The metabolic syndrome as a contributor to morbidity

or: How fat in the gut causes heart attacks

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The components of the metabolic syndrome vary a little according to your reference, but central obesity, impaired glucose tolerance, dyslipidaemia, hypertension and hyperuricaemia are usually seen. Recently there have been suggestions that polycystic ovarian syndrome should be included and I would agree with that view.

The end result for individuals with these features is a markedly increased risk of premature death from heart disease. Because of the difficulties in 'measuring' the metabolic syndrome (see the work of Jean-Pierre Despres later), the best data comes from looking at obesity per se. This also highlights that it is obesity which underpins the metabolic syndrome in most individuals. A study of more than 260 000 women and 60 000 men – all white, non-smoking adults over the age of 30 – revealed a strong correlation between BMI and death from all causes, with an even stronger relationship for death from cardiovascular disease. The effect was greatest in younger individuals with a BMI of 30, resulting in a doubling of risk for individuals aged 30–44, but after the age of 75 the effect was no longer present. Among other things, this data tells us that if our patients have survived to the age of 75, there is no reason to promote weight loss unless it is for specific reasons, such as the presence of type 2 diabetes or joint disease etc.[1]

More recent data to come from the Framingham study has demonstrated that independent of known risk factors, obesity itself causes a doubling in the risk of heart failure. The mechanism for this is poorly understood, but the feeling is that the metabolic syndrome is the major risk factor and its presence may not be adequately detected in the Framingham cohort.[2] Increasingly, effort is being put into identifying which are the key features of the metabolic syndrome. We have good evidence that lowering blood pressure prevents heart disease, strokes and renal impairment. Similarly, we know that lowering cholesterol in even normolipidaemic patients protects against all forms of macrovascular disease, but perhaps there is more that can be done to reduce the risks associated with the underlying syndrome.

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Diabetologists all hoped that lowering blood glucose levels would protect against heart disease, but the most comprehensive study to look at this, the UKPDS, did not confirm that that was so.[3] We were surprised at this finding, as abnormal glucose tolerance is a powerful, independent marker of heart disease risk. For example, a patient with type 2 diabetes but no history of ischaemic heart disease has a higher risk of a heart attack over the next five years than an age-matched, non-diabetic patient who has just been discharged from coronary care having had an MI. The diagnosis of diabetes is not, however, necessary to confer this increase in risk. There is a continuum of risk associated with blood sugar levels right down into the normal range. An example of this is a study which looked at patients aged 50–89 years with no history of either heart disease or diabetes who underwent an oral glucose tolerance test. In women who demonstrated isolated postchallenge hyperglycaemia (with normal fasting levels), there was a doubling of risk for developing heart disease over the seven year follow-up period.[4]

If impaired glucose tolerance itself does not cause heart attacks, what about the stage prior – the situation of insulin resistance? Resistance to insulin stimulated glucose uptake is seen in patients with impaired glucose tolerance or diabetes, but also in about 25% of non-obese individuals with normal glucose tolerance. Regardless of the blood sugar levels, insulin resistance is associated with central adiposity, dyslipidaemia, hypertension, hyperuricaemia and increased cardiovascular risk.

Alternatively, is there a common precipitant – responsible for diabetes, hyperinsulinaemia and macrovascular disease? More and more this is looking like being visceral adiposity. Insulin action on the liver is markedly affected by changes in circulating fatty acids so it's not surprising that increased portal vein fatty acids from visceral fat can lead to hepatic insulin resistance. In addition, muscle insulin resistance is related to intramyocellular triglyceride levels and there are suggestions that alterations to fatty acid oxidation may play a role in muscle as well.

A study of the Japanese population of Brazil found that the rate of glucose intolerance was amongst the highest in the world and that there had been a significant increase in the incidence over the previous seven years. Most interestingly, waist circumference was highly correlated with increased risk with a 5% increase in risk for each centimetre of waist circumference.[5]

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The expert in the field of obesity/dyslipidaemia, type 2 diabetes and the metabolic syndrome is a French Canadian, Jean-Pierre Despres, and he has come up with a triad of 'unconventional' metabolic risk variables which, when measured simultaneously, are more powerful predictors of cardiovascular risk than the usual lipid measures. These are hyperinsulinaemia, hyperlipoprotein B (hyperapo B) and small, dense LDL. He also identified that this atherogenic triad was highly prevalent among abdominally obese men, especially when a high accumulation of visceral adipose tissue is present. Because the costs associated with measurement of visceral fat or the lipid parameters in his triad are expensive, he conducted a study to see if he

could identify clinical correlates which would work well in normal practice. The result of his study of middle-aged men was that more than 80% of men with a waist circumference of ≥90cm and a fasting triglyceride level of ≥2mmol/L were characterised by the metabolic triad and high risk of CAD.[6]

So now we have good clinical tools for identifying the metabolic syndrome in our patients, but do we fully understand the mechanism by which visceral adiposity leads to heart disease? And does the effort to unravel this mystery lead us to novel approaches for treatment? Two interesting new developments in this area are the discovery that visceral adipose tissue is a key regulator of inflammation, coagulation and fibrinolysis and, secondly, that it produces novel hormones such as resistin and adiponectin.

Many studies have demonstrated a strong correlation between C-reactive protein (CRP) with body fat mass, waist circumference and visceral fat. Adipose tissue is now known to secrete proinflammatory cytokines and fibrinolytic regulators such as plasminogen activator inhibitor-1 (PAI-1) and interleukin-6. Inflammatory markers such as these may lead to a disregulation of natural anticoagulation and thrombosis. What this means clinically is that, at least in some individuals, modification of the inflammatory status may be an effective treatment. What is more, it appears that not only agents such as aspirin but also statins, fibrates, glitazones and of course weight loss are capable of doing this.[7]

In addition to the cytokines above, the adipocyte is known to secrete leptin, adiponectin and, in mice at least, resistin. The latter hormone is expressed in the white adipose tissue but also detected in serum in obese mice. Experiments have shown that expression of this hormone is down regulated by thiazolidinediones such as rosiglitazone and pioglitazone.[8] Rather more is known about adiponectin which is a protein specific to adipose tissue but inversely related to atherosclerotic disease. It is low in individuals with obesity and other features of the metabolic syndrome. It is thought to have beneficial effects, which again are anti-inflammatory, but it has also been shown to reduce cholesterol ester accumulation. Studies in animals with recombinent adiponectin have shown a decrease in fatty acid levels and an increase in insulin receptor signalling in skeletal muscles. While adiponectin tablets seem some way off at the moment, the thiazolidinedione rosiglitazone has been shown to increase levels of this hormone and it may be one of the mechanisms by which it works as an insulin sensitiser.[9]

For those unfamiliar with the thiazolidinediones, these are also referred to as PPAR-c or peroxisome proliferator-activated receptor-c agonists. They are new oral agents for the treatment of diabetes and work as insulin sensitisers at the level of the nuclear receptor. These agents have been found to lower the levels of insulin, CRP and fatty acids as well as blood sugar and the hope is that they modify the underlying metabolic syndrome in addition to treating diabetes.

I am not sure that we fully understand the connection between visceral adiposity and the metabolic syndrome, but there is no doubt that adipose tissue is more than the passive parking space for excess energy that we once thought of it as. In addition to functions related to the metabolic syndrome, there is the production of leptin and its role in weight homeostasis and fertility. But that's a whole new story.

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