3. HOW IS THE METABOLIC SYNDROME RELATED TO THE DYSLIPIDEMIA?

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1. Some historical aspects on the metabolic syndrome

The contemporary definition of the metabolic syndrome refers to a cluster of metabolic abnormalities related to a state of insulin resistance, which is often associated with a high-risk overweight/obesity phenotype. Because such cluster increases the risk of coronary heart disease (CHD) and type 2 diabetes, numerous consensus groups have attempted to provide recommendations to identify in clinical practice patients with these atherogenic/diabetogenic metabolic abnormalities. Although there has been an exponential proliferation of scientific papers and conferences on the metabolic syndrome, the concept of a cluster of abnormalities such as obesity, diabetes, dyslipidaemia and hypertension is not new and several physicians/investigators have contributed to the development of such concept through astute clinical observations or epidemiological/metabolic studies.

The observation that obesity, dyslipidemia, diabetes and hypertension occur simultaneously in many people was first made by Crepaldi in 1967. In the late 1970s this clustering of conditions was termed the metabolic syndrome by German researchers. Since then the syndrome is described under a number of guises as " Insulin resistance syndrome, Syndrome X, Plurimetabolic syndrome and the metabolic syndrome" The syndrome is a multi-component disease brought on by combination of lifestyle and environmental factors, with some populations exhibiting a genetic susceptibility for its development. The original terminology-the metabolic syndrome-remains the most appropriate, as it is well established and best describes the conditions that comprise it. The escalating prevalence of the syndrome has important health implications. Each component of the metabolic syndrome is an established cardiovascular disease risk factor, and the presence of multiple components confers greater risk than the sum of the risk associated with the individual ones. The NCEP ATP III criteria were used to estimate the prevalence of the metabolic syndrome. The incidence of individuals exhibiting the syndrome is rising dramatically, it is currently estimated that 47 million US residents have the metabolic syndrome increasing their risk for coronary heart disease and stroke threefold. The prevalence of the syndrome increased with age from 7 % at the age of 20-29 year old to 44 % in 60-69. However alarmingly, the prevalence is increasing amongst children and adolescents very fast.

3.2. Defining the metabolic syndrome: an urgent need for an universal definition

In order to reduce the confusion in the medical community, universal agreement on the definition and clinical tools to assess the metabolic syndrome would be very helpful and efforts for additional international consensus activities have been made. Recent meetings have contribute to emphasize the notion that even if insulin resistance is indeed at the core of the metabolic syndrome, abdominal obesity is by far the most prevalent form of the metabolic

syndrome. Therefore, to dissociate abdominal obesity/insulin resistance would be for the time being of little help. We should rather work on cut-off values proposed for the various clinical tools used to optimally discriminate for the presence of the metabolic syndrome in several population of the world.

3. The concept of the metabolic syndrome

It is now well accepted that obesity represents a heterogeneous condition from a metabolic standpoint. A preferential deposition of adipose tissue in the abdominal cavity has been associated with a cluster of atherogenic and diabetogenic metabolic complications characterizing the metabolic syndrome. For instance, many studies have reported that excess visceral adipose tissue accumulation is associated with elevated plasma triglyceride concentrations, marked reductions in plasma HDL-cholesterol levels and an increased proportion of small, dense LDL particles, despite normal LDLcholesterol. Furthermore, there is also solid evidence to suggest that among obese patients, the most severe disturbances in indices of plasma glucose-insulin homeostasis resulting from an insulin resistant state are observed in patients with a high accumulation of visceral adipose tissue. Finally, abdominal obesity has been associated with hypertension and with a pro-inflammatory and thrombotic state. It is important to keep in mind that presumably normal weight individuals may nevertheless be characterized by an excess of visceral adipose tissue and therefore at increased risk of metabolic complications. Thus, under those circumstances, such normal weight subjects characterized by an excess of visceral adipose tissue may also show the features of the metabolic syndrome.The concept of the metabolic syndrome viewed as precursor to the development of both type 2 diabetes and cardiovascular disease has progressively emerged with a formal recognition by the World Health Organization (WHO) in 1998 and the National Cholesterol Education Program Adult Treatment Panel III in 2001 (NCEP ATP III), which have recently proposed a formal definition of the metabolic syndrome.

Table 3.1. *Definitions of the metabolic syndrome according to World Health Organisation (WHO) and National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria.*

Risk factors	Defining level
NCEP ATP III definition: 3 or more of the following criteria	
Abdominal obesity	> 102 cm, Men
Waist circumference	> 88 cm, Women
Triglycerides	>=150 mg/dL
HDL-cholesterol	< 40 mg/dL, Men < 50 mg/dL, Women
Blood pressure	>=130/85 mm Hg
Fasting glucose	>=110 mg/dL
WHO definition Impaired fasting glucose or impaired glucose tolerance or diabetes plus 2 or more of:	
Waist-to-hip ratio	> 0.85 (women) or > 0.9 (men) and/or BMI >30 kg/m2
Triglycerides	>=150 mg/dL and/or HDL-cholesterol < 40 mg/dL
Blood pressure	>=140/90 mm Hg

Microalbuminuria	urinary albumin excretion rate >=20 µg/min or albumin/creatinine ratio >= 30 µg/min

The respective criteria proposed to define the metabolic syndrome are listed in Table 3.1. Both definitions include type 2 diabetes and impaired fasting glycaemia, as well as hypertriglyceridaemia and a low HDL-cholesterol concentration as component traits.The WHO definition included also the presence of impaired glucose tolerance determined with a glucose load test. There are also a few differences between these two definitions. The WHO criteria consider both central obesity (defined by the waist-to-hip ratio) and overall obesity (defined by the BMI) while the NCEP criteria consider only central obesity (defined by the waist circumference).Furthermore, blood pressure thresholds differ between the two criteria with a higher value in the WHO definition. In addition, elevated microalbuminuria is a component trait in the WHO definition while it is not considered for NCEP ATP III. These differences in the definition and proposed criteria for the definition of the metabolic syndrome show that some uncertainty persists in this area.

4. The "hypertriglyceridaemic waist" phenotype: review of evidence

The metabolic syndrome increases the risk of cardiovascular disease and type 2 diabetes. The simultaneous measurement and interpretation of waist circumference and triglyceride level, "the hypertriglyceridaemic waist", may be a simple tool to identify individuals at high risk.

The National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) has recognised the metabolic syndrome as a cluster of abnormalities increasing the risk of both cardiovascular disease (CVD) and type 2 diabetes. The NCEP-ATP III guidelines have also underlined the central role of abdominal obesity in the development of this syndrome. Nowadays, it is generally accepted that abdominal obesity is associated with numerous metabolic complications increasing the risk of type 2 diabetes and CVD .Results of the prospective Québec Cardiovascular Study have revealed that the presence of some features of metabolic syndrome found in viscerally obese men was predictive of a substantially increased risk of coronary heart disease (CHD). For instance, it has been shown in this study that men with the simultaneous presence of fasting hyperinsulinaemia, elevated apolipoprotein B levels, and an increased proportion of small LDL particles (a cluster that we have referred to as the atherogenic metabolic triad) were characterised by a 20-fold increase in the risk of developing CHD over the 5year follow-up period of the study, compared with men without this cluster of non-traditional risk markers.

In addition, the risk of CVD associated with the atherogenic metabolic triad remained significant even after adjustment for traditional risk factors such as LDL-cholesterol, triglyceride and HDL-cholesterol levels.Thus, waist circumference and fasting triglyceride levels were tested for their ability to identify high-risk men who might be carriers of the atherogenic metabolic triad (hyperinsulinaemia, elevated apolipoprotein B, and small LDL particles). In this regard, sensitivity and specificity analyses conducted in a sample of adult men (aged between 28 and 63 years) showed that a cut-off point of 90 cm for waist circumference combined with a cut-off point of 2.0 mmol/l for triglyceride levels provided the best indication

to identify men with these features of the metabolic syndrome. For instance, 84% of men with the hypertriglyceridaemic waist phenotype (waist circumference ≥90 cm and fasting triglyceride levels ≥2.0 mmol/l) were carriers of the atherogenic metabolic triad. Additional analyses also underlined the clinical importance of the hypertriglyceridaemic waist phenotype in the assessment of risk of coronary artery disease (CAD) and type 2 diabetes.

Indeed, in a sample of 287 men who underwent coronary angiographic procedures for symptoms of CAD, it was found that men with both elevated waist circumference (≥ 90 cm) and triglyceride levels (≥ 2.0 mmol/l) were characterised by a 3.6-fold increase in the risk of CAD compared with men without the hypertriglyceridaemic waist phenotype 4. Moreover, the prevalent odds ratio of being affected by diabetes was also markedly increased (12-fold increase) in men with simultaneous elevations in waist circumference and triglyceride levels. On the other hand, it has been suggested that the hypertriglyceridaemic waist phenotype (waist circumference ≥ 90 cm and fasting triglyceride levels ≥ 2.0 mmol/l) had a greater impact on CAD risk than the presence and/or absence of impaired fasting glucose.

5. The metabolic syndrome: role and importance of the lipid components

Individuals with the metabolic syndrome, particulary those with abdominal obesity, exhibit a highly atherogenic lipid profile which may account for their high risk of cardiovascular disease and premature death. The metabolic syndrome is characterised by the co-occurrence of obesity (especially central obesity), dyslipidaemia, hyperglycaemia, and hypertension.

The presence of the metabolic syndrome is of relevance to public health since it has been linked to an increased risk of both cardiovascular disease (CVD) and type 2 diabetes. In particular, recent evidence shows that the presence of metabolic syndrome is associated with an increased risk of coronary heart disease (CHD), myocardial infarction, and stroke in both sexes. This substantially higher risk of CV morbidity and mortality associated with the presence of metabolic syndrome appears independent of other significant, potentially confounding factors such as smoking, plasma LDL cholesterol levels or alcohol consumption.
Dyslipidaemia is an integral part of the metabolic syndrome since both definitions include hypertriglyceridaemia (defined as serum triglycerides >= 150 mg/dl) and a low HDL cholesterol concentration (defined as HDL-C < 40 mg/dl for men and <50 mg/dl for women by NCEP ATP III, or HDL-C < 35 mg/dl for men and < 40 mg/dl for women by WHO) as component traits. Individuals with the metabolic syndrome, particularly those with abdominal obesity, exhibit a highly atherogenic lipid profile, which may account for their high risk of CVD. Central fat accumulation and presence of insulin-resistance have both been associated with a cluster of dyslipidaemic features, i.e., elevated plasma triglyceride level, an increase in very-low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL), presence of small dense LDL particles, and a decrease in HDL-cholesterol. These abnormalities of lipoprotein metabolism are more likely to occur together than separately and constitute key component traits of the metabolic syndrome.

1. Hypertriglyceridaemia

Beyond the LDL-cholesterol level, the presence of elevated serum triglycerides substantially increases the risk of CVD. Recent prospective studies indicate that elevated triglycerides are an

independent risk factor in CHD. Hypertriglyceridaemia is associated with several atherogenic factors including increased concentrations of triglyceride-rich lipoproteins and the atherogenic lipoprotein phenotype consisting of small dense LDL particles, and low high- density lipoprotein (HDL) cholesterol. Factors contributing to hypertriglyceridaemia in the general population include obesity, overweight, physical inactivity, excess alcohol intake, high-carbohydrate diet, type 2 diabetes, and some other diseases (e.g. chronic renal failure, nephrotic syndrome), certain drugs (e.g. corticosteroids, estrogens, retinoids, higher doses of adrenergic blocking agents), and genetic disorders (familial combined hyperlipidaemia, familial hypertriglyceridaemia, and familialdysbetalipoproteinemia). In daily practice, elevated serum triglycerides are predominantly observed in persons with metabolic syndrome. Many previous studies indicate that hypertriglyceridaemia is strongly associated with all components of metabolic syndrome.

Patients with metabolic syndrome who have hypertriglyceridaemia most often exhibit elevated level of triglyceride-rich lipoproteins which are considered atherogenic. The latter are partially degraded VLDL, commonly called "remnant lipoproteins". In clinical practice, VLDL cholesterol is the most readily available measure of atherogenic remnant lipoproteins. Thus, VLDL cholesterol can be a target of cholesterol-lowering therapy. Recent guidelines identify the sum of LDL+IDL+VLDL cholesterol (termed "non-HDL cholesterol" [total cholesterol minus HDL cholesterol]) as a secondary target of therapy in persons with hypertriglyceridaemia.

2. Low HDL-cholesterol

Low levels of HDL-cholesterol are associated with increased risk of coronary artery disease (CAD). This relationship was observed irrespective of age, blood pressure level, obesity, total cholesterol or LDL-cholesterol levels. The term "isolated low HDL" has been used to describe the situation where total cholesterol or LDL-cholesterol are considered normal but HDL-cholesterol is low. Long-term follow-up of subjects with low HDL-C has demonstrated that their risk of developing CAD is similar to the risk for subjects with elevated total cholesterol or LDL-cholesterol. Low HDL-cholesterol is the strongest predictor of subsequent CV events in patients with angiographically proven CAD and levels of total cholesterol within the normal range. According to current guidelines, the presence of low HDL-cholesterol should be considered a major CV risk factor, which modifies the goal for LDL-lowering therapy and is used as a risk factor to estimate the 10-year risk for CHD. A low HDL-cholesterol level has several causes, some of which are associated with insulin resistance, i.e. elevated triglycerides, overweight and obesity, physical inactivity, and type 2 diabetes. The combination of a low HDL-C with elevated plasma triglyceride level has therefore been considered an insulin-resistant state. It should be noted that certain drugs also reduce the level of HDL-C (e.g. beta-blockers, anabolic steroids, progestational agents). Nevertheless, low HDL-cholesterol is an important component trait of metabolic syndrome and deserves close clinical attention and management since these patients are at high risk of CVD.

3. Total cholesterol/HDL-cholesterol ratio

The total cholesterol/HDL-cholesterol ratio is a well known predictor of CHD risk. We have recently shown that men characterised by the hypertriglyceridaemic waist phenotype had a substantially elevated total cholesterol/HDL-cholesterol ratio compared with those without this phenotype. In this study, only 3% of men with waist circumference < 90 cm and triglyceride

levels < 2.0 mmol/l had a total cholesterol/HDLcholesterol ratio of 6 or higher. However, almost 50% of subjects characterised by the hypertriglyceridaemic waist phenotype had a ratio above 6. Similar conclusions were reached in other study populations.

6. Lipid Risk factors

There are different risk factors for identifying individuals at risk of developing the metabolic syndrom, it is important to consider the patients case history and to conduct a physical examination as visceral obesity. Risk assessment include a list of biological parameters wherein lipids play an important role especially Tg and HDL-particles. The traditional factors associated with the syndrome are obesity, insulin resistance, hyperglycemia, dyslipaemia, hypertension and microalbuminia. Is the increase of the FFA flux due to excess of calories and sedentary lifestyle in favour of insulin resistance predominantly in muscles or stimulate the increased lipid flux trough all its metabolic pathways the oxidative stress, stimulating inflammation and disrupting insulin signalling.

Multivariate analysis revealed that dyslipidemia, insulin resistance and hypertension were significantly independent risk factors of coronary heart disease with dyslipidemia conferring the greatest risk. LDL levels are associated with increased CVD risk however the LDL particle distribution is more important and should be discussed in the metabolic syndrome. There are also data available where we can show the linear relationship between circulating LDL-ox and the metabolic syndrome. However the HDL-C is inversely related to CVD risk, and long-term follow-up of patients provided the protective effect of HDL-C, determining CVD outcomes. The low HDL-C levels in the metabolic syndrome is a missing link to CV-events. Special attentions should be given to low LDL versus low HDL.

7. Experts opinion

The metabolic syndrome: is it an important medical issue in your opinion (and specialty)? Why?
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For many years, it has been recognised that several risk factors for cardiovascular disease cluster together. These factors are low HDL-cholesterol and high triglyceride concentrations, overweight, hyperglycaemia, and high blood pressure.

The metabolic syndrome is now accepted as the term to define this condition. The key concept is that these risk factors combine to increase cardiovascular disease, even when they are just slightly abnormal. This is why the definition of the metabolic syndrome sets cut-off points for these risk factors that include a large portion of the population.

For example, in the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) definition, the cut-off point for high triglycerides is > 150 mg/dL (approximately 1.7 mmol/L), which is about the average for the population over age 50 years. The cut-off point for low HDL-cholesterol is < 40 mg/dL (1 mmol/L) for men and < 50 mg/dL (1.3 mmol/L) for women, which includes about 35% of the population. Thus, the definition of metabolic syndrome recognises that these lipids continuously increase risk throughout their

ranges in the population. Even mild abnormalities in triglyceride and HDL levels, when coexisting with other risk factors of the metabolic syndrome, become an important indicator of high risk.

It is very important to recognise that high LDL or high total cholesterol are not components of the metabolic syndrome. In fact, LDL is often below average in patients with the metabolic syndrome. Thus, physicians must be aware that patients can still have a high risk of cardiovascular disease even if they have low LDL or total cholesterol. In essence, one can conceptualise the metabolic syndrome as a "non-LDL" type of risk, and just as important as LDL to recognise and to treat.

The incidence of the metabolic syndrome has been increasing throughout Europe and North America, in parallel with an increase in overweight, obesity, and diabetes. Since LDL has been emphasised in treatment guidelines quite effectively, it is now time to turn the attention of clinicians to the metabolic syndrome. If this epidemic of overweight and diabetes is not stopped,cardiovascular disease will increase, and we will lose the progress we have made in the past 20 years.

The metabolic syndrome requires a multi-factorial approach to treatment, since all of its components combine to increase the risk of cardiovascular disease. Firstly, diet and exercise will improve all components by lowering triglycerides, glucose and blood pressure, and raising HDL. In fact, much of the metabolic syndrome can be attributed to "over nutrition". Secondly, pharmacological therapy for improving the components of the metabolic syndrome should be individualized in each patient.

8. Treatment of dyslipidemia in metabolic syndrome

Treatment of the dyslipidemia of metabolic syndrome should involve no pharmacologic interventions, including weight loss, exercise, and a low-fat diet. Reducing LDL-C levels with use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors ("statins") is also appropriate for patients with metabolic syndrome. The ATP III guidelines recommend that LDL-C be the primary target of lipid-lowering therapy when a patient's triglyceride level is below 500 mg/dL (5.65 mmol/L).

Metabolic syndrome can be considered a coronary artery disease (CAD) equivalent. Thus, it is appropriate to have target LDL-C levels that are below 100 mg/dL (2.59 mmol/L). Achieving this goal usually requires addition of a cholesterol-lowering agent, such as a statin. However, for many patients, statin therapy does not correct abnormalities of triglyceride and HDL-C concentrations.

Modifying triglyceride and HDL-C levels with drug therapy improves cardiovascular risk beyond the benefits achieved with statins alone. The Coronary Drug Project and the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VAHIT) used drug interventions (niacin and gemfibrozil) designed to modify triglyceride and HDL-C levels, and these interventions were associated with a reduction in cardiovascular events in both studies. Caution should be exercised when using both a fibric acid derivative and a statin, because the risk of myositis is increased with combination therapy. In addition, creatine kinase levels

should be monitored if symptoms such as myalgia develop, especially in the setting of combination therapy.

9. Conclusion

Metabolic syndrome represents a clustering of cardiovascular risk factors linked through their association with insulin resistance. Since insulin resistance is an independent risk factor for cardiovascular disease, its presence can lead to macro vascular complications long before other features of metabolic syndrome are evident.

Challenges remaining in the identification of high-risk persons include the introduction of clinical markers of insulin resistance, integration of post challenge glucose and lipid concentrations, and better definition of the role of inflammatory, prothrombotic, and genetic factors. Improved understanding of the risk factors for metabolic syndrome is required, and clinical trials of therapeutic interventions specifically targeted to this syndrome need to be conducted.

Recommended literature:

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