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HYPERLIPEDIMIC RELATED METABOLIC DISORDER

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ABSTRACT:

Metabolic disorder is related with risk for type 2 diabetes and cardiac disease. According to this review it shows that the fundamental features of the pathophysiology, diagnosis and the treatment of the metabolic disorders of hyperlipidaemia. Due to cause of this metabolic disorder hyperlipidaemia distinguish by hypertriglyceridemia and decreased level of highdensity lipoprotein or good cholesterol. The therapeutic management of the metabolic syndrome, regardless of the control of the bodyweight, BP, hyperglycaemia or overt diabetes mellitus, aims at maintaining optimum plasma lipid levels. Therapeutic goals are likely to those for high-risk situations because of the coexistence of many risk factors. The primary goal in treatment should be achieving an LDL-C level of n LDL-C level of < 100 mg/dL or (<70 mg/dL in cases with established ischemic heart diseases or risk equivalent) A further goal is increasing the HDL-C level to ≥40 mg/dL in men or 50 mg/dL in women. A non-HDL-C goal of 130 mg/dL should also be aimed at in cases of hypertriglyceridemia.

Keywords: hyperlipidaemia, hyperglycaemia, diabetes mellitus, LDL-C, n LDL-C, HDL-C, chole sterol etc

INTRODUCTION:

The metabolic syndrome is occurred when the abnormalities that represent major risk factors for both type 2 diabetes mellitus and cardiovascular disease (CVD). When the opposition to insulin-mediated glucose disposal and compensatory hyperinsulinemia are central to both the metabolic syndrome and diabetes, and appear to be responsible for most, if not all, of the associated abnormalities. Atherogenic dyslipidaemia is

an important component of the cluster of abnormalities characteristic of the metabolic syndrome, which also consists of abdominal obesity, insulin resistance (with or without glucose tolerance), raised blood pressure, and prothrombotic and proinflammatory states [1]. Hermann Haller used for first time the term "metabolic syndrome" to associate diabetes, obesity, high plasma lipids, high uric acids and hepatic steatosis to gather. In 1998, the World Health Organization (WHO) first included insulin resistance in metabolic syndrome [2] There are three main components of dyslipidaemia that occur in insulin resistance: increased fasting and postprandial triglyceride-rich lipoproteins (TRLs), reduced high-density lipoprotein (HDL), and increased small, dense low-density lipoprotein (LDL) particles. Because the metabolism of all lipoproteins is maximumly interrelated, it is likely that a common fundamental metabolic defect explains all of the lipoprotein changes in the dyslipidaemia of insulin resistance. It is sure rare that they are found different in insulin resistant individuals. Population-based studies have universally and continuously found positive associations of measures of insulin resistance with plasma total or very low-density lipoprotein (VLDL) triglyceride, and negative connection with HDL cholesterol concentration. These connections have remained significant when adjusted for main covariates such as obesity, age, smoking and physical activity, and appear to be consistent in both sexes and among various populations, such as white subjects [3]

Definition of metabolic syndrome: lipoprotein (HDL)-cholesterol < 40 mg/dL for men, or <50mg/dL for women. Mets was defined by a combination of abdominal obesity, impaired fasting glucose, atherogenic dyslipidaemia, and elevated blood pressure. Revised NCEP ATP III criteria (4,5) require at least three of the following components: (1) abdominal obesity (waist circumference [WC] ≥90 cm for men, or ≥85 cm for women) (2) triglycerides ≥150 mg/dL, and/or drug treatment for elevated triglycerides; (3) high-density.

Pathophysiology:

The pathogenic procedure of Mets is complex and remain to be fully elucidated. Whether the separate components of Mets represent distinct pathologies or manifestations of a common pathogenic mechanism is still debated. The broad variation in geographic division of Mets and the recent 'catch up' in the developing world highlight the importance of environmental and lifestyle factors such as the consumption of excess calories and lack of physical activity as being vital contributors. Visceral adiposity has been indicating to be a primary trigger for most of the pathways involved in Mets, thus stressing the importance of a high caloric intake as a major causative factor. (6) increased fasting triglycerides the hepatic overproduction of VLDL appears to be the primary and crucial defect accompanying insulin resistance and compensatory hyperinsulinemia. In ability to suppress hepatic glucose production, impaired muscle glucose uptake and oxidation, and inability to suppress release of non-esterified fatty acids (NEFA) from adipose tissue are the most essential consequences of insulin resistance in liver, muscle, and adipose tissue, respectively. These events give rise to increased NEFA and glucose flux to the liver, an important regulator of hepatic VLDL production [7]. Mets is a state of chronic low-grade inflammation as a effect of complex interplay between genetic and environmental factors. Insulin resistance, visceral adiposity, atherogenic dyslipidaemia, endothelial dysfunction, genetic susceptibility, elevated blood pressure, hypercoagulable state, and chronic stress are the several factors which constitute the syndrome.

There are many hypothesized mechanisms for the underlying pathophysiology of Mets, and the most widely accepted of these is insulin resistance with fatty acid flux. Other potential mechanisms include low-grade chronic inflammation and oxidative stress. [8,9,10]

Hyperlipidaemia subdivides into two broad classifications: primary (familial) or secondary (acquired) hyperlipidaemia. Primary hyperlipidaemia derives from a plethora of genetic disorders that a patient may inherit through birth, while secondary hyperlipidaemia typically originates from an alternate underlying etiologic, such as an unhealthy diet, medications (amiodarone, glucocorticoids), hypothyroidism, uncontrolled diabetes, and/or a poor lifestyle regimen.[11]

Underlying disruption in lipoprotein metabolism are often familial, making a patient's family history that much more valuable. For example, about 54 percent of patients (in one study) with a history of precocious coronary artery disease had an underlying hereditary disorder. In most patients, hyperlipidaemia has a polygenic inheritance pattern, and manifestations of the disorder are largely influenced by secondary factors such as (central) obesity, saturated fat intake, and the cholesterol content within a person's diet.[12]

Epidemiology of Mets:

The prevalence of Mets differs around the world and often corresponds with the prevalence of obesity. There is a broad difference in prevalence based on age, gender, race/ethnicity, and the standard used for diagnosis. Mets influence a fifth or more of the population of the USA and about a quarter of the population of Europe. South-east Asia has a lower prevalence of Mets but is quickly moving towards rates similar to the western world. Beltrán-Sánchez and teammates reported a decrease in the age-adjusted prevalence of Mets in the USA, from 25% in 2000 to 22.9% between 1999/2000 and 2009/2010 based on National Health and Nutrition Examination Survey (NHANES) data.[13]

The global prevalence of Mets varies depending on geographic and sociodemographic component, as well as the diagnostic criteria used. National Health and Nutrition Examination Survey data estimate that 35% of adults in the United States, and as much as 50% of the over60 population, had a diagnosis of Mets (30.3% in men and 35.6% in women), based on the National Cholesterol Education Program Adult Treatment Panel III criteria, with recent trends suggesting a stable overall prevalence and a reduced prevalence in women [14] Worldwide prevalence of Mets ranges from greater than 10% to as much as 84 percent depending on the region, urban or rural environment, composition (sex, age, race, and ethnicity) of the population studied, and the definition of the syndrome used[15,16]The following factor are responsible for the cause of metabolic disorders.

- Positive family history [17]
- Smoking [18]
- Obesity [19]
- Physical inactivity [20]
- Excessive television watching [21]

- Use of antiretroviral drugs in human immunodeficiency virus infection [22] **Hyperlipidaemia Related Diseases:**

1 Overweight and Obesity

2 Hypertension

3 diabetes mellitus

4 insulin resistance

Overweight and obesity:

In the last decades the number of obese patients has expanded considerably. It is especially alarming that in recent years the expand was most pronounced in children and that it occurs both in developed, but perhaps even more, in developing countries [23] Visceral obesity leads to insulin resistance in part mediated by adipokines and free fatty acids (FFA). Adipokines such as resisting and retinol-binding protein 4 decrease insulin sensitivity, whereas leptin and adiponectin have the opposite effect. In addition, cytokines like TNF-α and IL-6, which originate from macrophages in adipose tissue, are involved [24]

There is strong and widespread belief that lifestyle modification aimed at weight loss are an effective therapy for obesity associated with the metabolic syndrome.[25] the waist-hip ratio has long been accepted as an mark of central obesity and, even though the risk cut-off values have not been clearly defined, limit values of <1 in men and <0.90 in women have been proposed.[26]

The hallmark of hyperlipidaemia in obesity is elevated fasting and postprandial TG in combination with the preponderance of small dense LDL and low HDL-C (Figure 1). Hypertriglyceridemia may be the major cause of the other lipid abnormalities since it will lead to delayed clearance of the TG-rich lipoproteins [27-28] In the presence of hypertriglyceridemia, the cholesterol-ester content of LDL decreases, whereas the TG content of LDL enhanced by the activity of CETP. However, the enhanced TG content within the LDL is hydrolysed by hepatic lipase, which leads to the formation of small, dense LDL particles. The development of small dense LDL in obesity is mainly due to increased TG concentrations and does not depend on total body fat mass [29].

The Pharmacological Treatment of Obesity:

Apo B constitute the total number of atherogenic particles (chylomicrons, chylomicron remnants, VLDL, IDL and LDL), whereas non-HDL-C constitute the amount of cholesterol in both the TG-rich lipoproteins and LDL. Recently, a meta-analysis has shown that execution of non-HDL-C or apo B as treatment target over LDL-C would prevent an additional 300,000– 500,000 cardiovascular events in the US population over a 10-year period [30]. Nevertheless, the presence of obesity can affect treatment targets since obesity may contribute to enhanced remnant cholesterol, higher TG levels and lower HDL-C concentrations. Therefore, apo B or non-HDL-C levels are recommended as secondary treatment targets next to LDL-C levels in the presence of the hyper triglyceridemic waist [31,32,33].

Hypertension:

Hypertension [HT] is very common disorder particularly past middle age.it is no a disease in itself' important risk factor for cardiovascular mortality and morbidity. The cut-off manometric reading between normotensive and hypertensive arbitrary. for practical purpose hypertensin could be that level of BP at or above which on term antihypertensive treatment will reduce the cardiovascular mortality. almost all HT management guidelines including NICE (2011) JNC (2014) WHO-ISH (2003), European Society of Hypertension (2007,2013) define the cut-off level to be 140 mm Hg systolic and 90 mm Hg diastolic. However, the JNC8 raised the defining level to 150/90 mm Hg for individuals above 60 years of age. Epidemiological studied conformed that higher the pressure (systolic or diastolic or both) greater is the risk of cardiovascular disease.

Majority of cases are of essential (primary)) hypertension, i.e., the cause is not known. sympathetic and renin angiotensin system (RAS) may or may not be overactive, but they contribute to the tone of blood vessel and c.o. in hypertensive drug interfere with these regulatory system at one level or the other antihypertensive drug by chronically lowering BP, may reset the barostat to function at a lower level of BP .[34] There is also evidence that insulin resistance and hyperinsulinemia lead to SNS activation, and, as a result, the kidneys increase sodium reabsorption, the heart increases cardiac output, and arteries respond with vasoconstriction resulting in hypertension.[35]

Blood pressure classification:

Category	Systolic (mmHg)	Diastolic (mmHg)
Optimal	<120	<80
Normal	120-129	80-84
Prehypertension	120-139	80-89
Stage 1 hypertension	140-159	90-99
Stage 2 hypertension	160-179	100-109

DIABETES MELLITUS

The hyperlipidaemia of type 2 diabetes is distinguished by high triglyceride levels and decreased high-density lipoprotein (HDL) cholesterol, changes notice many years before the onset of clinically relevant hyperglycaemia [36,37] Dyslipidaemia is one of the major modifiable risk factor for the development of type 2 diabetes mellitus (T2DM), atherosclerosis, stroke and cardiovascular diseases.[38] It is essential to rectify the commonly held misconception that triglyceride concentration is a poor mark of cardiovascular risk. There is a strong relationship between triglycerides and CHD in both type 1 and type 2 diabetes. increased serum triglycerides herald the development of type 2 diabetes mellitus, particularly when related

with other features of metabolic syndrome or CHD, and once diabetes has developed, they continue to predict CHD risk, often independently of other risk factors [39]

Dyslipidaemia is one of the important risk factors for vascular complications in diabetic patients. It increases free fatty acid flux secondary to insulin resistance and aggravated by increased inflammatory adipokine [40]

INSULIN RESISTANCE:

insulin-resistant individuals demonstrate an impaired glucose metabolism or tolerance by an abnormal response to a glucose challenge, an elevated fasting glucose levels and/or overt hyperglycaemia, or a reduction in insulin action after intravenous administration of insulin (euglycemic clamp technique) with decreased insulin-mediated glucose clearance and/or depletion in the suppression of endogenous glucose production. It is defined as a pathophysiological state in which a normal insulin concentration does not acceptably produce a normal insulin response in the peripheral target tissues such as adipose, muscle, and liver.

Under this condition, pancreatic beta cell secretes more insulin (i.e., hyperinsulinemia) to overcome the hyperglycaemia among insulin-resistant individuals. Although hyperinsulinemia may make up for insulin resistance to some biological actions of insulin, that is, maintenance of normoglycemia, however, it may cause an overexpression of insulin activity in some normally sensitive tissues. This accentuation of some insulin actions coupled with a resistance to other actions of insulin results in the clinical manifestations of Mets [41]

Insulin resistance-mediated enhance in circulating free fatty acids (FFAs) is trust to play a pivotal role in the pathogenesis of Mets. Insulin enhances glucose uptake in muscle and liver, and inhibits lipolysis and hepatic gluconeogenesis. Insulin resistance in adipose tissue impairs insulin-mediated inhibition of lipolysis, leading to an increase in circulating FFAs that further inhibit the antilipolytic effect of insulin.[42] FFAs serve as a substrate for the synthesis of TGs. FFAs also stabilize the production of apo B, the major lipoprotein of very low-density lipoprotein (VLDL) particles, resulting in a more VLDL production. Second, insulin normally degrades apo B through PI3K-dependent pathways, so an insulin resistance directly enhance VLDL production. Third, insulin controle the activity of lipoprotein lipase, the rate-limiting and vital mediator of VLDL clearance. Thus, hypertriglyceridemia in insulin resistance is the result of both an enhance in VLDL production and a decrease in VLDL clearance. VLDL is metabolized to remnant lipoproteins and small dense LDL, both of which can encourage an atheroma formation. The TGs in VLDL are transferred to HDL by the cholesterol ester transport protein (CETP) in exchange for cholesteryl esters, resulting in the TG-enriched HDL and cholesteryl esterenriched VLDL particles. Further, the TG-enriched HDL is a better substrate for hepatic lipase, so it is cleared rapidly from the circulation, leaving fewer HDL particles to participate in a reverse cholesterol transport from the vasculature. Thus, in the liver of insulin-resistant patients, FFA flux is high, TGs synthesis and storage are increased, and excess TG is secreted as VLDL [43] Leptin is an adipokine that regulate energy homeostasis conciliate by the hypothalamus and is known to stimulate the immune cells activating the Th1 pathway. Obesity increases leptin levels and higher leptin levels are directly correlated to increased cardiovascular risk. Adiponectin is

an anti-inflammatory and antiatherogenic adipokine and its effects counter those of leptin. Adiponectin has anti-atherogenic properties and it decreases both vascular reactivity and smooth muscle proliferation, and improves plaque stability.[44}

Treatment on hyperlipidaemic related disorder:

1.Life management - The clinical guidelines for obesity stress the need to reduce. bodyweight by using behavioural changes in order to reduce caloric (energy) intake and increase physical activity. The most effective long-term diet involves a modest limit of the energy intake, by some 500–1000 calories/day. An adequate goal is to achieve a 7–10% bodyweight reduction over a period of 6–12 months. The major lifestyle intervention has two main and fundamental aspects: (i) an adequate caloric (energy) intake; and (ii) achieve an increment in physical activity. A moderate decrease of the daily caloric intake will achieve a slow but progressive weight reduction (~500 g/week). For most patients, the weight reduction diets should provide at least 1000–1200 kcal/day for women and 1200–1500 kcal/day for men [45]. The effective and healthful methods for the long-term weight loss are decreased-energy diets, consisting of a modest 500 to 1000 calories/day reduction. Sustained dietary changes may require a referral to a registered dietician to help apply the suggestions and ensure an adequate micronutrient intake (e.g., calcium, iron, and folate) while reducing calories. In the SUN (Seguimiento University of Navarra) prospective cohort study.[46]

2.Physical monitoring - For high-risk patients (e.g., those with recent acute coronary syndromes or recent revascularization), physical activity should be carried out under the medical management. Clinicians should evaluate which type of activity is practicable for the patient, considering the barriers (e.g., arthritis and time constraints) that can prevent a successful increase in the physical activity. Accordingly, they should help patients in developing a physical activity plan based on the initial assessment. However, any type of physical activity should be inspired. Lifestyle activity should be enhanced slowly in intensity and duration (by 5 min/session/week), starting from a low-intensity exercise (3 metabolic equivalent) in sedentary subjects, to avoid excessive fatigue, muscle pain, strains, or injuries [47] Long term maintenance if weight loss is better and more easily achieved when regular physical exercise is included in the weight Loss regime. A sedentary lifestyle is believed to be a major component of the metabolic syndrome through multiple mechanisms, mainly the weight gain that increases arterial BP and worsens the metabolic profile causing hyperglycaemia, increased insulin resistance, and dyslipidaemia with increased triglycerides and LDL-C, and decreased HDL-C levels. Because of the relationship between a stationary lifestyle and the metabolic syndrome, the therapeutic regimen should include a regular physical exercise program. Regular physical exercise improves the metabolic risk factors and decreases the risk of all-cause mortality, as well as the development of many chronic disease conditions.

Periodic, moderate physical exercise is recommended, for ex ample, 4–5 weekly sessions of 30–60 minutes' duration. Physical exercise is a signal lifestyle component that reduces cardiovascular risk [48]

3. Behaviour treatment - The emphasis in behavioural change should cover the benefit of social support, stress management, the value of a regular exercise regimen, and a development in eating habits (e.g., setting goals, planning meals, reading labels, eating regular meals, reducing portion sizes, self-monitoring, and escaping eating binges). Originally, the treatment was completely based on the learning theory (behaviourism). The theory assumed that the behaviours causing obesity (excess eating and low exercising) are largely learnt and therefore could be modified or relearnt. The theory further assumed that the positive changes in eating and exercising can be attain by modifying the environmental cues (antecedents) and the reinforcements of these behaviours [49]

Conclusion:

Understanding the molecular mechanisms and regulation of lipoprotein metabolism may help in devising ways to limit lipoprotein production. Influencing the expression of transcription factors or miRNAs that are involved in lipid and lipoprotein metabolism, such as those regulating lipid synthesis and secretion, MTP and apoB production, or fatty acid oxidation, could serve as therapeutic targets for the prevention and treatment of lipoprotein overproduction in metabolic syndrome. Lifestyle management remains the initial mediation of choice for this population. Modern lifestyle management therapy combines specific recommendations on diet and exercise with behavioural strategies. Pharmacological treatment should be considered for those whose risk factors are not acceptably reduced with lifestyle changes.

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