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REVIEW

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The insulin resistance/metabolic syndrome is characterised by the variable coexistence of hyperinsulinaemia, obesity, dyslipidaemia, and hypertension. The pathogenesis of the syndrome has multiple origins, but obesity and sedentary lifestyle coupled with diet and still largely unknown genetic factors clearly interact to produce the syndrome. Dyslipidaemia, the hallmark of the metabolic syndrome, includes increased flux of free fatty acids, raised triglycerides, apolipoprotein B, and small dense low density lipoprotein, and decreased high density lipoprotein cholesterol. The widely prevalent nature of the metabolic syndrome emphasises the importance of its diagnosis and treatment. This review analyses the clinical and dynamic features of this syndrome in the aspect of dyslipidaemia and its management.

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The insulin resistance/metabolic syndrome (MetS) is characterised by the variable co-existence of hyperinsulinaemia, obesity, dyslipidaemia, and hypertension.[1 2] Other features of the syndrome include the proinflammatory states, microalbuminuria, and hypercoagulability.[3–5] Despite abundant research and clinical application of the MetS, the various cut offs for its components have varied widely. The pathogenesis of the syndrome has multiple origins. Obesity and sedentary lifestyle coupled with diet as well as still largely unknown genetic factors clearly interact to produce the syndrome.[6] In 1988, Reaven introduced the term syndrome X, with insulin resistance as a common denominator for the syndrome.[7] In addition to syndrome X, several other synonyms have been proposed such as deadly quartet, DROP syndrome (dyslipidaemia, insulin resistance, obesity, and high blood pressure), multiple metabolic syndrome, and insulin resistance syndrome.[1 2 8] To aid in the research and clinical application of the MetS, the World Health Organisation consultations for the classification of diabetes and its complications and the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III expert panel have published definitions.[9 10] The latter is the most widely used. Table 1 summarises the MetS definitions of both the WHO and NCEP ATP III. Additionally, the NCEP ATP III guidelines define the MetS as a new secondary target for cardiovascular risk reduction therapy, recommending both lifestyle modification and treatment of individual risk factors.

PREVALENCE

Using the WHO definition and data from the national health and nutrition examination survey III (NHANES III) and the NCEP ATP III criteria, the age adjusted prevalence of the MetS in the USA is currently estimated at 24% and increases to 44% in adults who are over 60 years.[9–11] The prevalence of two or more MetS components is 43.9%, showing that a large group is at risk for its development. Based on the data from the 2000 US census, an estimated 47 million US residents have the MetS.[11] There is a 3.2 relative risk of acute coronary events in subjects with characteristics of the MetS (body mass index $\geq$25.0 kg/m^2 and waist to hip ratio $\geq$0.91).[12] In the women's angiographic vitamin and oestrogen trial the prevalence of the MetS was 60% and clinical cardiovascular events were significantly more frequent compared with those without MetS.[13] However, going throughout the studies recently published the prevalence of the MetS varies from 7% to 84%.[14 15] The criteria involved in the MetS, especially type 2 diabetes mellitus, as well as other parameters such as age, sex, study's populations, and ethnic differences may explain these differences. For example, the prevalence of the MetS among American adults seems to be the highest in Mexican American women (33%) and the lowest in white American women (21%).[16] The prevalence of coronary heart disease or cardiovascular disease also varies. These variations suggest that some people have a genetic predisposition that leaves them more susceptible to the development of the metabolic disturbances produced by the Western lifestyle. An example of this can be found in the Pima Indians. The group that moved to Arizona 700–1000 years ago and progressively adopted a Western diet, by the age of 35 developed obesity in >85% and diabetes in >50% in contrast with the group who still lives in Mexico and is characterised by a traditional lifestyle, where obesity and diabetes do not seem to be an important health problem.[17]

The MetS is a multifactorial complex trait that is influenced by both environmental and genetic factors. Mutations and polymorphisms in the genes associated with insulin resistance, adipocyte abnormality, hypertension, lipid abnormalities may underlie the aetiological basis of the MetS. Table 2 lists some of the genes associated with the MetS. The diagnosis of the MetS seems

Abbreviations: MetS, metabolic syndrome; LDL, low density lipoprotein; HDL, high density lipoprotein; VLDL, very low density lipoprotein; apo, apoliprotein; TG, triglyceride

Table 1 Metabolic syndrome criteria defined by the WHO and NCEP ATP III

WHO[9]	ATP III[10]
One of the following Insulin resistance HOMA-IR ⩾ 2.5 Impaired glucose tolerance 2 hour OGTT 8–11 mmol/l Type 2 diabetes mellitus Fasting glucose ⩾7 mmol/l or 2 hour OGTT ⩾11 mmol/l Plus at least two of the following Blood pressure ⩾140/9 mm Hg BMI ⩾30 kg/m^2 or Waist to hip ratio Men >0.90 Women >0.85 Fasting triglycerides ⩾1.7 mmol/l and/or Low serum HDL concentration Men <0.9 mmol/l Women <1 mmol/l Albumin creatinine ratio Men >2.5 mg/mmol Women >3.5 mg/mmol	At least three of the following Waist circumference Men >102 cm Women >88 cm Fasting triglycerides ⩾1.7 mmol/l HDL cholesterol Men <1 mmol/l Women <1.3 mmol/l Blood pressure ⩾130/85 mm Hg Fasting glucose ⩾6.1 mmol/l

HOMA, homoeostasis model assessment; OGGT, oral glucose tolerance test; BMI, body mass index. HOMA-IR, fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5.

to identify substantial additional cardiovascular risk above and beyond the individual risk factors. Therefore, the clinical diagnosis of the MetS may be a valuable tool for identification of the elusive high risk patients.

DYSLIPIDAEMIA IN THE MetS

Dyslipidaemia, the hallmark of the MetS, is summarised as (a) increased flux of free fatty acids, (b) raised TG values, (c) low high density lipoprotein (HDL) cholesterol values, (d) increased small, dense low density lipoprotein (LDL) values, and (e) raised apolipoprotein (apo) B values (table 3).[31] Dyslipidaemia is widely established as an independent risk factor for cardiovascular disease.[32] Low HDL cholesterol and hypertriglyceridaemia have been found to be independently and significantly related to myocardial infarction/stroke in patients with MetS.[33] Additionally, a combination of high fasting glucose and low HDL cholesterol were shown to have primary predictive ability for coronary heart disease.[34] Moreover, in the study of Sacco and colleagues, the role of HDL cholesterol values, as an important modifiable stroke risk factor, was further supported.[35] The dyslipidaemia in MetS patients may be caused by a combination of overproduction of very low density lipoprotein (VLDL) apo B-100, decreased catabolism of apo B containing particles, and increased catabolism of HDL-apo A-I particles. These abnormalities may be the consequence of a global metabolic

Table 2 Genes associated with the metabolic syndrome

MetS characteristics	Genes
Abdominal obesity	Leptin,[18] POMC,[18] PC1,[18] melanocortin receptor 4,[18] leptin receptor,[18] adiponectin,[19] PPARγ2,[20] TNFα[20]
Hypertriglyceridaemia	UCP1,[20] LPL,[20 21] β_2 and β_3 adrenergic receptor.[20] FATP1,[20] apo CIII,[22] apo AV,[22] CETP[23]
Low HDL cholesterol	LPL,[21] apo AV,[24] SR-BI,[25] ABCA1,[26] CETP[27]
Hypertension	AGT,[28] UCP2,[29] ACE,[30] α-adducin,[30] aldosterone synthase[30]
Impaired fasting glucose	Adiponectin,[19 20] TNFα[20]

POMC, pro-opiomelanocortine; PC1, prohormone convertase 1; PPARγ2, peroxisome proliferators activated receptor γ2; TNFα, tumour necrosis factor α; UCP1, uncoupling protein 1; LPL, lipoprotein lipase; FATP1, fatty acid transport protein 1; apo, apolipoprotein; CETP, cholesteryl ester transfer protein; SR-BI, scavenger receptor class B type I; ABCA1, ATP binding cassette A1 transporter; AGT, angiotensinogen; UCP2, uncoupling protein 2; ACE, angiotensin converting enzyme.

effect of insulin resistance. Although the underlying mechanisms for this pattern are not fully understood, a cascade of events has been proposed for the observed phenotype, which ties in with all of the abnormalities present in these disorders.

Increased free fatty acids

The primary defect is probably focused in the inability to incorporate the free fatty acids to TGs by the adipose tissue (inadequate esterification).[31] This results in reduced fatty acid trapping and consequent retention by the adipose tissue. The insulin resistance also causes reduced retention of free fatty acids by the adipocytes. Both these abnormalities lead to increased flux of free fatty acids back to the liver (fig 1). However, some studies have shown that hepatic fatty acid metabolism is required for the development of insulin resistance.[8]

Adipose tissue, for a long time, was regarded as a comparatively passive side of energy storage (accumulated in the form of TGs). However, recent studies show that adipose tissue is an endocrine organ producing various proteins (adipocytokines).[36] Adipocytokines include leptin, angiotensinogen, tumour necrosis factor α, interleukin 6, plasminogen activator-inhibitor 1, transforming growth factor β, adipsin, adiponectin, resistin. These proteins are increased (with the exception of adiponectin, which decreases) in obesity and, at least under experimental settings, possibly can induce obesity related insulin resistance or diabetes.[37 38] Additionally, adipose tissue is a prominent source of cholesteryl ester transfer protein.[39] 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.[40] In obese subjects, cholesteryl ester transfer protein activity and mass are increased.[41]

Table 3 Fasting abnormalities in lipid, lipoprotein, apolipoprotein values, and in enzymes or proteins involved in the metabolic syndrome

Lipids	Lipoproteins	Apolipoprotein	Enzymes, proteins
Increased FFA	Increased VLDL	Increased apo B-100 and apo B-48	Decreased L
Increased TGs	Increased small dense LDL Decreased HDL	Decreased apo A	Increased HL Increased CETP

FFA, free fatty acid; TG, triglyceride; VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; apo, apolipoprotein; LPL, lipoprotein lipase; HL, hepatic lipase; CETP, cholesteryl ester transfer protein.

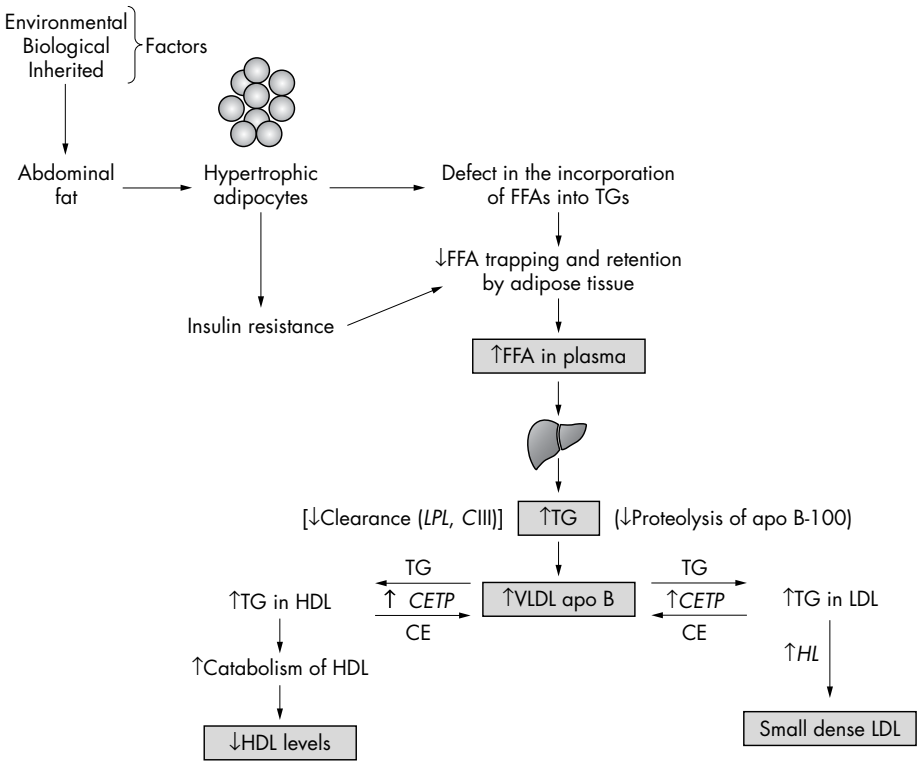

Figure 1 Schematic representation of dyslipidaemia of metabolic syndrome. FFA, free fatty acid; TG, triglyceride; LPL, lipoprotein lipase; CIII, apolipoprotein CIII; apo, apolipoprotein; HDL, high density lipoprotein; CETP, cholesteryl ester transfer protein; CE, cholesteryl ester; VLDL, very low density lipoprotein; LDL, low density lipoprotein; HL, hepatic lipase.

Increased TGs

Increased flux of free fatty acids from the periphery to the liver in the insulin resistant state stimulates hepatic TG synthesis, which in turn promotes the assembly and secretion of TG containing VLDL,[42] as well as the apo B production in the liver.[31 43] Under normolipidaemic 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 ($VLDL_2$).[44] While insulin suppresses the formation of large VLDL particles, $VLDL_1$ does not have any impact on the production of the smaller $VLDL_2$ fraction.[45] When insulin resistance occurs, the high insulin values make the liver resistant to the inhibitory effects of insulin on VLDL secretion.[46]

Visceral obesity and increased intra-abdominal fat have been shown to precede development of insulin resistance.[47] Increasing insulin resistance is proposed to be the precursor for two events. Firstly, in the presence of insulin resistance, the visceral adipocyte is more sensitive to the metabolic effects of the lipolytic hormones glucocorticoids and catecholamines.[48] This hormonal lipolytic activity produces an increased release of free fatty acids into the portal system, which serves as hepatic substrate to assemble TGs and TG rich VLDLs. Secondly, increasing insulin resistance leads to increased production of apo B, the major protein of LDL, and as a consequence to the increased synthesis and secretion of TG containing VLDL cholesterol particles.[49] Experiments in cell cultures suggest that VLDL assembly is complex and entails a two step process.[45] Firstly, a small lipoprotein particle containing little TG is formed in the rough endoplasmic reticulum, and secondly, the bulk of the TG core is added to this at the junction of the rough and smooth endoplasmic reticulum. It is possible that the release of small VLDL follows the addition of a comparatively small quantity of TG (or of cholesteryl ester) to the nascent particle while large VLDL is formed by the addition of a substantial TG core in a second quantum step. In subjects with a low circulating concentration of TG, the liver has insufficient TG to assemble a $VLDL_2$ sized particle and intermediate density lipoprotein/LDL are secreted. The substantial decrease in clearance rates of both $VLDL_1$ and $VLDL_2$ appears as plasma TG rises leading to accumulation of large VLDL particles.[50] This fall off of 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 apoCII/CIII ratio (modulators of lipoprotein lipase activity) in VLDL.[51]

However, studies in animals and humans are needed in which the impact of hepatic TG synthesis on VLDL TG production is carefully assessed. It is probable that the causes of raised TG values in the MetS are multifactorial and not simply a function of increased free fatty acid flux to the liver.

Small dense LDL

In the insulin resistant state, the LDL levels are usually within normal limits or only mildly raised; however the LDL particle is often of abnormal composition (small, dense LDL). The underlying abnormality causing small dense LDL is hypertriglyceridaemia. It has been found that small dense LDL is not seen until plasma TG levels exceed 1.5 mmol/l.[52] Under these conditions, large TG rich VLDL ($VLDL_1$) molecules accumulate. When $VLDL_1$ is lipolysed by lipoprotein lipase, a population of LDL particles with changed apo B conformation is produced. These particles fail to bind efficiently to LDL receptors and so have a prolonged residence time in the circulation. By the action of cholesteryl ester transfer protein, cholesteryl esters are replaced by TG in LDL and HDL particles (fig 1). TG rich LDL is a good substrate for hepatic lipase that finally generates small dense LDL, which is associated with increased cardiovascular risk.[52 53] 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.[54] The heterogeneity of LDL is based on the variable content of the cholesteryl ester molecules in the core of LDL, while the absolute amount of apo B on the surface of LDL may remain unchanged.[49] As a result, the LDL particles are not only small and dense but also comparatively enriched in apo B molecule compared with normal LDL. In the increased TG state, small dense LDL with hyperapolipoprotein B is more likely to be formed.[49] In the Johns Hopkins coronary artery disease study, higher apo B levels predicted coronary heart disease better than did LDL cholesterol.[55] Hyperapobetalipoproteinaemia was the most prevalent lipoprotein phenotype in the Johns Hopkins coronary artery disease study population and was found in about 33% of patients with premature coronary heart disease.[56]

Low HDL cholesterol

Low HDL cholesterol in patients with the MetS is often considered as secondary to raised TG.[1] In the presence of increased plasma TG levels, the cholesteryl ester transfer protein mediates TG-cholesteryl ester exchange between LDL and VLDL, as already mentioned above. Similar lipid exchange is taking place between VLDL and HDL particles, forming TG rich HDL (fig 1). These TG rich but cholesterol depleted HDLs are more prone to be catabolised. They undergo hydrolysis of their TG component and dissociation of their protein component, apo A (the main protein of HDL).[57] There are additional mechanisms that contribute to the low HDL cholesterol levels. One possibility is that changed lipid flux in the liver attributable to insulin resistance may reduce the hepatic production of apo A.[1] However, there are studies showing that the diameter of HDL is affected by insulin resistance (see section of familial combined hypercholesterolaemia). Alternatively, the insulin resistance may cause the destabilisation of ATP binding cassette A1 transporter protein, a key molecule that mediates the transfer of cellular phospholipids and cholesterol to apo A for the formation of mature and functional HDL particles.[26] Mutations in the ATP binding cassette A1 transporter are associated with Tangier disease, which is characterised by extremely low HDL cholesterol levels.[58] In the absence of sufficient cholesterol efflux, apo A is rapidly cleared from the circulation by the kidneys. The consequence of that is low HDL cholesterol in plasma, whose pleiotropic (antioxidant, anti-inflammatory, and other) effects besides the reverse cholesterol transport, have been recently established.[31 59] Furthermore, the increase of HDL cholesterol levels with lipid lowering drugs has been shown to be beneficial.[60 61] Another possibility is that people with the MetS, even with normal fasting TG levels, have frequently abnormal postprandial responses to dietary fat.[62] This transient increase of TGs increases cholesteryl ester transfer protein mediated lipid exchange and formation of HDL particles, as described above.

Postprandial lipaemia

Under conditions of insulin resistance, the antilipolytic effect of insulin on adipose tissue is weak.[63] This can explain the raised free fatty acid levels seen postprandially. There is a progressive increase in plasma free fatty acid levels, which results in an eight hour plasma free fatty acid concentration that remains above fasting levels.[64] Additionally, insulin resistance has two potential effects on chylomicron remnant metabolism, the main lipoprotein formed postprandially. Firstly, it downregulates LDL receptor expression, and secondly, it increases hepatic cholesterol synthesis and VLDL secretion.[65 66] These effects increase competition between chylomicron and VLDL remnants for hepatic receptors, thereby impairing the uptake of chylomicron remnants by this pathway.[67] Another possible explanation is that the disturbances in TG postprandially may be related to the cholesterol homoeostasis. The hepatic cholesterol synthesis and intestinal cholesterol absorption are responsible for the cholesterol content in the liver. The increased intestinal cholesterol absorption reduces hepatic cholesterol synthesis and as a consequence the secretion of VLDL decreases and the LDL receptors are upregulated.[68] The upregulation of LDL receptors may increase the removal of both chylomicron and VLDL remnants. In the postprandial state of subjects with the MetS, the increased hepatic cholesterol synthesis and the decreased intestinal cholesterol absorption result in a non-decrease of the catabolism of TG remnants.[69] Studies have shown that abnormal postprandial lipaemia is found in patients with coronary heart disease, and other conditions related to an increased risk of cardiovascular disease.[69–71]

TYPE 2 DIABETES, FAMILIAL COMBINED HYPERLIPIDAEMIA, AND THE METS

Type 2 diabetes

The pathophysiology of the development of type 2 diabetes mellitus is complex, multifactorial, and develops over a protracted period of time. Resistance to the action of insulin arises first. It is believed that obesity leads to insulin resistance and increased circulating insulin concentrations over time.[47] Hyperglycaemia occurs later, as pancreatic insulin secretion eventually fails to provide sufficient insulin for the metabolic needs of the body. It seems that at some point a loss of control of blood glucose begins to emerge, resulting in dietary glucose intolerance. This ultimately results in type 2 diabetes.[72] It is known that obese people may develop different degrees of insulin resistance, and not all people develop glucose intolerance. The factors that make some people more likely to develop type 2 diabetes mellitus are not well understood at the present time. A strong family predisposition is known to exist. Type 2 diabetes mellitus has long been considered a disease of adults.[73] During the past 10 years, however, an increasing frequency in the occurrence of type 2 diabetes mellitus has been reported in adolescents.[74] The lipid and lipoprotein abnormalities seen in type 2 diabetes are similar to those found in the MetS, but more severe. The raised TG rich lipoproteins are attributable to increased availability of free fatty acids in the liver. Raised levels of free fatty acids produce lipotoxicity, which hampers the glucose induced insulin secretion and worsens the insulin resistance.[75] Furthermore, the increased TG causes the formation of small dense LDL particles and reduction of HDL cholesterol. Patients with diabetes mellitus have higher risk for cardiovascular events compared with those without diabetes mellitus. About 80% of deaths of patients with diabetes mellitus are caused by cardiovascular disease.[76] These data support the ATP III guidelines for treating patients with diabetes mellitus as aggressively as patients without diabetes mellitus but with myocardial infarction.[10]

Familial combined hyperlipidaemia

The metabolic abnormalities associated with the MetS are also present in patients with familial combined hyperlipidaemia. Familial combined hyperlipidaemia is characterised by a varied expression of hypertriglyceridaemia and hypercholesterolaemia.[77] It is a highly atherosgenic disorder affecting 1%–2% of the Western world and is found in up to 10% of patients with premature myocardial infarction. Familial combined hyperlipidaemia was originally described in families of myocardial infarction survivors by the presence of hypertriglyceridaemia, hypercholesterolaemia, or both in the affected family members as a monogenic disorder.[78] However, the inheritance of the familial combined hyperlipidaemia associated phenotype has been shown to be

complex. The three major lipoprotein abnormalities observed in the MetS (increased fasting and postprandial TG rich lipoproteins, decreased HDL, and a shift to small, dense LDL particles, proved to contribute to the pathogenesis of atherosclerosis) are probably the same in familial combined hyperlipidaemia. Insulin resistance is often seen in patients with familial combined hyperlipidaemia and is associated with impaired suppression of lipolysis by hormone sensitive lipase in adipocytes, producing an increased flux of free fatty acids to the hepatocyte, culminating in increased synthesis of VLDL. Insulin resistance, which also diminishes lipoprotein lipase activity, as mentioned before, would amplify the extent of hypertriglyceridaemia. Obesity is seen in patients with familial combined hyperlipidaemia, independently of insulin resistance, which would further contribute to hyperlipidaemia. Increased insulin concentrations are associated with the phenotype of smaller diameter HDL particles, but not with concentrations of apo A-I or apo A-II (main proteins of HDL particle). This suggests the existence of genes, which pleiotropically influence variation in both HDL and insulin levels, contributing to the clustering of proatherogenic traits in insulin resistance states.[79] In 2001, the third workshop on familial combined hyperlipidaemia redefined this syndrome.[80] Hypertriglyceridaemia and small dense LDL were characterised as the underlying metabolic defects. The hypertriglyceridaemia in familial combined hyperlipidaemia can be attributed to multiple factors. Many patients present a significant reduction of lipoprotein lipase, responsible for hydrolysis of TG in chylomicrons and VLDL and others an overproduction of apo B. This overproduction of apo B cannot be explained only by the MetS phenotype but probably specific genes are involved.[81] Additionally, patients with familial combined hyperlipidaemia also manifest increased plasma free fatty acids that accompany the delayed removal of postprandial lipoproteins.

MANAGEMENT OF DYSLIPIDAEMIA OF THE METS

There are several non-pharmacological as well as pharmacological interventions that may increase sensitivity of insulin and therefore improve lipoprotein abnormalities.

Lifestyle changes

Weight reduction, increased physical activity, and moderate alcohol intake are first line treatments to improve lipid abnormalities (effectively reduce plasma TG and LDL cholesterol, and raise HDL cholesterol) in the MetS. In visceral obesity, weight loss reduces VLDL-apoB secretion and reciprocally upregulates LDL-apoB catabolism, probably because of reduced visceral fat mass, increased insulin sensitivity, and decreased hepatic lipogenesis.[82] Although, even a 10% reduction of body weight can improve insulin sensitivity, it is generally desirable to reduce weight to the ideal level, achieving body mass index <25 kg/m^2. According to the amount of exercise, even the low levels of exercise (walking for 30–45 minutes three or more times a week) are useful in improving insulin sensitivity. The foundation for treatment of dyslipidaemia is dietary modification such as reduction of saturated fat, cholesterol, and overall caloric intake. Despite the general interest in the MetS, comparatively few studies have focused on the influence of insulin resistance on lipid and lipoprotein response to dietary intervention. Knopp *et al* found a decreased LDL cholesterol response to a low fat diet in subjects with markers of insulin resistance.[83] However, underlying mechanisms are still not very clear. The cholesterol absorption and synthesis represents two important, interrelated regulatory mechanisms in cholesterol homoeostasis, and both are affected by overall diet. Changes in one of the pathways may result in compensatory changes in the other, such as an increase in hepatic cholesterol synthesis seen during selective inhibition of cholesterol absorption.[84] Furthermore, inhibition of both these pathways by combination of cholesterol synthesis inhibitors (3-hydroxy-3 methyl glutaryl coenzyme A reductase inhibitors (statins), and the recently available cholesterol absorption blocker (ezetimibe), has proved synergistic in reducing LDL cholesterol levels.[84] Only a limited number of studies have evaluated a possible link between cholesterol absorption and insulin resistance in human.[85] During weight reduction, cholesterol absorption increased in parallel with improvements in glucose metabolism parameters, suggesting that low cholesterol absorption could be an additional feature of the MetS.[85] Recently, a relation between cholesterol absorption and body weight in patients with type 2 diabetes was reported but also in non-diabetic subjects, obesity was associated with reduced dietary cholesterol absorption, possibly because of an increased biliary cholesterol secretion. Furthermore, patients with the MetS had a low campesterol/cholesterol ratio, indicative of reduced cholesterol absorption.[86] This ratio was inversely correlated with plasma levels of TG, remnant cholesterol, and apo B48.

Another useful tool in reduction of serum TG levels is ω-3 fatty acids. High dose ω-3 fatty acids (6 to 12 g/day) provide 40% to 80% reductions in serum TG levels. The mechanism is unknown. Although dietary intake of 9 to 12 oz salmon per day can provide this benefit, it is more easily achieved by concentrated fish oil supplements.

Lipid changing drugs

Therapeutic improvements in lipid and lipoprotein profiles in MetS can be achieved by several mechanisms of action, including decreased secretion and increased catabolism of apo B, as well as increased secretion and decreased catabolism of apo A-I.

There is evidence supporting the use of three major groups of lipid changing drugs, namely nicotinic acid (niacin), fibric acid derivatives (fibrates), and statins for the treatment of MetS (table 4).

Niacin effectively treats each of the common lipid abnormalities found in the MetS, and much progress has recently been made in understanding its mechanisms of action. It is known to lower plasma cholesterol and TG levels, reducing VLDL and LDL cholesterol levels. Niacin is also effective in raising HDL cholesterol. Until recently, the mechanism of its action has not been fully elucidated. However, it was speculated that niacin reduces the production of free fatty acids by inhibition of lipolysis in adipose tissue, which results in a reduced availability of substrate for VLDL synthesis in the liver.[95] Lately, this speculation was confirmed by the identification of a G-protein coupled receptor that is highly expressed in adipose tissue and to which niacin is a high affinity ligand. The binding of niacin to its receptor activates a G-protein signal, which reduces cAMP concentrations and thus inhibits lipolysis. However, a ''rebound'' increase in free fatty acids has been described.[96] Karpe and Frayn suggest that the effect of niacin is on the down regulation of the activity of hormone sensitive lipase.[96] The lowering of free fatty acid concentration results to a TG reduction, which in turn leads to increased HDL-cholesterol.[96] Another potential mechanism by which niacin raises HDL-cholesterol levels is through the stimulation of the ATP binding cassette A1-mediated transfer of cholesterol.[97] It has also been suggested that niacin directly inhibits the synthesis of apo B containing lipoproteins in the liver.[95]

Fibrates are a class of hypolipidaemic drugs used to treat hypertriglyceridaemia and mixed hyperlipidaemia. Fibrates effectively lower plasma TG and increase HDL cholesterol levels. These drugs also reduce LDL cholesterol, particularly small dense LDL, which is associated with increased risk of

Table 4 Drug interventions in studies treating dyslipidaemia in the metabolic syndrome

Study (reference)	Number of patients with MetS* or T2DM†	Drug	Major CHD‡ or CVD§ event (%)
AFCAPS/TexCaps[87]	155†	lovastatin	44‡ reduction
LIPID[88]	1077†	pravastatin	19‡, 21%§ reduction
CARE[89]	586†	pravastatin	25‡ reduction
4S[90]	483†	simvastatin	42‡ reduction
	458*		19‡ reduction
HPS[91]	5963†	simvastatin	27‡ reduction
WOSCOPS[92]	1691*	pravastatin	26§ reduction
VA-HIT[93]	627†	Gemfibrozil (fibrate)	24§ reduction
CDP[94]	563*	niacin	24‡ reduction

T2DM, type 2 diabetes mellitus; CHD, coronary heart disease; CVD, cardiovascular disease; AFCAPS/TexCAPS, air force/Texas coronary atherosclerosis prevention study; LIPID, long term intervention with pravastatin in ischaemic disease; CARE, cholesterol and recurrent events; 4S, Scandinavian simvastatin survival study; HPS, heart prevention study; WOSCOPS, West of Scotland coronary prevention study; DAIS, diabetes atherosclerosis intervention study; VA-HIT, Veterans Affairs high-density lipoprotein cholesterol intervention trial; CDP, coronary drug project. *Corresponds to patients with MetS; †corresponds to patients with T2DM; ‡corresponds to patients with CHD; §corresponds to patients with CVD.

atherosclerosis. The TG lowering activity of fibrates has been attributed to both inhibition of hepatic fatty acid synthesis and increased catabolism of TG rich lipoproteins. This increase in VLDL catabolism results from up-regulation of lipoprotein lipase expression and increased lipoprotein lipase activity because of a reduction in serum apo C-III levels. The increase in HDL cholesterol seen with fibrates correlates with increased expression of apo A-I and apo A-II.[98] Several studies in animal models and cultured cells have established that the normolipidaemic effects of fibrates occur mainly through transcriptional modulation of target genes involved in fatty acid, TG, and cholesterol metabolism and also in lipoprotein formation and remodelling.[99] This fibrate mediated transcriptional regulation is caused by binding and activation of a specific nuclear receptor termed peroxisome proliferators activated receptor α.[99] Peroxisome proliferators activated receptor α is principally expressed in tissues exhibiting high rates of β oxidation such as liver, kidney, heart, and muscle.[100] Whereas, the role of fibrates in the regulation of plasma HDL cholesterol levels through changes in expression of plasma apo A-I, apo A-II, phospholipid transfer protein, lipoprotein lipase, and macrophage ATP binding cassette transporter A1 transporter has been studied extensively, much less is known about fibrate dependent regulation of scavenger receptor class B type I. Recently, Chinetti *et al* have shown that peroxisome proliferators activated receptor activation increased scavenger receptor class B type I protein levels in cultured human monocytes as well as in fully differentiated macrophages.[101] In addition, fenofibrate treatment increased scavenger receptor class B type I protein content in macrophages of atherosclerotic lesions in apo E knockout mice.[101] These findings suggest that fibrates might modulate HDL metabolism by increasing scavenger receptor class B type I expression in peripheral tissues.

Fibrates seem to be particularly effective in patients for whom a disturbance of the TG-HDL axis is the primary lipid disorder. Fibrates also seem to influence a number of emerging risk factors, including haemostatic and inflammatory markers and indicators of improved vascular wall biology, which may contribute to their cardioprotective effects.

Statins are commonly used to control blood lipid disorder. After its ingestion, the inactive lactone is hydrolysed in β-hydroxyl acid and inhibits the 3-hydroxy-3 methyl glutaryl coenzyme A reductase. The role of the regulatory enzyme 3-hydroxy-3 methyl glutaryl coenzyme A reductase essentially limits the mevalonate pathway through which cells synthesise cholesterol. Although the pharmacokinetics and the metabolic pathway of statins are complex, they basically reduce the synthesis of LDL cholesterol by the liver and other cells and increase its catabolism. Currently, the effect of statins on the HDL metabolism is being studied. HDL and apo AI promote the removal and transfer of cholesterol from artery walls back to the liver.[102] Statins have been shown to increase HDL cholesterol and apo AI. This increase may results from a decrease in the fractional catabolic rate of apo AI and/or increased production of apo AI through the action of its promoter, the peroxisome proliferators activated receptor. In addition, statins have non-lipid lowering pleiotropic effects such as an influence on thrombotic parameters, on inflammatory markers, and on the endothelium that are not discussed here.

Two additional potent drugs are peroxisome proliferators activated receptor γ agonists and cholesteryl ester transfer protein inhibitors. Peroxisome proliferators activated receptor γ is expressed at high levels in adipose tissue and it is activated by dietary fats, eicosanoids as well as by pharmacological drugs, such as glitazones. Glitazones exert a hypotriglyceridaemic action via peroxisome proliferators activated receptor γ mediated induction of lipoprotein lipase expression in adipose tissue.[100] Inhibition of cholesteryl ester transfer protein has been proposed as a strategy to raise HDL cholesterol levels. Cholesteryl ester transfer protein inhibitors

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such as JTT-705 and torcetrapid have been shown to increase plasma HDL levels in experimental animals, as well as in humans.[103 104] In addition, torcetrapid has been shown to reduce slightly LDL levels both when given as monotherapy or in combination with a statin.[103]

Combination treatment

Combination therapy for dyslipidaemia may have advantages over single drug therapy improving lipoprotein risk factors when monotherapy fails. Such combination therapy includes statin/fibrate, statin/niacin, and statin/fish oils. Although the treatment with statin/fibrate, statin/niacin have been reported to increase the risk of drug induced myopathy and rhabdomyolysis, such combination therapies are considered safe.[105 106] Low or intermediate doses of statins (10–40 mg/day) with fenofibrate (200 mg/day) or bezafibrate (400 mg/day) are considered effective and safe for the treatment of atherogenic dyslipidaemia.[107 108] It seems that the comparative safety of combined therapy may depend upon using low or moderate statin doses. In general, risk factors that predispose patients to myopathy caused by the above combinations include increased age, female sex, renal or liver disease, diabetes, hypothyroidism, debilitated status, surgery, trauma, excessive alcohol intake, heavy exercise, uncontrolled dose of niacin or fibrate and use of additional medications (cyclosporine, protease inhibitors, or drugs metabolised through cytochrome P450).[109 110] Patient education about warning signs of myopathy is of great importance.

Newer treatments, such as cholesterol absorption inhibitors, cholesteryl ester transfer protein antagonists, could also be used alone or in combination with other agents to optimise treatment.

Is treatment of MetS associated with reduced cardiovascular disease risk?

Because the MetS was defined relatively recently, part of the evidence that lipid changing drugs can reduce coronary vascular disease risk in the MetS comes from data of patients with type 2 diabetes mellitus, where the MetS is very common.[15] Subgroup analyses of patients with diabetes in primary and secondary prevention trials show that treatment with lipid changing drugs can reduce the coronary vascular disease risk (table 4).

CONCLUSIONS

The constellation of characteristics called the MetS is an important risk factor for premature cardiovascular disease. Dyslipidaemia, the major constituent of the MetS, is characterised as an increased free fatty acid, TG, small, dense LDL and apo B levels, and low HDL cholesterol levels. The widely prevalent nature of the MetS emphasises the importance of its diagnosis and treatment. Weight reduction, increased physical activity, and moderate alcohol intake are first line treatments to improve lipid abnormalities in the MetS. Three major groups of lipid changing drugs such as niacin, fibrates, and statins have provided evidence supporting their use for treatment of MetS. Subgroup analyses of patients with diabetes (where MetS is very common) or MetS in primary and secondary prevention trials show that treatment with lipid changing drugs can reduce the coronary vascular disease risk. Further prospective investigations in large trials are required to confirm these findings. However, the treatment of dyslipidaemia is only one component. The management of the MetS is a ''multi risk factor'' approach where, except for cardiovascular disease, diabetes mellitus should be prevented as well.

MULTIPLE CHOICE QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AT END OF REFERENCES)

1. Dyslipidaemia in the MetS is characterised by?

(A) Increased serum triglyceride levels
(B) Low serum HDL cholesterol level
(C) Small dense LDL cholesterol
(D) Raised cholesterol
(E) Raised free fatty acids

2. Adipose tissue produce adipocytokines such as:

(A) Leptin
(B) CETP
(C) Hepatic lipase
(D) Adiponectin
(E) TNFα

3. Small dense LDL have atherogenic properties such as:

(A) Increased LDL oxidation
(B) Increased arterial wall retention
(C) Increased LDL receptor clearance
(D) Prolonged resistance time in plasma
(E) Promotes endothelial dysfunction

4. Drugs changing lipids in MetS are:

(A) Statins
(B) Fibrates
(C) Nicotinic acid
(D) Cholestyramine
(E) ω-3 fatty acids

5. The definition of MetS is based on existence of:

(A) Insulin resistance/hypertriglyceridaemia/low HDL
(B) Insulin resistance/hypertriglyceridaemia/hypertension
(C) Obesity/hypertriglyceridaemia/low HDL
(D) Blood glucose ⩾6.1 mmol/l/low HDL/obesity
(E) Insulin resistance/hypertriglyceridaemia/high HDL

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ANSWERS

1. (A) T, (B) T, (C) T, (D) F, (E) T; 2. (A) T, (B) T, (C) F, (D) T, (E) T; 3. (A) T, (B) T, (C) F, (D) T, (E) T; 4. (A) T, (B) T, (C) T, (D) F, (E) T; 5. (A) T, (B) T, (C) T, (D) T, (E) F.