The epidemic of the metabolic syndrome

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ABSTRACT

The incidence of metabolic syndrome (MS) is rising worldwide. This is partly due to a significant increase in the prevalence of obesity. Observational cross-sectional studies as well as demographic health surveys from the Middle East, point out that the prevalence of obesity increases from an average of 6% in healthy children to 20% in adolescent males and to a further 32% in elderly patients. The impact of obesity on our population is expected to be considerable; especially, as it feeds into further rising in the prevalence of hypertension, diabetes, MS and cardiovascular disease. The prevalence of MS in nondiabetic adults in Europe was recently reported to be 15%. In the Middle East, as pointed out by pilot observational projects, is estimated to be anywhere between 15-25%. The medical system is unprepared to deal with this epidemic partly due to scanty knowledge on the clinical significance of the MS and importantly as there is a limited number of specific treatments that we can offer these patients.


Metabolic syndrome (MS), obesity and diabetes are multifactorial diseases of considerable heterogeneity. In 1983, the clustering of the atherosclerotic risk factors comprising the MS was first recognized and in 1988 Reaven et al was among the first to coin the term syndrome X, which he thought to be mainly a consequence of insulin resistance. Since then 2 major international bodies have looked into defining MS.

In 1998, the World Health Organization (WHO) defined MS as evidence of dysglycemia (diabetes, impaired fasting glucose, impaired glucose tolerance) along with at least 2 other factors: hypertension, dyslipidemia, microalbuminuria, obesity [central obesity defined by waist circumference or overall obesity defined by body mass index (BMI)]. In 2001, the National Cholesterol Education Program (NCEP) issued a more clinically friendly definition that does not require a glucose tolerance test or checking urine for microalbuminuria. At least 3 of the following factors should be present: high triglycerides, low high-density lipoprotein (HDL) cholesterol, central obesity as defined by waist circumference, hyperinsulinemia, and a fasting blood sugar ≥110 (6.1 mmol/L). Table 1

Observational and demographic health survey from the Middle East point out the prevalence and impact of obesity, hypertension and diabetes on local population. The prevalence of MS in non diabetic adults in Europe is estimated to be 15%. Prevalence. The prevalence of obesity has risen dramatically in North America. In the United States, there has been a 61% increase in prevalence of obesity since 1991. This has led to an increase in the prevalence of MS. Based on data from the 2000 US census, an estimated 47 million US residents have MS. Recent data from 6 cross-sectional national population surveys in Canada point out that between 1985 and 2000, the national population attributable risk for overweight and obesity increased from 5.1-9.3%. There are no data on the prevalence of MS in the general population in Canada. In a population of 1108 consecutive patients with documented coronary artery disease (CAD), mostly Caucasians of French Canadian origin, Solymoss et al found the prevalence of MS to be 49% among men and 54% among women.

Pathophysiology. Metabolic syndrome results from interaction between genetic susceptibility and lifestyle. It is thought that approximately 20-40% of

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To date, the genetic basis of MS is yet to be elucidated. The general population is genetically predisposed to MS.

Metabolic syndrome can be looked at as the result of a combination of the effects of insulin resistance in some tissues (fat cells, skeletal muscles, endothelial cells) and the effects of hyperinsulinaemia on other systems (enhanced sympathetic response, enhanced renal sodium reabsorption). There is also a heightened inflammatory response [increased interleukins, TNF-α, as well as elevated creatine phosphate (CRP)], and an atherothrombotic milieu (small dense low-density lipoprotein (LDL) particles, elevated levels of fibrinogen and plasminogen activator inhibitor-1).

Clinical implications. Metabolic syndrome is associated with high incidence of cardiovascular events, such as myocardial infarction, stroke and heart failure. This risk is independent of other conventional risk factors such as smoking and age. It is still a matter of debate whether MS confers added risk when its individual components are taken into account. There is also evidence that MS predisposes patients to developing type II diabetes. Botnia study is a prospective study that followed individuals from families with diabetes to identify early metabolic defects for a median period of 6.9 years. Reports on 4,883 subjects reveals that MS (using WHO criteria) conferred a threefold increase in the risk for CAD and stroke (p<0.001). In a univariate analysis model incorporating the usual Framingham risk factors.

The West of Scotland Coronary Prevention Study prospectively followed 5,947 men for 4.9 years to predict incident of diabetes. In a univariate model, subjects with 4 or more baseline abnormalities of MS had a 24.5 times fold increased incidence of type II diabetes compared to those with no abnormalities (p<0.001). In a multivariate regression model BMI, triglycerides and fasting glucose remained significant independent predictors for diabetes (p<0.01). Notably, CRP enhanced prognostic information on coronary heart disease (CHD) outcomes and new onset diabetes (multivariate analysis; p<0.001).

Therapeutic interventions. The Adult Treatment Panel Guidelines III recommends that obesity be the primary target for intervention in MS. Clinical management should focus first on lifestyle modification, particularly weight reduction and increased exercise. This can be achieved as part of a cardiac rehabilitation program or else individually with the aid of several specialists (example, a dietician).

There are no data in the guidelines on the target blood pressure (BP) in MS patients, but if we are to extrapolate from data on diabetes patients, a BP of ≤130/≤85 mm Hg should be set as target. Although there is no class of medication that has shown clinical supremacy in the treatment of MS patients, there is evidence that angiotensin-converting enzyme inhibitors can lower the incidence of diabetes, among other contributors to cardiac risk.

Statins are the mainstay of treatment for patients with high LDL; it is still a matter of debate whether they are the best therapy for patients with a lipid profile typical for MS. Recent subgroup analysis of statin trial reveals that statins reduce risk of cardiovascular disease (CVD) in MS patients.

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**Table 1 - NCEP / ATP III definition of metabolic syndrome.**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Defining level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&gt;102 cm / 40 inch</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;88 cm / 35 inch</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dL / 1.70 mmol/L</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt;40 mg/dL / 1.03 mmol/L</td>
</tr>
<tr>
<td>Women</td>
<td>&lt;50 mg/dL / 1.29 mmol/L</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130 / ≥85 mmHg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥110 mg/dL / 6.1 mmol/L</td>
</tr>
</tbody>
</table>

HDL - high-density lipoprotein  
NCEP - National Cholesterol Education Programme  
ATP III - Adult Treatment Panel Guidelines III

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Post hoc analysis of the Veterans Affairs High-Density Lipoprotein Intervention Trial also attests to the efficacy of fibrates in treatment of MS associated dyslipidemia. There might arise a clinical need to combine both groups of medications, though there is no evidence from clinical trial to this approach. Whether insulin resistance should be targeted for treatment is still a matter of debate. Two classes of medication are currently under consideration for this goal; namely metformin and thiazolidinediones (TZD). In the United Kingdom Prospective Diabetes Study,27 metformin reduced the incidence of CAD in obese patients with diabetes. Thiazolidinediones show promise in preventing CAD through their favorable effects on insulin resistance, thereby modifying several risk factors. Nonetheless, there are currently no CVD end-point studies on MS patients treated with either metformin or TZDs. Likewise, there are currently no medications available to target the prothrombic state in patients with MS. Alternatively, low dose aspirin reduces CVD events in the setting of both primary and secondary prevention. There is also evidence that several lipid lowering medications (example, statins) will reduce CRP levels, which is an individual cardiac risk factor. Also, the benefits of statin therapy in people with diabetes have been observed from post hoc sub group analyses of major statin trials.18

The prevalence of MS is closely related to the prevalence of obesity (which increased by 61% between 1991-2000) and will become epidemic in the 21st century. In addition to behavioral intervention (diet, weight loss and exercise) early aggressive therapy directed at dyslipidemia and insulin resistance is a key and an attractive treatment strategy for the MS.

References

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