulin diminish free fatty acids, the substrates of VLDL in circulation (as the anti-lipolytic effect) resulting in reduced VLDL synthesis, and also by the direct inhibition effect in the hepatocytes [31]. Insulin is the activator on the lipoprotein lipase (LPL) gene to promote LPL synthesis [32]. Insulin is also an activator and enhancer of LPL activity to promote the TG-rich lipoproteins catabolism [33]. Insulin is also enhances LDL B/E receptor expression and activity to promote the clearance of LDL in the circulation [34,35]. Insulin is also activates on LCAT and hepatic LPL activities to promote in the action on HDL metabolism [36]. It has been demonstrated that insulin has an inhibitory effect on the PLTP activity both in normal subjects and T2DM patients [37]. Arii et al. demonstrated that insulin reduces CETP activity, it is not a direct inhibitory action on CETP but this inhibitory effect depend on the consequence of the insulin-induced reduction of free fatty acids in the circulation [38].

Atherogenic Dyslipidemia Pattern

Lipoproteins in circulation exist as the spectrum of particles size difference and the difference in atherogenicity or anti-atherogenic potential (Figure 2). Metabolic syndrome and T2DM diabetes mellitus as the insulin-resistant state, exhibit the characteristic pattern of abnormalities in serum lipids: low levels of HDL-C and elevated TG and sdLDL [39,40]. This dyslipidemia pattern is also demonstrated sapolipo protein B (apoB) elevations and the sdLDL particles are depleted in cholesteryl ester (Table 2) [41]. The elevation of apoB-carrying lipoproteins of dyslipidemia is also decreases in apolipoprotein A-I–carrying lipoproteins as the central abnormalities. This complex dyslipidemia is termed dyslipidemia of insulin resistance or diabetic dyslipidemia. Then, insulin resistance reflects the underlying dyslipidemia state or plays the major role in the increased cardiovascular risk in MetS and T2DM patients with increased atherogenic dyslipidemia. Dyslipidemia pattern demonstrated lipoprotein abnormalities in both quantitative and qualitative phenomena in these patients [42-48]. Hypertriglyceridemia and low HDL-cholesterol levels is the main quantitative lipid abnormalities while the qualitative lipid abnormalities are occur in all lipoproteins. These lipoprotein abnormalities may promote atherosclerosis in these patients. Main lipoprotein modifications are shown in Table 2 and in (Figure 3).

Lipoproteins	Plasma level	Abnormalities	Qualitative or type of abnormalities
VLDL	Hypertriglyceridemia	Increased production Decreased catabolism	-Large VLDL (VLDL1) -Glycation
LDL	Normal or slightly increased	Decreased catabolism Decreased turn-over	-sdLdL (TG-rich LDL) -Oxidation -Glycation
HDL	Decreased HDL	Increased catabolism	-TG-rich HDL -Glycation

Table 2: The major lipid abnormalities in MetS and T2DM.

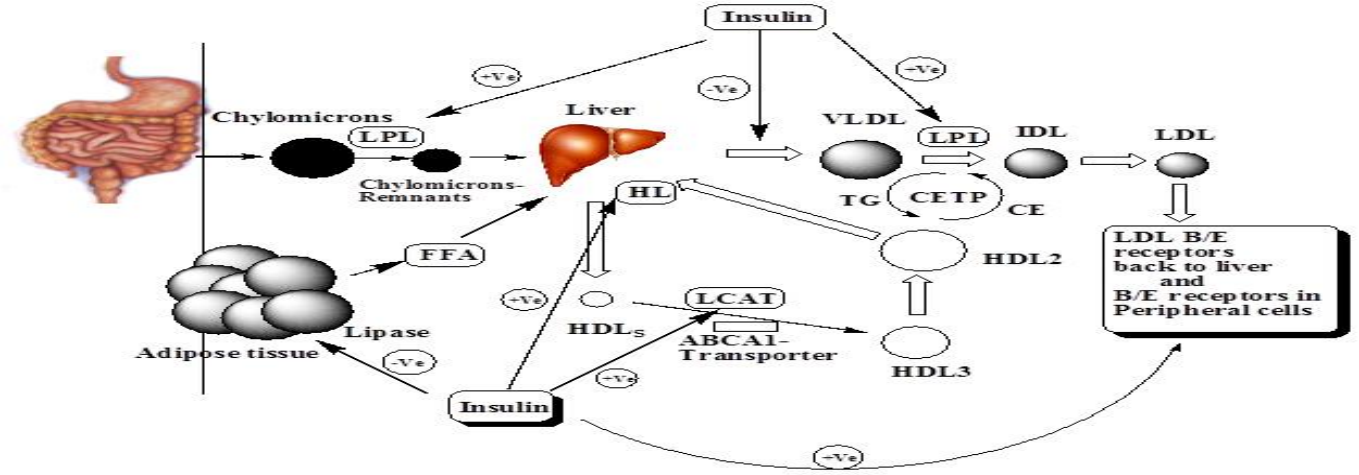

Figure 2: The major point effects by insulin on lipoprotein metabolism:
For insulin activates [+ve]: LPL; HL; LCAT; LDL B/E receptors.
For insulin inhibits [-ve]: hepatic VLDL production, hormone-sensitive lipase.LPL; lipoprotein lipase, HL; hepatic lipase, VLDL; very low density lipoprotein, IDL; intermediate density lipoprotein, LDL; low density lipoprotein, TG; triglycerides, CETP; cholesteryl ester transfer protein, CE; cholesteryl ester, HDL; high density lipoprotein, LCAT; lecithin-cholesterol acyl transferase, ABCA1; ATP binding cassette A1 transporter.

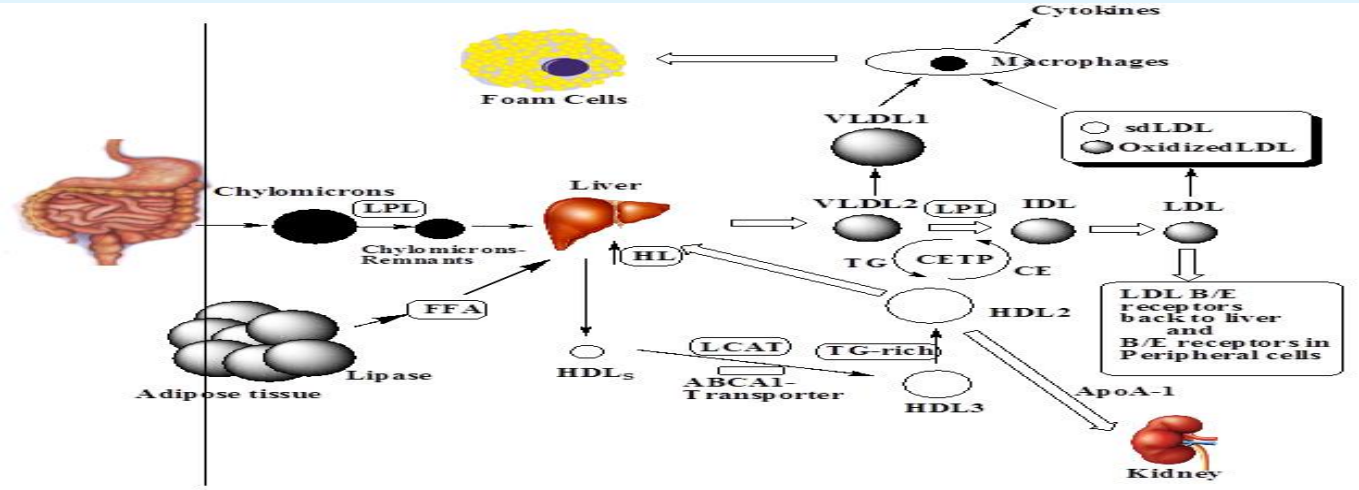

Figure 3: The major qualitative or types of lipid abnormalities in MetS and T2DM: Qualitative or type of lipid abnormalities
– Hypertriglyceridemia (increased VLDL production),
-Increased HDL catabolism due to low HDL-C levels,
-Increased large VLDL (VLDL1) production,
-Increased sdLDL (TG-rich) and oxidized LDL,
-Increased CETP activity (due to increased transfer TG to LDLs and HDLs)
-Increased TG content in HDL,
-Increased taken up of VLDL1, sdLDL and oxidized LDL by macrophages.
-Decreased LDL B/E receptors (reduction of LDL turn over),
-Decreased TG catabolism in TG-rich lipoprotein (due to reduced LPL activity).

Triglyceride-rich Lipoproteins

Triglyceride levels are increased in both MetS and T2DM, due to the elevation of the number of VLDL particles in circulation [42,46] and also in the number of IDL particles was observed [49,50]. The major determinant of the hypertriglyceridemia is the VLDL-TG overproduction in the circulation of both MetS and T2DM patients [51]. This may cause increase and accumulate a large number of lipids in the hepatocytes and also to cause hepatic resistance to insulin for the inhibitory effect of VLDL production [52-54]. In this stage, increasing of lipid pool in hepatocytes is the increase flux of free fatty acids (FFA) into the liver [55] and may accelerate to increase de novo lipogenesis, which correlates with the accumulation of fat in liver. This evidence was demonstrated by the observation of sterol regulatory element-binding protein-1c (SREBP-1c) elevation in the liver of insulin-resistant animals [56,57]. The SREBP-1c expression in the liver is associated with the 2 enzymes of de novo lipogenesis: (i) acetylCoA carboxylase and (ii) fatty acid synthase activation. Many studies demonstrate the decreasing of the inhibitory effect of insulin on the hepatic VLDL production is the major role [31,54] and elevated FFA level in circulation [58]. Many studies have been demonstrated these inhibitory effects of insulin on hepatic VLDL production [30,31,59-65] and also demonstrated the inhibition of VLDL particles formation and secretion by increased apoB degradation and reduction of the MTP expression in hepatocytes [61,62,64]. Elevation of MTP expression lead to enhance VLDL assembly and secretion has been demonstrated in insulin-resistant hamsters, obese diabetic mice [65,66] and T2DM patients. In normal subject, insulin also activated enzyme phosphoinositide 3-kinase (PI 3-kinase) using for the phosphoinositol biphosphate (PIP2) transformation to phosphoinositol triphosphate (PIP3). The reduction of PIP2 was induced by insulin is the activator of ADP ribosylation factor-1 (ARF-1) and phospholipase D which leads to decrease in the ARF-1 and phospholipase D activation that were involved in VLDL formation[28]. In T2DM present the defective in PI 3-kinase activation from the insulin resistant state. This situation in T2DM causes an elevation of PIP2 that activates ARF-1 and Phospholipase D leading to increase VLDL formation. Thus, VLDL overproduction, in both MetS and T2DM may due to hepatic resistance to insulin action of the inhibitory effect of insulin on hepatic VLDL production [30,67]. In T2DM, overproduction of VLDL-TG may be greater than in the production of VLDL-apoB result from the larger TG-rich VLDL particles (VLDL1) formation [68] and also reduced in catabolism of VLDL and IDL particles as the factors in promoting diabetic hypertriglyceridemia in T2DM [51,68,69]. Both increased VLDL and IDL particles mainly effects on the reduction of lipoprotein lipase activity. Many studies have been demonstrated the reduction of adipose tissue lipoprotein lipase activity in T2DM [68,70,71]. Since insulin action is a major activator of lipoprotein lipase. Then, reduction in insulin activity may be relates with insulin deficiency and/or insulin resistance, observed in T2DM and MetS. There are several qualitative abnormalities of VLDL particles have been demonstrated in T2DM patients. The mainly overproduction of VLDL is an increased large VLDL particles synthesis (VLDL1), characterized by large amount of TG than the smaller VLDL2 particles. VLDL1 are easily taken up by the scavenger receptors of macrophages and accumulate of lipid within macrophages to cause foam cells formation in vessel walls [72]. Type 2 diabetes mellitus patients demonstrate both in fasting hypertriglyceridemia and postprandial hypertriglyceridemia. The majority of TG-rich lipoproteins during the postprandial state in T2DM patients are VLDL1 particles [73,74]. Apolipoproteins (apoB, apoC, apoE) glycation in VLDL particles may occur in T2DM and cause this glycated VLDL particle and the B/E receptor binding reduction on the catabolism [75].

LDL

Low density lipoprotein-cholesterol (LDL-C) is usually normal level in T2DM patients but the modifications in LDL particles metabolism are observed. *In vivo* study has been demonstrated the featuring of LDL-cholesterol values in T2DM similar with non-diabetic controls [69]. However, T2DM demonstrate the reduction in the turn-over of LDL particles by the reduction of LDL catabolism, leading to increase LDL circulation and to promote cholesterol deposition in the vessel wall. Duvillard et al. [76] reported insulin treatment in T2DM patients can be normalized LDL catabolism. The reduction of the number of LDL B/E receptors is the other caused of impaired LDL catabolism in T2DM. Indeed, T2DM patients demonstrate the significant LDL B/E receptors reduction on cell surface [77], but insulin treatment can restore the number of LDL B/E receptors on cell surface in T2DM patients [77]. Apo Bglycation on the LDL particles could be decrease affinity of LDLs with their receptors to cause the reduction in LDL catabolism [78]. The important atherogenic LDLs in T2DM patients are small dense, triglyceride-rich, LDL particles [79,80] and this appears to be mainly related to hypertriglyceridemia phenotype in T2DM [81]. Then, VLDL1-TG is the major predictor of LDL size in T2DM [73]. Elevation of TG-rich lipoproteins stimulates CETP activity in T2DM to promote TG transfer to LDLs to form TG-rich LDL particles which are favor

substrate for hepatic lipase to produce sdLDL particles. Many studies have been demonstrated presence of sdLDL particles is associated with increased cardiovascular risk [82-84]. Many research studies indicate that sdLDL particles have atherogenic properties as follow: (i) sdLDL particles reduce affinity for the LDL B/E receptor and are easy taken up by the scavenger receptor of macrophages to form the foam cells (ii) sdLDL particles have higher affinity for intimal proteoglycans to penetrate into the vessel wall than large LDL particles [85,86] (iii) patients with sdLDL particles elevation demonstrated an impaired response to the endothelium acetylcholine vasodilatator [87,88] (iv) sdLDL particles are susceptible for oxidation [88,89], LDL oxidation is the marked atherogenic potential that observed in increased in T2DM [47,48,90,91]. Oxidized LDLs are rapid uptake by macrophages resulting in foam cell formation. Oxidized LDLs produce chemotactic stimulates monocytes by increasing the adhesion molecules formation (such as intercellular adhesion molecule 1; ICAM-1) from endothelial cells. Oxidized LDLs also stimulate the macrophages cytokines production including TNFα, IL1, as the amplifiers of the inflammation of atherosclerotic process. Indeed, glycated LDL (glycation of apoB within LDL particles) observed in T2DM patients to cause the reduction in affinity of LDL B/E receptor effect in LDL metabolism [92-94] and are also favor taken up by macrophages to cause foam cells formation [95]. Furthermore, this glycated LDL is easy oxidized in the circulation [96,97].

HDL

The decrease in HDL-cholesterol in T2DM patients related to the reduction in HDL2 sub-fraction [98,99] and elevation of HDL particles catabolism [100,101]. The HDL2 level reduction in T2DM has been demonstrated correlation with both hypertriglyceridemia and obesity. Many studies indicated the elevation of hepatic lipase activity in HDL catabolism, is observed in T2DM patients [100,102]. Elevation of HDL catabolism is associated with insulin-resistant state and obese insulin resistant non-diabetic patients [103,104]. This elevation of HDL particles catabolism in these states will increase TG-rich lipoproteins pool (mainly VLDL). The large amount of TG-rich lipoproteins in circulation, CETP can transfer TG from TG-rich lipoproteins to HDL particles to form TG-rich HDL particles [105]. Now, TG-rich HDL particles become the good substrate for hepatic lipase which increased HDL particles catabolism in insulin resistant states and T2DM. This catabolism process is responsible for increased HDL particles catabolism. ApoA-I dissociated from TG-rich HDL particles, is filtered and degraded by the renal glomerular and renal tubular cells. Furthermore, HDL particles in T2DM can be glycated and demonstrated the correlation between glucose level with apoA-I glycation [106]. The apoA-I glycation may reduce the binding of HDL to its receptor [107]. These abnormalities of HDL particles may cause HDL dysfunction in mediated cholesterol efflux and the process of reverse cholesterol transport [108-110].

Lipid Transfer Proteins

In the qualitative abnormalities of lipoproteins such as TG-rich LDL and TG-rich HDL particles are occur in insulin resistance state and T2DM patients. This may indicate an increased activity of CETP in the transfer of TG and cholesterol esters between lipoproteins [111,112]. Both hypertriglyceridemia (TG-rich lipoproteins) and the hyperglycemia accelerated lipoproteins glycation may direct stimulate and increase CETP activity in insulin resistance state and T2DM [113]. Many research studies reported increased PLTP mass and activity in T2DM [112,114]. But the exact process of this increased PLTP activity remains unclear.

Some Roles of Adipokines Relate the Pathophysiology of Dyslipidemia

Beyond the storage fat, visceral, subcutaneous depots and widely dispersed throughout the body of adipose tissue may be participate in influencing cardiovascular disease. In the present day, white adipose tissue is well recognized as an endocrine tissue function. Its can produce several adipokines levels in circulation and are altered in obesity and T2DM. The difference of adipose tissue depots in one with another is based on the relative adipokine levels production. In obesity will favor to produce pro-inflammatory adipokines [115-117]. Interestingly, in research studies of visceral adipose tissue in aging mice demonstrate the expression of pro inflammatory adipokines (TNFα and IL-6) even the absence of diet-induced obesity [118,119]. We can classify adipokines to pro-inflammatory and anti- pro-inflammatory adipokines. Most adipokines are identified as pro-inflammatory and they are up-regulated in the obese state and T2DM.These adipokines functions are promoting metabolic and cardiovascular diseases in these conditions. Pro-inflammatory adipokines include TNFα, leptin, IL-6, resist in, RBP4, lipocalin 2, IL-18 and ANGPTL2. The smaller number adipokines are anti-pro-inflammatory factors. These adipokines include adiponectin [120,121] and SFRP5 [122]. Inflammatory stimulation increase leptin levels both in adipose tissue and plasma [123].

Leptin can stimulate the multiple types of immune cells (monocytes/macrophages, neutrophils, and T cells), to release the inflammatory cytokines [124-127]. Leptin increases TH1-type cytokines production and suppresses TH2-type cytokine IL-4 production in T cells [124], leading T cells polarizing to TH1 cell phenotype. Consistent with the observations of leptin deficiency can protect against liver damage as in the models of T cell-mediated hepatitis and autoimmune encephalomyelitis [124,128,129]. By these evidences accepted that leptin plays the major role in pro-inflammatory adipokine. Many research studies demonstrated the important role of leptin in cardiovascular diseases. Elevation of leptin levels are identified in patients with myocardial infarction [130] and heart failure [131]. Faraj et al. reported adiponectin and/or TNFα involve in lipid metabolism [132]. Thus, adipokines could play the pathophysiology role in dyslipidemia of obese and T2DM. Adiponectin increases FFA uptake and oxidation in muscle and decreases TG content in muscle, liver and also reduces FFA level in plasma [132-134]. Many research studies reported the reduction of adiponectin levels and expression in white adipose tissue of obese and T2DM patients [135,136] and also demonstrate the negative correlation with plasma TG levels and positive correlation with plasma HDL-cholesterol in T2DM and non-T2DM subjects [137-140]. The associations of adiponectin and plasma lipids are independence from insulin-resistance indexes [137-139]. Ng et al. reported the positive correlation of circulating adiponectin level with VLDL apoB catabolism, independent from HOMA-IR index [141].

These research data suggest the action of adiponectin on lipid metabolism independent from the action of insulin. However, the opposite mechanisms to decrease adiponectin may affect lipid metabolism in obese and T2DM still unclear. Adiponectin may reduce plasma triglyceride level via promoting of FFA oxidation through acetyl CoA oxidase, carnitine palmitoyltransferase-1 and AMP kinase activation [142]. Adiponectin may indirectly stimulate lipoprotein lipase activity [143] via the expression of PPAR-α in the liver and adipocytes [134]. Production of tumor necrosis factorα (TNFα), pro-inflammatory adipokine, from white adipose tissue is increased in obesity and T2DM [132,144,145]. TNFα has been demonstrated involved in lipid metabolism. TNFα reduces FFA uptake in the adipose tissue, promotes lipolysis and FFA efflux [132]. TNFα also suppresses lipoprotein lipase, fatty acid transport protein and acetyl CoA synthetase production which involved in triglyceride accumulation [132, 139]. Indeed, no correlations were found between plasma TNFα and lipids levels in obese or T2DM patients [140] and has not found the association of TNFα and TG-rich lipoprotein metabolism [141,146]. Resist in, another Pro-inflammatory adipokine is found negative correlation with HDL-cholesterol levels in T2DM subjects, after adjustment for BMI and HbA1c [140]. However, also found no correlations between resist in and TG-rich lipoprotein metabolism [141,146]. Apelin is another adipokine effects on feeding behavior and glucose utilization. Sörhede Winzell et al. demonstrated that apelin can activate both apelin receptor and APJ receptor expression in islets for inhibiting the insulin secretion [147], and PI3K–phosphodiesterase 3B activation [148]. Ringström et al. [149] demonstrated that apelin can express by itself in β- and α-cells of pancreatic islets possible for autocrine/paracrine effects.Sfrp5 is the one of the anti-inflammatory adipokine.

Sfrp5 was identified as the soluble modulator of Wnt proteins to protect against metabolic dysfunction [150]. Sfrp5-deficient mice with high caloric diet feeding display impaired glucose catabolism and increased lipid accumulation in liver, even metabolically normal and on regular diet [150]. Association of Sfrp5-deficiency with increased lipid accumulation in macrophages and increased pro-inflammatory cytokines production. The mechanism causes by the deletion of JUN N-terminal kinase 1 (JNK1). Because of the Sfrp5 suppress Wnt5a which mediated the JUN N-terminal kinase 1 (JNK1) activation in adipose tissue. Then, in Sfrp5-deficient mice reverses the metabolic and inflammatory phenotypes. Thus, the over activation of JNK1 signaling in Sfrp5-deficient mice induces increased inflammation and metabolic dysfunction in adipose tissue. These consist with the role of JNK1 in insulin resistance regulation and lipid inflammation [151,152,153]. Many studies have been reported the detection of Wnt5a expression in lesions of atherosclerosis in mouse and human [154,155]. Furthermore studies are needed to identify the putative role of adipokines on lipid abnormalities.

Using Lipoprotein Ratios for Insulin Resistance Estimation

According in described above, the major characteristics of quantitative dyslipidemia in MetS and T2D patients are increase plasma TG levels, reduce HDL-C levels and sdLDL particles, increased TG-rich remnant lipoprotein (TGRLs) and increase insulin levels in circulation[156]. The major change is increased TGRLs and decreased HDL-C levels are associated with insulin resistance syndrome. Insulin involves in the role of TG metabolism (Figure 2). In normal condition, TGRLs particles were less synthesized by the distinct pathways than VLDL particles synthesis [73,157]. In insulin resistant state or T2DM, insulin fails

to suppress the synthesis of VLDL particles [52-54], and associate with increased FFAs flow to the liver and increased lipid synthesis in the liver and decreased VLDL particles clearance from the circulation resulting in the elevated VLDL particles [54,158]. These phenomena indicated the problems of VLDL and HDL particles and concurrent with increased insulin levels. Reduction of HDL-C level is correlated with the insulin resistance or hyperinsulinemia and defected in insulin signaling for insulin-mediated glucose disposal [159]. These features are associated with the risk factors for coronary heart disease in obesity, MetS and T2DM patients. We can use these lipoprotein ratios such as TC/HDL-C, TG/HDL-C ratios and non-HDL-C (as TC - HDL-C) to estimate insulin resistance. Then, TC/HDL-C, TG/HDL-C ratios and non-HDL-C (as TC - HDL-C) were used as the markers for insulin resistance estimation. Tangvarasittichai et al. reported the using of TC/HDL-C, TG/HDL-C ratios and non- HDL-C as markers of insulin resistance and CVD risk factor [157,160] and reported the cut-off points of the highest % sensitivity and % specificity of TC/HDL-C, TG/HDL-C ratios and non-HDL-C corresponding to 3.58, 2.48 and 130.4, respectively [157]. These results of lipoprotein ratios were from Asian subjects and lower than the subjects from Western [161-163]. All of these lipoprotein ratios, TC/HDL-C, TG/HDL-C ratios and non-HDL-C are the simple mathematical analysis and easy to calculate and order with the lipid profiles available for clinician and no costs gain. Then, we can use these lipoprotein ratios as markers of insulin resistance estimation. For atherosclerotic risk assessment in higher risk subjects; obesity, MetS and T2DM patients need more attention for lipid screening.

Conclusion

Increased prevalence of the MS and T2DM is global as the consequence of the obesity and abdominal obesity pandemic. Several factors in the definition of MetS are the major characteristics of atherogenic dyslipidemia same as T2DM. The same lipid disorder in both cases contributes to increase the CVD risk in these individuals. These characteristics of lipid disorders include quantitative and qualitative abnormalities. Hypertriglyceridemia and low HDL-cholesterol levels are the main lipid quantitative abnormalities, include large VLDL particles (VLDL1), sdLDLs, increase TG content in LDLs and HDLs, increase apolipoproteins glycation and increase oxidized LDL. The involvement of adipokines in pathophysiology of lipid abnormalities in MetS and T2DMis complex and not complete explained. Need more studies to get insight into the in the detail mechanisms of these dyslipidemia. The improvement in understanding of lipid abnormalities and disorders in MetS and T2DM will get the better treatment and outcome of these dyslipidemia.

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