Metabolic complications of visceral adipose tissue

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Summary

Visceral adipose tissue (VAT) is now known to predispose to many of the coronary artery risk factors. There is an increased predisposition to metabolic complications such as hyperlipidaemia, hypertension, insulin resistance and even non-insulin dependent diabetes in patients who have an intra-abdominal accumulation of fat (visceral adipose tissue). This cluster of complications is known as the 'metabolic syndrome'. The most important issue in obesity management and research is to accurately recognise patients at risk and be able to monitor progress as treatment is commenced. Thus, there is a great emphasis on body composition techniques to detect and monitor visceral adipose tissue. The focus of obesity management is now aimed at a selective reduction in visceral adipose tissue rather than total body fat.

Introduction

The general consensus throughout much of the obesity research undertaken since Vague's paper in 1956 (1) is that increasing amounts of visceral adipose tissue, also known as intra-abdominal fat, determines metabolic complications such as hyperlipidaemia, insulin-resistance, hyperuricaemia and hypertension and hence increases the risk of vascular complications such as coronary artery disease and stroke. This constellation of symptoms was originally described as Syndrome X by Reaven in 1988 (2) and is now more commonly known as the metabolic syndrome or the insulin resistance syndrome.

Abdominal obesity and metabolic sequalae

Abdominal or visceral obesity is thought to play a central role in the metabolic syndrome possibly due to differences in adipocytes from various areas of the body. Those from visceral adipose tissue are more prone to release free fatty acids after lipolytic stimulation and thus increase the portal free fatty acid flux. The consequence of this increased fatty acid flux seen with higher levels of visceral adipose tissue is a reduction in insulin clearance by the liver. This subsequently leads to higher peripheral levels of insulin and contributes to insulin resistance. It is not certain whether excess intra-abdominal fat results directly in increased insulin resistance or whether it is somehow moderated through the liver (3), however, the end result is decreased insulin stimulated glucose disposal, reduced hepatic insulin clearance and increased insulin produced by the pancreas.

A further metabolic complication of the increased free fatty acid flux is increased synthesis and secretion of very low density lipoprotein (VLDL). Patients with visceral obesity have reduced levels of lipoprotein lipase activity in their plasma resulting in a reduction in HDL precursors. Hepatic lipoprotein lipase activity is increased leading to increased conversion of HDL_2 to HDL_3. Thus the lipid profile in patients with increased visceral adipose tissue is seen to be more atherogenic with elevation in triglycerides, low plasma HDL cholesterol and a poor HDL_2/HDL_3 ratio.

Measuring visceral vs subcutaneous obesity

One factor which has continued to hamper research over the years is the difficulty involved in accurately documenting visceral adipose tissue. At the moment, only computerised tomography (CT) or magnetic resonance imaging (MRI) have been shown to accurately measure subcutaneous and visceral adipose tissue and these techniques have been validated against cadaver studies in both humans and in animals. While volumetric studies would be more appropriate they are very

time consuming and so most work is done using a single scan technique at the level of either L3-L4 or L4-L5. These have been shown to correlate well with total visceral adipose volume (r >0.95)(4). Unfortunately CT scanning and MRI are expensive investigations and are not readily available. They provide the best available method, short of post-mortem studies, to evaluate visceral adipose tissue and to relate it to metabolic complications. At present they are useful mainly in the research setting where much of the focus is to find an accurate and reproducible anthropometric measure of visceral adipose tissue suitable for clinical use.

Many of the traditional methods of assessing body fat such as underwater weighing, skinfold thicknesses, ultrasound and dual energy X-ray absorptiometry (DEXA) do not directly measure intra-abdominal fat. They are able to measure total body fat, or perhaps give an estimate of this but do not differentiate between visceral adipose tissue and subcutaneous adipose tissue. As such they do not determine the metabolic risk related to obesity. There is some recent work, however, which suggests that DEXA may be able to approximate visceral adipose tissue and give a better indication of this.

Until recently the most frequently used method of assessing risk related to obesity has been using the body weight and height to calculate the body mass index (A) (weight in kg ÷ height in m^2). This measure is only an index and although a BMI >30 suggests increased body fatness, it does not indicate body fat distribution. Other anthropometric techniques such as waist circumference and the waist:hip ratio (WHR) have been compared to MRI and CT studies and show variable levels of correlation with visceral adipose tissue (5). Unfortunately these techniques have not been well standardised until recently with the development of WHO guidelines. The waist circumference is now measured at the point midway between the costal margin and the iliac crest in the mid-axillary line while the hip is measured around the greater trochanters including the maximum protrusion of the buttocks posteriorly.

The sagittal diameter is a newer anthropometric measure which is thought to correlate reasonably well with visceral adipose tissue. It also has lacked standardisation and requires a specially designed caliper. While this measure has shown promise as a 'better' estimate of visceral adipose tissue, our own studies suggest that it is more useful in patients with lower BMI than with higher BMI (unpublished data). In the Baltimore Study on Ageing it was a good predictor of total mortality in the younger group (age < 55 years) but not in the older group of subjects (6).

Difficulties arise in measuring abdominal fat in patients with increasing amounts of body fat as any measure becomes less precise and technically more difficult. Patients with morbid obesity who have BMI > 50 do not fit on to either CT scanners or MRI instruments and so the correlation between anthopometric measures and visceral adipose tissue in extreme obesity cannot be validated. In a recent study we have looked at visceral fat as assessed by MRI and anthropometric measures in 30 obese men (mean BMI=35, WHR > 1.0) and found almost no correlation between traditional measures of fat such as WHR and waist circumference and visceral adipose tissue as measured on MRI (unpublished data). It is clear that as yet there is no gold standard anthropometric measure by which to assess visceral adipose tissue.

Improving the metabolic profile versus weight loss

Although Pouliet et al (7) have suggested trigger points of > 100 cm for the waist circumference and > 25 cm for the sagittal diameter above which the patient is at increased risk of metabolic complications, many patients already have metabolic complications at levels well below this. In a group of 10 non-obese men with both abdominal obesity and NIDDM the mean sagittal diameter was only 21.2 ± 2.1 cm while the mean waist circumference was 94.7 ± 6.8 cm prior to treatment (8). After treatment for 12 weeks with dexfenfluramine the sagittal diameter and waist circumference reduced significantly indicating a reduction in visceral adipose tissue as seen on MRI. In these patients we were able to see a significant improvement in metabolic parameters. Insulin sensitivity improved (p=0.01), C-peptide production reduced (p=0.002) and total

cholesterol and triglyceride levels also improved ($p=<0.001$, $p=0.021$ respectively). These changes are consistent with those seen by Bremer et al who also reported a reduction in fasting glucose, fibrinogen levels and systolic blood pressure after 12 weeks on dexfenfluramine (9). In a rat model, dexfenfluramine has been reported to also reduce cholesterol, triglycerides and insulin levels while decreasing the occurrence of myocardial lesions and end-stage cardiovascular disease (10).

It is clear that treatment of obesity needs to focus more exclusively on improving cardiovascular risk factors and therefore on reducing visceral obesity. Weight loss per se is part of the overall outcome, however, it is improvement in the features of the metabolic syndrome which should be the primary aim of any weight loss program. Treatment may then be considered to be successful even if weight loss does not occur. Long-term benefit from any such program would necessitate continuing treatment well past the point where weight loss no longer occurs. This will require a shift in concept for most involved in weight loss strategies as short-term therapy has, until recently, been the main stay of treatment.

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