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COMMENTARY SECTION

Prognostic aspects of the metabolic syndrome

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Abstract: Is the "good life" syndrome taken seriously enough in medical underwriting?

We all know the insurance applicant with the typical signs of having lived the "good life" of Western industrialized countries: overweight with slightly elevated blood lipid levels, hypertension and, not uncommonly, slightly elevated liver function tests and hyperuricaemia. Though it bears witness to an overindulgent lifestyle, this constellation of findings is quite often accepted as normal. This article describes the "good life" syndrome as a clinical entity, discusses the significance of this syndrome for medical underwriting and identifies prognostic factors. It deals mainly with those stages of the condition in which neither diabetes mellitus nor coronary heart disease (CHD) has yet developed.

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Definition and epidemiological significance

As far back as 1968 the constellation of these typical findings was described by Mehnert — a leading European diabetes specialist — as "affluence syndrome" was not until the end of the 1980s, however, that attempts were made to analyze and explain this clinical picture — mostly in terms of pathophysiology — in a large number of medical publications. Even today, the terminology used to refer to the metabolic syndrome in the international literature shows a notable lack of uniformity. In addition to "affluence syndrome", a dozen or so other terms including "syndrome X", "Reaven syndrome", "hyperinsulin syndrome", "sympatho-adrenergic syndrome", "insulin resistance syndrome", and "deadly quartet" have been used to refer to the metabolic syndrome.

The syndrome is characterized by a multiplicity of metabolic disturbances and clinical manifestations though, here again, there are discrepancies in the international literature as to precisely what features form part of the condition. Certainly, insulin resistance must be regarded as the common denominator, as it plays a key role in the pathogenesis of the syndrome. The clinical picture includes obesity, impaired glucose tolerance or even type II diabetes mellitus, and hyper- or dyslipidaemia. There may also be hypertension, hyperuricaemia, fatty liver, cholelithiasis, and coagulation disturbances. A family history of type II diabetes mellitus and/or coronary heart disease is commonly present.

The fact that these findings tend to occur together is well known. Thus, for example, obese people are two to three times as likely to have hypertension, and twice as likely to have diabetes mellitus, as people of normal weight. [15] Up to 50% of non-insulin-dependent diabetics have hypertension,[25] up to 40% are hyperlipidaemic,[27] and up to 80% are obese.[16]

Exact figures on the prevalence of the metabolic syndrome in Western industrialized countries are, as yet, difficult to obtain because

of the absence of a precise definition of the condition. Nevertheless, conservative estimates suggest that some 10 to 25% of the population have some degree of metabolic syndrome.[30,31,34,44] Subgroup analysis reveals even higher figures. Thus, for example, up to 50% of hypertensive patients have "syndrome X". [43] In addition to this — if only assumed — high prevalence of the condition another important consideration, from the point of view of medical underwriting, is the prognostic fact that the population concerned has a high long-term risk of developing atherosclerotic vascular disease.[28,42]

Aetiology and pathogenesis

A large number of epidemiological studies indicate that the metabolic syndrome is, to a large extent, genetically determined.[13,17] Predisposition to the syndrome is certainly not determined by a single gene, but rather by a number of genes, though it has not yet been possible to identify the ones concerned. Nevertheless, indirect pointers are often available in the form of a positive family history for such manifestations of "affluence syndrome" as, type II diabetes mellitus and coronary heart disease.

It is also generally agreed that environmental factors play a crucial role in determining whether, and if so to what extent, a metabolic syndrome becomes manifest. Prominent among these are poor diet, smoking, alcohol consumption and physical inactivity; four factors that are typical of an affluent Western lifestyle.

Over the last few decades the composition of the average Western diet has undergone major changes. In addition to what was, in any case, a chronically positive energy balance as a result of excessive calorie intake, the proportion of the total calorie intake accounted for by carbohydrates has fallen from 70% to 45%. By contrast the proportion accounted for by animal fats has risen dramatically from 20% to almost 45%.[11] In association with the lack of physical exercise that has invariably accompanied these changes, especially in people in sedentary occupations, this high consumption of fat has led to overweight.

Certainly, it is not just changes in lifestyle that have led to the increasing frequency of the metabolic syndrome. Another reason may well lie in the far more comprehensive diagnostic options now available. Twenty years ago, for example, it was rather unusual for people to have their blood lipid levels determined, whereas nowadays a high proportion of the population are informed about the state of their "cholesterol".

The impact of the changes in lifestyle imposed by modern industrial society is seen with particular clarity in societies, such as the Polynesian, that have had to adapt in a very short space of time. When these people adopted Western-style dietary habits and less active lifestyles, it wasn't long before they developed disturbances of lipid metabolism, obesity, hypertension, insulin resistance and type II diabetes mellitus. In those who returned to their traditional way of life, all these metabolic parameters tended to return to normal, often within a few weeks.

In this context it is worth mentioning an interesting theory according to which the presence of a genetic predisposition to the metabolic syndrome in prehistoric times conferred an advantage in terms of natural selection. According to this theory, the anticatabolic effect of insulin results in more effective food utilization, which would give bearers of this genotype a decisive survival advantage during prolonged periods of hunger [33, 44]. Experiments with rats with and without insulin resistance lend evidence to the theory. When food was withdrawn the first to die were normal-weight rats, then overweight animals, and lastly rats with type II diabetes.

Insulin resistance

The core of the metabolic syndrome is peripheral insulin resistance. This means that peripheral tissue, in particular skeletal muscle, requires more insulin than normal tissue to

achieve a given insulin effect. First affected is muscle tissue, the principal site of utilization of glucose, while in later stages insulin resistance also develops in the liver. Insulin resistance occurs in patients not only with impaired glucose tolerance and type II diabetes, but also with obesity and essential hypertension, and even in individuals with reduced physical activity.[36,41]

The precise mechanism of insulin resistance is still unclear. A number of functional and morphological changes in skeletal muscle have been discussed, including changes in the composition of muscle fibres and muscle capillaries, reduced perfusion of muscle, and even some complex neuroendocrine disturbances. A reduction in the number of insulin receptors and in the intracellular effect of insulin, leads to insulin resistance and thus to compensatory hyperinsulinaemia. Increased levels of insulin lead to a variety of physiological changes, the most important of which are discussed in detail in the sections of this article dealing with the various clinical manifestations of the metabolic syndrome.

From the point of view of medical practice, however, there is as yet no cheap and practicable test for detecting insulin resistance.

Obesity

As long ago as 1959 the Metropolitan Life Insurance Company in America was able to demonstrate that overweight leads to extra mortality due to atherosclerotic diseases.

For a long time, however, the significance of overweight as an independent risk factor was disputed. Attempts were made to explain the extra mortality associated with overweight as being due to other coexistent risk factors. Subsequently, however, a number of studies — including the Framingham study, with its observation period of over 26 years — established that overweight is an independent risk factor for cardiovascular diseases. The extra mortality brought about by overweight was found to be due mostly to coronary heart disease, heart failure, sudden death and stroke.

In the early 1980s an increasing number of studies showed that the critical risk factor for vascular disease is not so much the mass of body fat, but rather the regional distribution of fat in the body.[3,45] In the android, or central, form of obesity the excess fat accumulates mostly on the trunk, in the subcutaneous tissue, and above all in the abdominal (visceral) region. It seems that, as a result of the development of voluminous fatty cells, abdominal obesity in particular leads to the release of large amounts of lipids into the blood.

The central form of obesity is probably genetically determined, though the development of this pattern of fat distribution is also favoured by excess calorie intake, physical inactivity, tobacco consumption and alcohol abuse.[2]

The other non-central (gynoid) form of obesity is the form in which fat tends to accumulate mostly in the hip and thigh regions. Though the prognostic significance of this form of obesity is disputed, it certainly does not appear to be metabolically neutral. A Canadian study recently published in the JAMA found is to be intermediate between normal weight and central obesity effects on metabolism and blood pressure.[19]

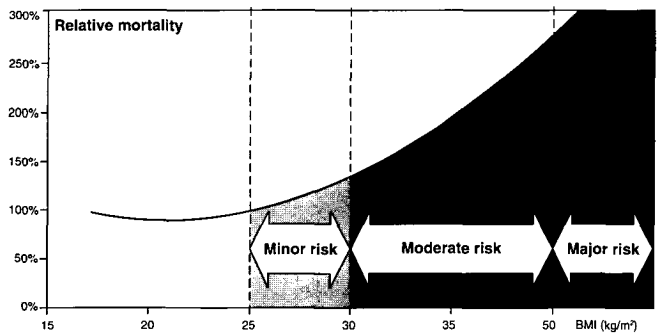
In addition to clinical inspection of the applicant, which is only rarely possible in everyday underwriting, there is a mathematical formula by means of which the two forms of obesity can be distinguished, namely the waist-to-hip ratio. The minimum possible waist circumference is divided the maximum circumference around the hips in a standing position. A ratio of over 1.0 in men or 0.85 in women is indicative of an abdominal (android), and thus prognostically more serious, obesity which is associated with a higher rate of diabetes, hypertriglyceridaemia, hypertension, elevated LDL-cholesterol levels and coronary heart disease. Measurement of abdominal circumference alone can serve as a rule of thumb in this respect, a circumference of over 100 cm being suggestive of the central, i.e.

android, form of obesity.[4]

It goes without saying that in addition to the distribution of body fat, it is the absolute degree of obesity that is decisive for the prognosis. In the international literature the prognostic risk is increasingly being quantified by means of the body mass index (BMI), obtained by dividing the body weight in kilograms by the square of the height. This index correlates very well with the vascular risk factors and must be ranked even above the waist-hip ratio in terms of prognostic significance.[19]

Of the many studies that have looked into the question of obesity, it might be appropriate to refer here to the "pooling project" of the 1960s, which considered a number of North American studies (including the Framingham study) together. This quite clearly demonstrated the dependency of mortality on body weight. It was found that mortality begins to rise from a BMI of 23 kg/m2 and becomes excessive from a BMI of 30 kg/m2 (see Fig. 1).[45]

Figure 1
Mortality as a Function of BMI
(Body Mass Index)



In summary, therefore, an optimal assessment of the risk factor overweight requires both the BMI and the waist-to-hip ratio, as between them they describe both the quantity and the quality of the obesity.

Hypertension

Essential hypertension is generally accompanied by insulin resistance.[5,32] This is usually much more pronounced in hypertensive patients with abdominal obesity than in those of normal weight. Whether the insulin resistance is responsible for the hypertension has yet to be established. Here is certainly a complex relationship between insulin and hypertension, and observations suggest a correlation between insulin level and the degree of hypertension.[48]

In terms of pathophysiology, the effect of insulin on blood pressure has been described as follows: an increased level of insulin results in increased sympathetic activity, increased reabsorption of sodium in the kidneys and muscular hypertrophy in vessel walls. Together with the resulting increase in peripheral vascular resistance, these three factors may be responsible for the development of hypertension.

On the other hand, there are also patients with hyperinsulinaemia who are not hypertensive. From this it can be concluded that in addition to insulin resistance, a further, possibly genetic, factor is required for the development of hypertension. Together with the degree of hypertension, another important prognostic criterion is the thickness of the myocardium of the left ventricle. Echocardiography shows left ventricular hypertrophy to be present in around 20% of patients with mild or moderate hypertension and the prevalence increases with age.[9,38] Here again, insulin resistance appears to play a specific role. A number of publications have found a positive correlation between insulin levels, or the degree of insulin resistance, on the one hand and the extent of left ventricular hypertrophy on the other hand, independent of any hypertension.[37,39]

The Framingham study showed hypertensive patients with left ventricular hypertrophy — in this case diagnosed only on the basis of an ECG — to have an eight-fold higher cardiovascular mortality (including coronary heart disease, sudden death and stroke) than a comparable group of hypertensive patients without ECG evidence of left ventricular hypertrophy. This study found cardiac hypertrophy to be a separate, prognostically unfavourable, risk factor that was independent of the other classical

risk factors (including hypertension!) [18,38]

To what extent myocardial hypertrophy favours the emergence of coronary heart disease is as yet unknown. It is known, however, that the degree of left ventricular hypertrophy correlates with the frequency of complex cardiac arrhythmias. It therefore seems possible that some of the extra mortality caused by cardiac hypertrophy may be brought about by sudden cardiac death.

Hyperlipidaemia

The changes in lipid patterns (dyslipidaemia) found in patients with the metabolic syndrome may likewise be explicable in terms of insulin resistance. The anticatabolic effect of hyperinsulinaemia reduces the burning rate of calories. This leads to an increase in the synthesis and deposition of fat and thus to an increase in triglyceride levels and body fat. In turn this further increases peripheral insulin resistance and thus has an additional unfavourable influence on metabolism.

Hypertriglyceridaemia is associated with a reduction in HDL-cholesterol, though the precise pathophysiological mechanism of this is unknown. There is evidence, however, of a reciprocal relationship between HDL concentration and insulin level. Depending on the remaining capacity of the LDL receptors, an increased triglyceride level can also lead to an increase in the level of LDL-cholesterol.[8,31]

Elevated triglyceride levels should not be ignored in underwriting, especially where a reduced HDL-cholesterol level is known to be present at the same time. The Framingham study showed the combination of increased triglycerides and reduced HDL-cholesterol to be associated with a markedly increased frequency of coronary heart disease. It is interesting to note in this context that over 50% of the study participants had a total cholesterol level of less than 250 mg%.[42]

Impaired glucose tolerance

Impaired glucose tolerance is diagnosed when blood glucose levels exceed certain limits after ingestion of a 100-g dose of glucose after three days on a high-carbohydrate diet. This condition, which is present in as many as 11% of US citizens aged between 20 and 74 years, is likewise characterized by insulin resistance and abnormally high insulin levels.[35]

Nevertheless, the diagnosis of impaired glucose tolerance must be viewed with caution, as the results of an oral glucose tolerance test are susceptible to a number of disturbing influences. For example, physical inactivity or a diet low in carbohydrates (how can this be checked?) prior to the test can produce misleading findings, as can failure to fast, fasting for too long, lack of sleep or performance of the test in the afternoon[12,29]. Even multiple glucose tolerance tests performed on the same subject under the same conditions often yield markedly different glucose values, hence abnormal glucose tolerance test results often cannot be replicated.

In the past, we have used terms such as latent, subclinical, or borderline diabetes; it was assumed that the condition was a precursor of diabetes mellitus. Numerous studies have shown, however, that not every case of impaired glucose tolerance evolves into diabetes mellitus. It may be assumed that within 10 years of the initial diagnosis of this metabolic disturbance some 20 to 30% of patients will have developed type II diabetes mellitus, 25% will still have the disturbance in unchanged form and 50% will have reverted to normal glucose tolerance.[35,46]

Possible risk indicators for subsequent development of diabetes include definitely pathological blood sugar levels (2-hour values of over 10.0 mmol/l, i.e. 180 mg/100 ml) in a glucose tolerance test, pronounced obesity, high fasting insulin levels and low insulin levels after a glucose load.[14] Thus, there appears to be a direct correlation between the degree of impairment of glucose tolerance (as indicated by blood sugar levels and the degree of insulin resistance) and the risk of subsequently devel-

oping of diabetes mellitus.

A number of studies have found patients with impaired glucose tolerance, but without manifest diabetes, to have both increased total mortality and increased coronary mortality, the respective figures lying between those of a normal (nondiabetic) population and those of manifest diabetics.[40]

Microalbuminuria

Microalbuminuria is defined as the occurrence of low-molecular-weight protein in urine in quantities of 30 to 300 mg/day in two out of three different samples. This finding is associated with increased morbidity and mortality from cardiovascular disease and in particular coronary heart disease. In diabetics it indicates incipient nephropathy. It is therefore of great prognostic significance. Some 20 to 25% of type II diabetics have microalbuminuria.[26]

Proteinuria is by no means confined to the late stages of diabetes, however, and in fact is not uncommonly found even in nondiabetics. The presence of microalbuminuria correlates with elevated blood pressure, elevated triglyceride and LDL-cholesterol levels, elevated blood sugar levels and overweight;[28] all of which form part of the metabolic syndrome. Thus, a study performed on overweight nondiabetics found microalbuminuria to be just as common in hypertensive as in normotensive subjects. The amount of albuminuria, however, was considerably greater in subjects with a family history of hypertension. Also, those study participants in whom microalbuminuria was demonstrated were considerably more overweight than those without.

Provided that other possible causes such as glomerular nephropathy and orthostatic proteinuria can be ruled out, the presence of microalbuminuria generally indicates a coexistent metabolic syndrome. A number of studies have shown that the presence of albuminuria in nondiabetics can be regarded as a possible indicator of subsequent development of diabetes.[10,28] In prognostic terms, therefore, the occurrence of microalbuminuria is associated with increased cardiovascular mortality both in diabetics and in nondiabetics.[10,20]

Atherosclerosis and the metabolic syndrome

As already pointed out, people with a metabolic syndrome are at high risk of developing atherosclerosis at an early age. This holds especially true of diabetics, a high percentage of whom already show definite atherosclerotic changes, particularly in the coronary arteries, at the time of diagnosis of their diabetes.[13] The overall incidence of macroangiopathic complications, in the form of peripheral arterial occlusive disease or strokes, is four to six times higher in diabetics than in nondiabetics, while the incidence of coronary heart disease is some three times as high as in nondiabetics of the same age.

Interestingly, the duration of diabetes does not in itself appear to have any decisive influence on the emergence of coronary heart disease.[40,47] Also, the influence of the quality of diabetic control on the extent of coronary macroangiopathy is disputed.[22] Hence, the factors that result in premature atherosclerosis in diabetics are the same factors that predispose to diabetes and promote the development of coronary heart disease and other atherosclerotic diseases.

To what extent insulin resistance and resulting hyperinsulinaemia are themselves responsible for increased incidence of coronary heart disease and other atherosclerotic diseases is still unclear. Therefore, the question as to whether insulin resistance is itself a "killer" or is merely an accompanying phenomenon cannot as yet be answered with certainty.

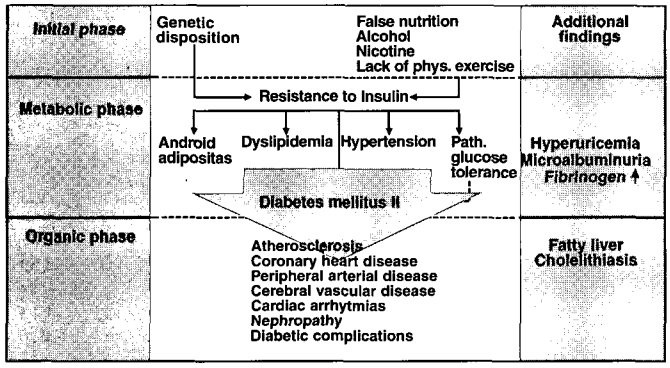
Elevated insulin levels and hyperglycaemia certainly have a number of deleterious effects on vessel walls that could explain the premature development of atherosclerosis. Thus, synthesis of connective tissue and smooth muscle cells is stimulated (leading to thickening of the vessel wall), blood coagulation is promoted and increased lipid synthesis favours the formation of lipid-containing plaques.

In many cases atherosclerosis remains clinically silent for decades despite the presence of a metabolic syndrome. Coronary heart disease, in particular, is apt to evolve in unpredictable bursts. Thus, in some coronary heart disease patients coronary sclerotic changes evolve rapidly within a few years, whereas in others severe changes including subtotal stenoses remain stagnant for years.

The crucial trigger for clinical manifestations such as myocardial infarction, unstable angina pectoris, transient ischaemic attacks, or strokes is the formation of thrombi. These cause an exponential further reduction in blood flow already reduced by stenoses, with corresponding results. Possible risk factors for clot formation are changes in the blood coagulation system that are likewise associated with the metabolic syndrome, such as increased fibrinogen level or increased platelet aggregability.[1,24]

In the light of the aspects considered here, therefore, type II diabetes mellitus can be seen to play a key role within the metabolic syndrome in that its clinical manifestations appear relatively late, in many cases at a time when the arterial system has already undergone irreversible atherosclerotic changes (see Fig. 2).

Figure 2
Metabolic Sundrome:
Clinical Manifestations and Damage to Organs



Other clinical manifestations

The remaining clinical features of the metabolic syndrome will be mentioned here briefly only for the sake of completeness, as they do not influence the risk for atherosclerosis.

Hyperuricaemia is often present in the metabolic syndrome. Possible mechanisms of this include increased purine synthesis associated with hyperinsulinaemia, and reduced renal excretion of uric acid.

Fatty liver is commonly associated with insulin resistance. The increased supply of free fatty acids leads via increased hepatic triglyceride synthesis to fat deposition in hepatocytes. Liver function tests are often completely normal, though depending on the degree of fatty infiltration of the liver and the integrity of the hepatocytes, gamma-GT and sometimes also GPT and GOT levels may be up to three times their normal levels.

The tendency to gallstones is explained via increased biliary secretion of cholesterol and a simultaneous reduction in bile acid synthesis. This shift in the ratio of cholesterol to bile acids leads to crystallization of cholesterol with formation of stones. The risk for gallstone formation is markedly increased especially during periods when the patient goes on a weight-reducing diet.

Treatment options

The varied clinical picture of the metabolic syndrome is reflected in the number of different treatment options available. A low-calorie, low-fat diet, antihyperlipidaemic drugs, antihypertensive drugs, increased physical activity, nonsmoking and reduction of alcohol consumption may all be indicated at the same time in patients with pronounced metabolic syndrome, though the likelihood of satisfactory patient compliance under such circumstances is questionable.

Crucial for the long-term success of therapy, however, and unlike the situation with most diseases, is compliance with nonpharmacological therapeutic measures. Increased and, above all, regular physical activity has a number of corrective effects on the various metabolic changes. It reduces insulin resistance,

overweight, and hypertriglyceridaemia, increases HDL-cholesterol, and gradually reduces the degree of hypertension. A simultaneous low-calorie diet significantly enhances the therapeutic effect. Use of these two non-pharmacological measures alone can result in the metabolic syndrome receding in up to 90% of cases.[45]

However, the most important factor for long-term therapeutic success, and thus also for the prognosis of this syndrome, is the seriousness and consistency with which the patient modifies his lifestyle. It goes without saying that none of us can return to the hunting and gathering lifestyle of our distant ancestors but the regular inclusion of at least three to four units of sport a week, each lasting at least 20 minutes, along with a balanced isocaloric diet, must be compatible even with our present-day lifestyle in industrialized countries. It cannot be denied, however, that the reality looks quite different to many patients.

As far as drug therapy is concerned, the choice of drugs for a patient with a metabolic syndrome must take account of the multiple metabolic changes in the organism. For example, certain antihypertensives (beta-blockers and thiazide diuretics) have a negative impact on insulin resistance, and the antihyperlipidaemic agent nicotinic acid can further impair glucose tolerance and increase uric acid levels. There is a risk, therefore, of treating one aspect of the metabolic syndrome at the expense of another.

Conclusions for medical underwriting

Given that the metabolic syndrome must be assumed to be present in a high proportion of the population, but that it is often not referred to as such in patients' medical files, the question arises as to how the presence of the syndrome can be identified.

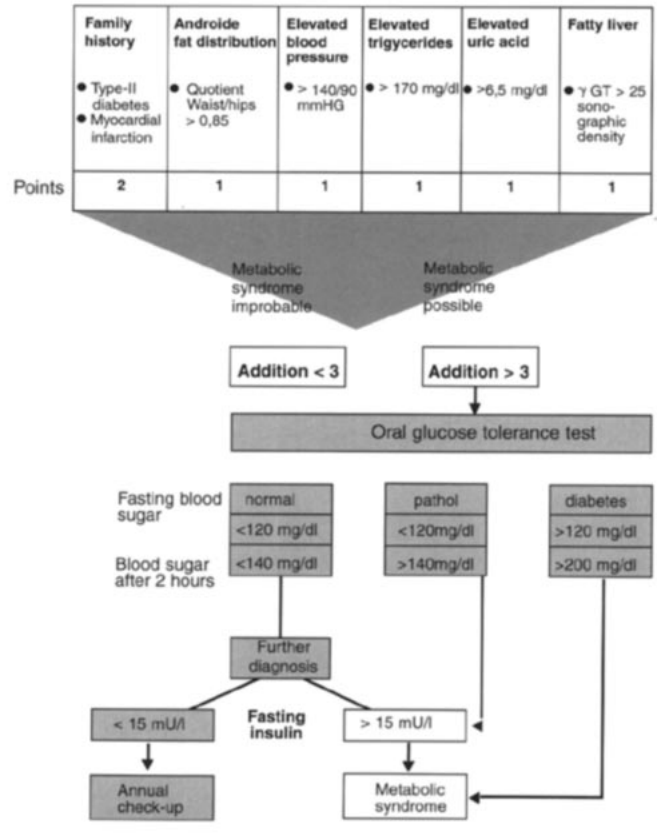
Direct determination of insulin concentration would seem an obvious step but must be ruled out on the basis of its cost and practical difficulty. Therefore, the suspicion of metabolic syndrome can be expressed only on the basis of the overall clinical picture in the individual applicant. In 1991 Rett proposed a scoring system (see Fig. 3) that appears to be usable both in clinical practice and - insofar as adequate information is available - for everyday practice in underwriting.[31] It must be emphasized, however, that not every metabolic syndrome is associated with overweight, nor does a normal glucose tolerance test exclude the possibility of metabolic syndrome.

Interestingly, most of the published articles on this syndrome have dealt only with pathophysiological aspects, whereas there have been very few studies on the natural history and prognosis of this impairment. By contrast, the studies dealing with the effects of the various risk factors have become enumerable.

For this reason we can only speculate on the natural history of this "affluence syn-

Figure 3

Metabolic Syndrome — Items to go by for the Diagnosis



drome". We know that a consistent change in lifestyle (exercise, diet) can cause the metabolic syndrome to resolve in a high proportion of cases. Such resolution does, however, assume that the metabolic changes, possibly accompanied by hypertension, have not already been present for many years, as in this case irreversible atherosclerotic damage is to be feared. Even where the metabolic syndrome has been present for only a relatively short time, however, there are good reasons to doubt whether the patient will succeed in keeping to his altered lifestyle in the medium and long term.

Underwriting the metabolic syndrome depends crucially on the question of whether, and if so to what extent, the extra mortality caused by the individual impairments (obesity, hypertension, hyperlipidaemia, abnormal glucose tolerance test, hyperuricaemia) can be regarded as additive.

A large number of studies have found the severity of the individual manifestations of the metabolic syndrome to be directly related to mortality. This is true of overweight — whether measured via the waist-to-hip ratio or via the body mass index[10,21,45] — both systolic and diastolic blood pressure,[23] triglyceride levels in the presence of a reduced HDL-cholesterol level[7,38] and to some extent also glucose levels in patients with an abnormal glucose tolerance test.[14]

From this it can be deduced that there is also a correlation between the amount of extra mortality and the severity of the metabolic syndrome. Is it then sufficient to add up the extra mortality of the individual impairments, or is the figure produced by simple addition too high, or is it perhaps necessary to apply an additional loading to account for potentiation of the overall risk?

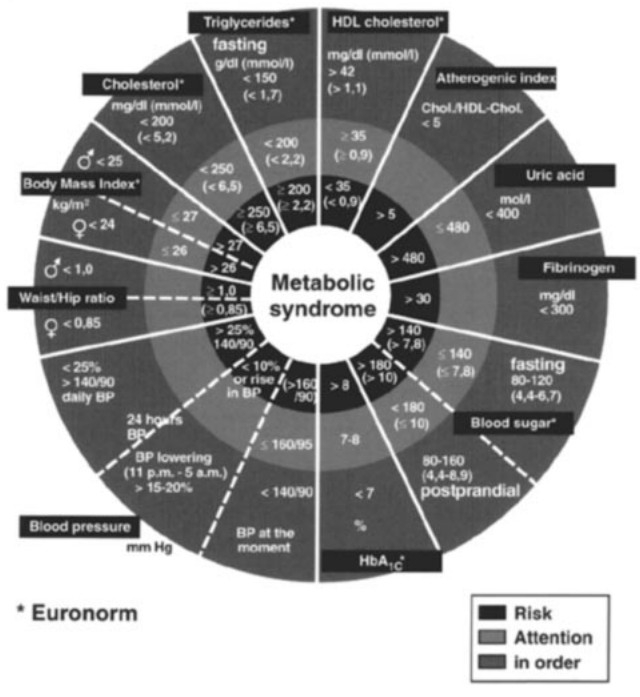
In view of the lack of mortality studies, the following underwriting approach to the metabolic syndrome can be regarded only as an initial approximation. This suggested procedure for risk assessment assumes that no manifest coronary heart disease is present.

A retrospective examination of Munich Re's own portfolio has shown that the results of the procedure outlined below are largely in line with the steps taken by Munich Re company to date when rating metabolic syndrome risks.

1. It is important to know how many individual features are present in the applicant and to what extent (see Fig. 4). Supposing an applicant has several impairments to only a minor or even marginal degree, e.g. a "touch" of hypertension, "a trifle" overweight or "minimal" hyperlipidaemia. He should by no means be classified as "borderline" in the final assessment, for in all likelihood he has a metabolic syndrome and therefore belongs to a high-risk group liable to develop premature atherosclerosis.

2. On the other hand, simple addition of extra mortality rates of the individual impairments would quickly lead to a very high overall extra mortality rate that might even exceed that of an applicant with coronary heart disease. In order to correct this exag-

Figure 4
Metabolic Syndrome — Risk Profile



erated additive effect, a deduction should be made on the basis of the sum of the individual rates. The higher the total rating of the individual impairments such as hypertension, overweight, and hyperlipidaemia, the higher the probability of imposing an excessive additional premium. The procedure adopted in our company provides for a discount ranging from 0 to 100% extra mortality. The actual amount of the reduction depends on the overall mortality and the considerations referred to in points 3 and 4 below.

3. Where a metabolic syndrome with type II diabetes mellitus is already present at the time of the application, there is a high probability that manifest atherosclerosis is already present, even if it isn't clinically evident. In such cases any deduction from the total rating of individual impairments should be made with extreme caution.

4. Besides the individual impairments hypertension, obesity, hyperlipidaemia, hyperuricaemia and impaired glucose tolerance, the medical files often provide information about other findings that are of prognostic significance and ought not to be ignored. The Table 1 contains a list of prognostic factors in descending order of importance. Depending on the number, weighting and direction of the various prognostic factors, the envisaged discount can be adjusted up or down. Microalbuminuria occupies a special position in this respect: in this case it is especially important to consider whether a discount should be made or whether the risk should be accepted at all.

Finally, it must be noted that the metabolic syndrome is by no means merely a minor transgression. Abnormally high laboratory parameters or blood pressure values are indicative of more than a particularly "good" lifestyle. The metabolic syndrome is a predictor of premature atherosclerosis and is related to the fact that cardiovascular diseases are the most common cause of death in Western societies.

Table 1
Metabolic Syndrome — Risk Constellations

Criterion	Unfavourable constellation	Favourable constellation
Urinary findings	Microalbuminuria	No (micro-) protein
card. findings	Left-ventr. hypertrophy	Normal (echo or ECG cardiography
Adipositas	Android pattern	Gynoid pattern
Age	Young patient	Older patient (e.g. > 45)
Nicotine	Smoker	Non-smoker
Occupation	Sedentary work	Physical work.
Blood pressure therapy	metabolism-activating medicaments e.g. diuretics, β-blockers	metabolism-neutral medicaments e.g. ACE-inhibitors, Ca^{++} antagonists

Summary
The metabolic syndrome is characterized by a large number of metabolic disorders, the findings being generally a combination of insulin resistance, obesity, hypertension, dyslipidaemia and in some cases impaired glucose tolerance or type II diabetes mellitus. Given that the prevalence of this condition in the population at large must be assumed to be at least 10%, the diagnosis of metabolic syndrome is made too seldom. Besides genetic disposition, the environmental factors diet, physical inactivity, smoking, and alcohol consumption play a decisive role in its clinical manifestation.

This article deals briefly with the pathophysiological relationships between the various individual findings and pays special attention to the central role of insulin resistance. With multifactorial therapy in which nonpharmacological measures predominate, generally poor compliance must be assumed. In prognostic terms this is a serious condition that very commonly leads to premature atherosclerosis. The article concludes with a consideration of the underwriting of metabolic syndrome, pointing out that the extra mortality rates of the individual impairments should not be applied on a purely additive basis.

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