

Syndrome X

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Case scenario

JS, a 34-year-old contractor, presented with a two day history of a sore throat. He was noted to have become increasingly centrally obese since his last visit – which he blamed on having gotten married in the interim – and was known to be a smoker. JS' sore throat was his priority. However, a family history of diabetes mellitus and his history of 'borderline' hypertension were of more concern to his doctor.

Is this the metabolic syndrome? How should this patient be managed?

With a name as elusive as Syndrome X, it is all too easy to dismiss the topic as a rather exotic phenomenon for the internists and researchers to deal with. Nevertheless, what was described as Syndrome X in 1988 by Gerald Reaven and is now referred to as metabolic syndrome, appears to be one of the commonest conditions encountered in general practice. The metabolic syndrome, being a syndrome should innately be a collection of signs and symptoms of a pathological process together constituting a picture of a particular clinical condition warranting particular management. The gist of it all can be seen to lie in different perspectives; the metabolic syndrome can be seen as:

- 'simply' a clustering of cardiovascular risk factors – possibly preventable and treatable or,
- a multiplex of metabolic risk conditions namely atherogenic dyslipidaemia, hypertension, glucose intolerance, a proinflammatory and a prothrombotic state. This offers, perhaps, a more pathophysiological description of the condition.

When it comes to the young gentleman described above, dismissing his possible collection of risk factors or failing to give them their due importance can result in the loss of a precious opportunity at preventive care which is definitely neither exotic nor beyond the scope of the primary care physician.

Key words

metabolic syndrome, syndrome X, cardiovascular risk

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The definition

In 2004 the International Diabetes Federation (IDF) revised its definition of Metabolic Syndrome.² According to this new definition, for a person to be defined as having the metabolic syndrome they must have **central obesity** (ethnicity specific values as outlined in Table 1) plus 2 of any of the following 4 factors:

- **Elevated triglyceride:** > 1.7 mmol/L or **specific treatment for this lipid abnormality**
- **Decreased HDL:** < 1.03 mmol/L in males; < 1.29 mmol/L in females.
- **Elevated blood pressure:** Systolic \geq 130 mmHg; diastolic \geq 85 mmHg or **on antihypertensive therapy**
- **Increased fasting plasma glucose:** > 5.6 mmol/L or previously diagnosed type 2 diabetes.

The IDF strongly recommends an OGTT. This is not a prerequisite to define the presence of the syndrome.

The WHO and the NCEP ATP III definitions of metabolic syndrome which are summarized in Table 2 pre-date the more recent IDF definition which has more stringent criteria and lower thresholds.

As Kahn rightly insists, the purpose of describing any syndrome is to inform medics – the ones actually dealing with patients – with regards to the necessary actions that need to be taken to provide control/cure.³ Without this provided guidance, there is a good 'chance' that the action taken would possibly be different.

The clinical relevance of the metabolic syndrome

Our aim as physicians, especially in primary care is, from the outset, to do no harm and from then on take a holistic approach to our patients' care.

As physicians, the true value of any knowledge attained can only be calculated by its relevance to our practice which, at the end of the day, boils down to the benefits gained by our patients by the application of said information "*...after all, the fundamental purpose of a medical label (diagnosis) is to inform physicians and/or patients to take (or not take) action that would otherwise be different*".³ Is identifying patients with metabolic syndrome clinically relevant?

Blaha and Elasy scanned the National Library of Medicine's Medline database for human studies published since 1988 looking up various versions of describing metabolic syndrome/

Table 1: Ethnicity-related values for Waist Circumference indicating Central Adiposity

	Waist Circumference	
	Males (cm)	Females (cm)
Europeids	> 94	> 80
South Asians	> 90	> 80
Chinese	> 90	> 80
Japanese	> 85	> 90

syndrome X/insulin resistance syndrome/dysmetabolic syndrome and the full text of over four hundred articles incorporating metabolic syndrome either as a variable or end-point were grouped according to the definition the respective studies opted to adopt.⁴ It was concluded that, categorically two main perspectives were taken when it came to describing the metabolic syndrome:

1. the pathophysiological perspective
2. the clinical epidemiological perspective.

The first perspective deals mainly with the sequelae of insulin resistance – atherogenic dyslipidaemia, hypertension, impaired glycaemia, pro-inflammatory state/endothelial dysfunction, prothrombotic state, disordered fat metabolism, fatty liver, abnormal uric acid metabolism and, also, abnormal ovarian androgen secretion. The clinical epidemiological perspective, on the other hand, seeks to group related metabolic risk factors and to use this grouping in predicting future risk of cardiovascular disease and to stratify patients accordingly. Cardiovascular disease is definitely the leading cause of premature, sudden and yet, preventable, deaths in many European populations. The implementation of evidence-based, preventive strategies would avert the majority of premature coronary heart disease world-wide.

Wannamethee *et al.* questioned the role of diagnosing metabolic syndrome over using the Framingham Risk Score as predictors of coronary heart disease, stroke and type 2 diabetes mellitus in middle aged men.⁵ It was concluded that metabolic syndrome, as defined by the National Cholesterol Education Programme (NCEP), is associated with a significant increase in risk of coronary heart disease, stroke and type 2 diabetes mellitus and is a far stronger predictor of type 2 diabetes than of coronary heart disease and stroke. Establishing a diagnosis of metabolic syndrome, did not imply improved prediction of coronary heart disease but it did identify those individuals predisposed to either cardiovascular disease or type 2 diabetes mellitus and hence may serve as a ‘simple’ clinical approach to identifying patients for clinical intervention to reduce cardiovascular disease and risk of type 2 diabetes mellitus.

Sundström *et al* hypothesized that the presence of the metabolic syndrome, applying World Health Organisation (WHO) and NCEP definitions, increases the subsequent risk of total and cardiovascular mortality.⁶ It was also assumed that the

prognostic impact of the metabolic syndrome may vary with age. In their community-based cohort study of men with a maximum 32.7 year of follow-up, the metabolic syndrome was found to be an independent risk factor in middle age (follow up from the age of fifty) for both total and cardiovascular mortality, when established risk factors for cardiovascular disease were taken into account. In fact, results showed a 40-60% increased risk for total and cardiovascular mortality in such circumstances. The syndrome, however, did not consistently predict adverse outcomes in elderly men (follow up from seventy years of age). This finding is quite surprising as it was precisely in this group of older individuals that the WHO definition’s criterion of microalbuminuria was actually applied. Microalbuminuria is known to be generally the first clinical sign of renal dysfunction in diabetes mellitus resulting from endothelial dysfunction which is not necessarily confined to the kidney rendering the individual at an ever-increasing cardiovascular risk.

Managing the metabolic syndrome

The key features that are generally acknowledged to occur in the metabolic syndrome:

1. certain metabolic factors seem to occur together at a greater frequency than could be put down solely to chance
2. these same factors – taken alone or in combination – are associated with an increased risk for cardiovascular disease and diabetes
3. there is no definitive treatment for the syndrome.

Considering all this, dealing with metabolic syndrome, from a practical point of view involves screening for as many cardiovascular risk factors possible – perhaps taking central obesity as such a risk factor and attempting to measure abdominal

Table 2: WHO and NCEP ATP III definitions of the metabolic syndrome

WHO	NCEP ATP III
Insulin resistance in the form of either:	At least three of the following 5 criteria:
<ul style="list-style-type: none"> • Type II DM • Impaired fasting glucose • Impaired glucose tolerance 	<ul style="list-style-type: none"> • Waist circumference: men \geq 102 cm women \geq 88 cm • Triglycerides \geq 1.69 mmol/L • HDL cholesterol < 1 mmol/L in males and < 1.3 mmol/L in females • Hypertension \geq 130/85 mmHg or on antihypertensive medication • Fasting glucose \geq 6.1 mmol/L
Plus any 2 of the following:	
<ul style="list-style-type: none"> • Hypertension (\geq 140/90mmHg) • Plasma triglycerides \geq 1.7 mmol/L or HDL cholesterol < 0.9 mmol/L in men or < 1.0 mmol/L in females. • BMI > 30 kg/m² • Microalbuminuria 	

girths and then advising the necessary lifestyle modifications. The NCEP concludes that most of the management will indeed consist of instituting TLC – therapeutic lifestyle changes. These lifestyle changes include weight loss and maintaining ideal weight once attained, changes to diet and increasing exercise. TLC requires the patient's commitment so as doctors it is important that we convince our patients that they are at an increased risk for preventable cardiovascular disease and there is something that can be done about it if they choose to.

Whilst the practicality of TLCs may be questioned, it definitely is dependent on a number of factors – both patient and doctor centred. Some patients may prove enthusiastic and receptive to these changes; others may find that bad habits die hard. Results of a randomized trial of lifestyle modification and pharmacotherapy for obesity underscored the importance of prescribing weight-loss medication in combination with, rather than instead of, lifestyle modification.⁷ It was found that combination of group lifestyle modification counseling and pharmacotherapy resulted in approximately twice as much total weight loss achieved by groups receiving either pharmacotherapy alone (sibutramine was administered in this study) or lifestyle modification counseling alone. Active participation, e.g. keeping a diary of daily food intake, reflected a direct proportion of weight loss throughout assessment. There was also a significant increased weight loss in the group prescribed sibutramine and a limited number of encounters with their primary care physician in those on sibutramine only. Thus, it appears there is scope for further research to identify effective methods of providing lifestyle counseling in primary care.

Risk calculation and guidelines regarding treatment initiation are available, tried and tested. Risk assessment models such as those derived from Framingham data and the, perhaps more locally relevant, Systemic Coronary Risk Evaluation (SCORE) system can be used to establish risk of cardiovascular disease.^{8,9} The latter is applicable even if a patient is already on treatment. This is where the physician can be offering most to his patient by using evidence-based and structured outlines to screen for the most relevant of risk factors efficiently, knowing when it is important to initiate treatment and be able to illustrate it to the patient who will then, hopefully be, in a better position to play a more-than-passive role in his own care. The SCORE risk charts enable the doctor to calculate not only a patient's total CVD risk but also his relative CVD risk (comparing with a normotensive, normolipidaemic age- and sex- matched counterpart) along with the impact of intervention (e.g. stopping smoking) on the total risk. Even in dealing with young adults – who are at a low absolute risk – the SCORE charts provide means of visualising increasing lifetime absolute risk by following the table upwards. Hence, these SCORE charts act to reinforce the relevance of breaking bad habits early and opting to adopt a healthy lifestyle. The NCEP's third report on detection, evaluation and treatment of high blood cholesterol in adults has put persons with diabetes without coronary heart disease to the risk level of coronary heart disease equivalent.¹⁰

It takes into consideration that most of these persons display multiple risk factors so the metabolic syndrome is considered as a secondary target of therapy and advises management with a two-fold objective:

1. the reduction of underlying causes
2. treatment of associated lipid and non-lipid risk factors.

A fasting total lipid profile (including triglyceride, low density lipoprotein and high density lipoprotein levels) and fasting blood glucose ± an oral glucose tolerance test can hence be seen to be very relevant investigations in screening for cardiovascular risk factors. The Federation itself acknowledges the importance of the oral glucose tolerance test in cases of impaired fasting glucose. Hence, it is the primary care physician who would be able to make most effective use of this investigation. A diagnosis of impaired glucose tolerance is associated with a significantly increased risk of premature mortality and cardiovascular disease.¹¹

The importance of the prevention of coronary heart disease in clinical practice basing intervention on an assessment of the individual's total risk burden rather than on the level of any particular risk factor making use of evidence-based tools such as SCORE is widely recognized.⁸

The primary care physician looking after JS should emphasise that:

- Diet needs to be a varied one and ideal body weight, once attained, is maintained by adjusting calorific intake. Whilst encouraging the consumption of fruit and vegetables, whole grain cereals and bread, low fat dairy products, fish and lean meat total fat intake should account for < 30% of energy intake.
- Increasing physical activity has its obvious advantages. European guidelines have set their goal at half an hour of physical activity on most days of the week: 4 to 5 times weekly at up to 75% of his maximum heart rate.
- Blood pressure readings of persistently $\geq 140/90$ mmHg, excluding diabetes mellitus where targets will be lower, imply drug treatment needs to be instituted along with lifestyle modification opting for a drug that not only brings JS' BP into a normal range but that has also been proven to reduce cardiovascular morbidity and mortality.
- An oral glucose tolerance test as this is the only way impaired glucose tolerance can be diagnosed.
- Assessment of total cholesterol (TC) and Low density lipoprotein (LDL) levels aiming at keeping TC < 5 mmol/L and LDL at < 3 mmol/L.

The European Guidelines on CVD Risk Prevention state that high total risk patients are those:⁹

- with established CVD
- asymptomatic patients with:
- multiple risk factors resulting in $\geq 5\%$ ten year risk now or if extrapolated to age 60y
- markedly elevated single risk factors:

- total cholesterol \geq 8mmol/L
- LDL cholesterol \geq 6 mmol/L
- blood pressure \geq 180/110 mmHg
- type II diabetes and diabetes type I with microalbuminuria.

High risk patients need to be treated. There is no real relevance of applying risk stratification in such cases. Treating with low-dose aspirin, a statin and an ACE-inhibitor is nearly an inevitable matter in these high risk patients.

Conclusion

It is undeniable that there are modifiable risk factors for cardiovascular and coronary heart disease which the physician needs to identify and treat accordingly. In a joint statement from the American Diabetes Association and the European Association for the Study of Diabetes clinicians are advised:¹²

- To screen adults known to have any CVD risk for **other** CVD risk factors.
- When risk variables are found to be out of recommended ranges, lifestyle modification should be advised. However when these are diagnostic of frank disease (e.g. FBG \geq 7.0 mmol/L) management should be initiated according to the relevant established guidelines.
- All risk factors for cardiovascular and coronary heart disease warrant individual and aggressive treatment.
- To avoid labelling of patients with the term *metabolic syndrome* as it is yet unclear that the syndrome does indeed carry a greater risk than its components and as there is no defined pharmacological treatment for it.

Every effort should be made to identify, minimise and treat cardiovascular risk in total.

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