Metabolic Syndrome

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Case presentation: The patient was a 38-year-old construction company manager who presented with mild stage 1 hypertension (office blood pressure [BP] ranging from 145/92 to 150/105 mm Hg) without end-organ damage. He worked long and irregular hours. Being single and often very tired at the end of the day, he simply bought take-away fast food as often as needed. He seldom drank alcohol except at weekend parties, when he had an excess. He smoked 15 to 20 cigarettes per day. He was overweight (body mass index=29 kg/m^2), with an enlarged waist circumference (42.5 inches [108 cm]). His plasma triglyceride level was 281 mg/dL (3.19 mmol/L), high-density lipoprotein (HDL) cholesterol was 35 mg/dL (0.9 mmol/L), calculated low-density lipoprotein cholesterol was 135 mg/dL (3.5 mmol/L), total cholesterol was 175 m/dL (4.5 mmol/L), and fasting plasma glucose was 101 mg/dL (5.6 mmol/L). Thus, he met the modified criteria of the Adult Treatment Panel III for clinical identification of the metabolic syndrome,[1] as he had 4 of the 5 components (hypertension, increased waistline, low HDL-cholesterol, and high triglyceride values [Figure], with borderline elevated plasma glucose). Of these, hypertension and lowered HDL values best predict coronary heart disease (CHD).[2]

Differing Definitions of the Metabolic Syndrome

Abdominal obesity is most strictly defined by the International Diabetes Federation, with different cut-off levels for different ethnicities.[3] The International Diabetes Federation emphasizes abdominal obesity as the initiating factor in the metabolic syndrome. Because risk factors cluster, and because the cardiovascular risk factors for the metabolic syndrome are linear in their damaging effects (Table 1), different definitions of the metabolic syndrome make little difference in the prognostic implications.[4]

Some argue that the syndrome does not exist, saying that the 5 components are merely borderline cardiovascular risk factors. However, if taken together, they significantly augment risk. The large international INTERHEART study has shown linear relationships between these risk factors and myocardial infarction.[5] Specifically, linear cardiovascular risks are (1) the degree of abdominal obesity[6]; (2) fasting or 2-hour postprandial glucose values[7]; (3) elevated average BP[8]; (4) decreased circulating HDL[9]; and (5) high triglyceride levels.[10] The metabolic syndrome gives a 2- to 3-fold increased risk for CHD, a similar risk for future ischemic stroke,[11] and a much greater risk for future diabetes.[4,12] The more features of the metabolic syndrome a patient has, the greater the risk, which is made much worse by concomitant low-density lipoprotein cholesterol elevation.[10]

Mechanism of Metabolic Syndrome

The syndrome can best be explained by viewing abdominal adipose tissue as an endocrine organ[13] that releases into the circulation excess harmful free fatty acids (FFA), angiotensin II, and adipokines. First, the increased blood FFA inhibit the uptake of glucose by muscle.[14,15] Excess FFA and angiotensin II damage the pancreas.[16] Although the pancreas manufactures extra insulin, there is not enough to counter the hyperglycemia, thus explaining the paradox of fasting hyperglycemia despite increased plasma insulin levels, which is known as insulin resistance.

Angiotensin II increases BP through its vasoconstrictive effects. Tumor necrosis factor-α and other cytokines (interleukins) provoke inflammatory reactions that also lessen the efficacy of insulin and may promote hypertension. Hyperglycemia and increased circulating FFA provide the correct substrates

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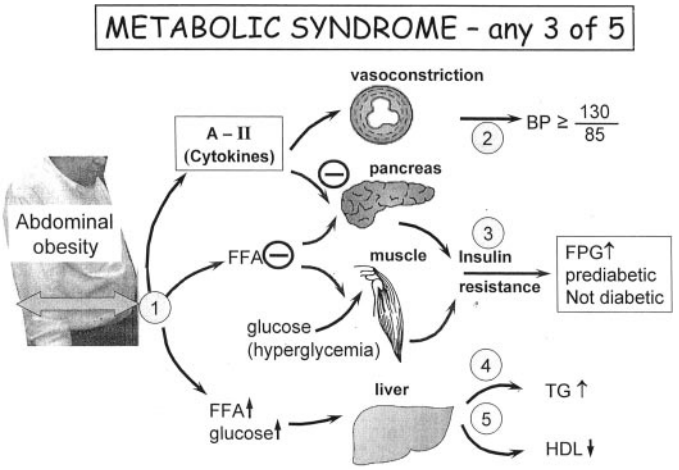
(*Circulation.* **2007;115:e32-e35.**)

Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/CIRCULATIONAHA.106.671057**



The diagnosis of metabolic syndrome requires a tape measure or accurate eye; fasting lipogram and plasma glucose measurements; and BP measurements. A-II indicates angiotensin-II; FFA, free fatty acids; BP, blood pressure; FPG, fasting plasma glucose; TG, triglycerides; and HDL, high-density lipoproteins. Figure modified with permission from Opie LH. The metabolic syndrome, does it exist? In: Opie LH, Kasuga M, Yellon DM, eds. *Diabetes at the Limits*. Cape Town, South Africa: University of Cape Town Press; 2006:95–110.

for increased manufacture of triglycerides by the liver. Circulating triglycerides increase so that lipoproteins carry more triglycerides and less HDL (note the complex reciprocal relationship between circulating triglyceride and HDL).[17]

Therapy

Lifestyle

Regular exercise is the first step in treating the metabolic syndrome because it increases glucose metabolism by muscle and helps in weight reduction (Table 2). Dietary therapy has 2 components. The first is weight reduction, which is chiefly a matter of achieving a sustained negative calorie balance, and the second is adherence to the Mediterranean diet, which is especially high in olive oil and nuts.[18] This enriched Mediterranean diet reduces BP, as well as fasting glucose and insulin and therefore the HOMA index (Homeostasis Model Assessment, calculated as a product of these 2 measures). It modestly increases HDL while decreasing triglyceride levels when compared with a low-fat diet[19] in a study that only lasted 3 months. When specifically applied to patients with the metabolic syndrome over 2 years, the Mediterranean diet decreased body weight and inflammatory markers.[20] In an observational study, those Greek subjects who adhered more closely to the Mediterranean style of diet had a 20% lower risk of the metabolic syndrome.[21] Healthy food choices together with regular exercise and not smoking reduce the risk of CHD, in part through antiinflammatory mechanisms.[22] Thus, the Mediterranean diet seems to be a good and palatable dietary choice, usually very acceptable to patients. Its major defect is that it does not result in weight reduction, which requires exercise and a decreased calorie intake.

TABLE 1. Linearity of Features of the Metabolic Syndrome as Risk Factors for Cardiovascular Disease

1. Plasma glucose levels and cardiovascular risk[7]
2. Waist measurements[6]
3. Blood pressure[8]
4. Serum triglycerides levels[10]
5. HDL-cholesterol, reflected in the plasma apolipoprotein B to A ratios[5]

Lessening the Risk of Future Diabetes

In the study by Tuomilehto et al,[23] those prediabetic patients with metabolic syndrome in the intervention group had a mean waist circumference of 102 cm, a fasting glucose level of 109 mg/dL, an HDL level of 46 mg/dL, and a triglyceride level of 154 mg/dL, with BP values of 140/86 mm Hg. The aims of the study were to reduce weight by more than 5%, reduce the fat intake, reduce the saturated fat intake, increase the fiber intake, and increase exercise to more than 4 hours per week. The exercise goal was the one most often achieved (86%), followed by reduction of the fat intake (47%), modest weight reduction (43%), decreased saturated fat intake (26%), and increased fiber intake (25%). The relative risk for diabetes in the intervention groups was 0.4 (ie, a 60% reduction). In another similar study,[24] metformin also reduced new diabetes but less so than did lifestyle measures. The glitazones (rosiglitazone and pioglitazone) specifically reduce hyperglycemia at the small risks of weight gain and increased heart failure. However, they decrease FFA levels, lessen insulin resistance, reduce triglycerides, and increase HDL.[25]

Antihypertensives

Here the risk of future diabetes also needs consideration. The combination of diuretics and ß-blockers should be avoided (Table 2). Angiotensin-

TABLE 2. Metabolic Syndrome: Therapeutic Strategies

1. Lifestyle changes,[31] exercise, adherence to the Mediterranean diet, and weight loss → less new diabetes
2. Metformin (less new diabetes, not as good as lifestyle changes)
3. Glitazones, for non-diabetics with high cardiovascular risk: ↓ fatty free acids, ↓ insulin resistance, ↑ HDL,[25] balancing these against possible weight gain
4. Rimonabant, cannabinoid receptor blocker; waist measurement ↓,TG ↓, ↑ HDL[29]
5. Glucagon-like peptide (future therapy, decreases plasma glucose and induces weight loss)
6. Choice of antihypertensives: β-blocker/diuretic much more likely to cause metabolic syndrome than calcium channel blockers/angiotensin-converting enzyme inhibitors[32]

converting enzyme inhibitors and angiotensin-receptor blockers should lessen the risk of new diabetes,[26] even though the absolute cardiovascular benefit is small.[27]

Low HDL and High Triglyceride Levels

This is a difficult problem to tackle. Powerful investigational HDL-elevating agents such as torcetrapib, an inhibitor of cholesterol ester transfer protein,[28] have the potential to increase HDL by about 50%. Formal outcome trials have resulted in drug withdrawal because of increased mortality. Existing agents that increase HDL and decrease triglyceride levels by about 10% include nicotinic acid and glitazones.[25] Fibrates have less effect on HDL and are especially active on triglycerides. In overly obese persons, high-dose rimonabant, the endocannabinoid receptor inhibitor, increases HDL by 19% and decreases triglycerides by 16%, with only modest weight loss.[29] Modest alcohol consumption increases HDL moderately. Genetically decreased hepatic alcohol dehydrogenase slows ethanol catabolism to give higher HDL levels and lower rates of myocardial infarction.[30] Almonds decrease the low-density lipoprotein:HDL ratio.[18]

What Therapy Was Chosen for Our Patient?

Besides candesartan as the antihypertensive, he was advised to exercise regularly on the way to work and to switch to a Mediterranean diet. He was encouraged to dine at a Greek restaurant, add high-quality olive oil and almonds to his Mediterranean food, emphasize vegetables and fruit, and have 1 or 2 glasses of wine but only with his food. On this regimen, his fasting glucose decreased to 96 mg/dL and his HDL rose to 40 mg/dL (1.1mmol/L). He did not stop smoking but genuinely cut down by half, therefore reducing this linear risk by half. Although therapy and lifestyle advice countered all the abnormal components of the metabolic syndrome, the effort required for a busy person to keep up the exercise routine in the morning and frequent restaurant dining in the evening may be too difficult to sustain. Hence, if hyperglycemia returns and worsens, he will be given metformin. If metformin does not lead to an adequate response, we may switch to rosiglitazone.

Conclusion

The untreated metabolic syndrome places individuals at risk both for diabetes and cardiovascular disease. Of the 5 features of the metabolic syndrome, abdominal obesity, high triglycerides, and modest elevations of blood glucose were not part of the original Framingham risk factor score, nor did Framingham prognosticate on the risks of future diabetes or ischemic stroke. For these reasons, diagnosing the metabolic syndrome extends our concepts of cardiovascular risk.[31,32]

Disclosures

None.

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