Obesity Epidemic - Time to Wake Up

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It is generally accepted that obesity is a health hazard due to its association with a number of metabolic complications such as type 2 diabetes, dyslipidaemia and cardiovascular disease. We as clinicians have been trained to define obesity on the basis of weight in kilogrammes expressed over height in metres squared, the so called BMI (Body mass index) initially described by Quetelet way back in 1869.

Indeed epidemiological studies have shown an increase in incidence of metabolic diseases with increasing BMI.[1] However despite this evidence many of us clinicians in our daily practice are often baffled by the differences in our patients; thus some patients who have considerable excess body fat show a normal metabolic risk profile whereas others who are moderately overweight show a whole range of metabolic complications such as type 2 Diabetes atherosclerosis and cardiovascular disease.

This thought has led to a rethinking of the notion suggested in the 1940's by a French Physician Dr Jean Vague,[2] whereby complications related to excess fat were related to where the fat was distributed rather than on the total amount per se. Thus android obesity or male obesity is considered to be a major risk factor for coronary heart disease and type 2 diabetes and their related mortalities.[3] Gynoid obesity or the accumulation of fat in the gluteofemoral area, is not related to increased cardiovascular risk.[4]

Thus there is currently enough evidence to suggest that abdominal obesity is a major risk factor which needs our serious consideration when we are assessing and managing an abdominally obese individual.

Fat, what fat?

As time goes by, an increasing proportion of our population is becoming more sedentary and is being habitually exposed to an energy rich and refined food which favours obesity. It is a fact that although abdominal obesity has a definite genetic basis, obesity will only develop in the presence of an energy rich environment.

Anthropometric variables such as waist to hip ratios and abdominal circumference, when compared to measurements obtained with sophisticated imaging techniques such as magnetic resonance imaging (MRI) and Computed tomography (CT) have shown that a simple measurement of waist circumference was the best anthropometric correlate of the level of visceral adipose tissue.[5]

Upper body obesity develops from adiposity in subcutaneous and intra-abdominal compartments. Intra-abdominal fat (visceral fat) is defined as the fat located around the viscera, within the peritoneum, the dorsal surface of the intestines and the surface of the kidneys. It is important to realise that BMI is not a reliable indicator of the extent of intra- abdominal adiposity, and two men with a similar BMI may have different distribution of visceral fat and also different cardiometabolic risk.

Visceral Obesity and metabolic complications

A number of prospective studies have shown that abdominal obesity is a major risk factor for the onset of type 2 diabetes which in turn increases the risk of retinopathy, neuropathy, nephropathy and atherogenic macrovascular disease[3]. Obese individuals with visceral adipose tissue distribution are more likely to have high triglyceride and low levels of high density lipoprotein. Despite this, viscerally obese individuals tend to have low density lipoprotein(LDL) levels in the normal range, yet have increased levels of apolipoprtotein B (a marker of the concentration of atherogenic lipoproteins)[6]. This observation indicates that doctors need to look carefully at results of cholesterol and LDL levels and interpret these in the context of whether the patient has visceral adiposity or not.

A prospective study of a group of asymptomatic middle aged men, who were followed up over a period of five years, indicated that a group of metabolic abnormalities found in viscerally obese men was associated with a significant increase in coronary heart disease risk. This group of deranged metabolic parameters included: fasting hyperinsulinaemia, increased small dense LDL particles and increased apolipoprotein B concentration, even in

the absence of type 2 diabetes was seen to be associated with a 20 times increase in risk of developing ischaemic heart disease in a five year follow up period in this group of men. [7]

The metabolic syndrome

The prognostic significance of increased waist circumference has been incorporated in the criteria used to identify persons with features of the metabolic syndrome. In the USA, the National Cholesterol Education Program- adult treatment panel III (NCEP-ATP) drawn criteria dating from 2001 include i) waist circumference (>102cm for men and >88cm for women) ii) elevated TG, iii) Low HDL cholesterol, iv) high BP and v) high FPG. The International Diabetes Federation (IDF) has made the presence of abdominal obesity a requirement for the diagnosis of metabolic syndrome along with any other 3 criteria from the NCEP-ATP III. Indeed the IDF sets lower cut–off points (men/women) for abdominal circumference, >94/>80 for European area,>90/>80 for South Asian and >85/>90 for Japanese persons [8].

How to identify high risk individuals with visceral adiposity?

It is indeed difficult in our practice, to use costly MRI or CT to determine if an individual who is obese, has visceral adiposity, as this would be too costly and involves irradiating the patient. We have come to realise that BMI does not provide a reliable indication of the extent of intra-abdominal adiposity. Fortunately anthropometric studies have shown that **abdominal circumference** (measured at mid- distance between bottom of ribcage and iliac crest) not only predicts presence of visceral adipose accumulation but also allows follow up over time. It is also difficult in practice to determine fasting insulin levels and apolipoprotein levels; however it has been shown that the **plasma triglyceride concentration measured in the morning after a 12hour fast** is a reliable indicator of small dense LDL[6, 9].

Sensitivity and specificity of abdominal circumference and triglyceride levels as predictors of hyperinsulinaemia and increased apolipoprotein B have been tested in an analysis of a sample of men aged 30 and 65 years [10]. This analysis has shown that a cut-off point of 90cm waist circumference provides the best discriminative ability to distinguish men with hyperinsulinaemia and high apolipoprotein B levels from those with normal levels. A cut off level of 2mmol/l fasting triglyceride concentration is the best predictor of the presence of small, dense LDL. Using these parameters one can identify correctly 80% of individuals, with only 10% being missed[10]. **These results highlight the importance of the measurement and correct interpretation of waist circumference and fasting TG concentration - *The Hypertriglyceridaemic waist.***

Short overview of the adipokines

Visceral obesity promotes increased secretion of a range of metabolites and biologically active substances from fat tissues, including free fatty acids (FFA), inflammatory mediators e.g. Tumor necrosis factor (TNF) and interleukin-6(IL-6), plasminogen activator inhibitor-1(PAI-1) and C- reactive protein.

Atherosclerosis has been shown to have an inflammatory component and adipokines may be involved in atherogenesis in abdominally obese individuals[12]. IL-2 is a systemic adipokine, and it impairs insulin sensitivity and is also a major determinant of hepatic production of C-reactive protein (CRP). Thus levels of CRP are elevated in persons who have abdominal obesity and conversely individuals with elevated CRP tend to have intra abdominal adiposity[13].

Adiponectin a cardioprotective adipokine is found to be decreased in abdominally obese individuals[11]. Chronic pancreatic exposure to FFA disrupts-cell function and acute exposure of skeletal muscle to elevated levels of FFA induces insulin resistance[14,15]. Adiponectin has also been shown to improve insulin sensitivity and glycaemic control and its levels correlate positively with levels of HDL-chol and inversely with TG or PAI-1[16]

Interventions in the management of Obesity

Treating obesity is a big challenge and often the outcome is unsuccessful or partially so. Current management guidelines promote the use of lifestyle interventions, primarily diet and exercise, as these have the potential to improve both cardiac and metabolic risk factors. These may be coupled with direct treatment of individual complications of obesity such as dyslipidaemia, diabetes and hypertension. However, sadly enough, lifestyle interventions are often unsuccessful, due in part to lack of patient compliance. Given this scenario pharmacotherapy is justified to control an elevated cardiometabolic risk.

Recent research has determined that over activity of the endocannabinoid system acting via the CB_1 receptor is an important factor in the pathogenesis of cardiometabolic risk[17]. CB_1 receptors have been identified in many organs including the adipose tissue, liver, skeletal muscle and centrally in the hypothalamus. Endogenous cannabinoids are derivatives of arachidonic acid and stimulate CB_1 receptors to cause a number of metabolic effects notably; decreased glucose uptake by skeletal muscle, hyperphagia, increased lipogenesis both in liver and adipose tissue and decreased adiponectin production[17] . Thus any substance which blocks CB_1 receptors would counter act these effects.

Rimonabant has been developed as the first CB_1 receptor blocker and has undergone extensive evaluation in patients with obesity and other metabolic disorders in the Rimonabant in Obesity (RIO) trial programme. This comprised four 1-2 year Phase III trials (RIO-Lipids[18], RIO-Europe[19], RIO North America[20], and RIO Diabetes[21]) in over 6600 overweight/obese patients on a mild hypo-caloric diet (reduced by 600 kcal daily) assessing the efficacy and safety of rimonabant 5 and 20mg /day.

RIO-Europe studied a group of obese (BMI>30kg/m^2)or overweight(BMI>27 kg/m^2) patients with a minimum of one cardiovascular risk factor such as treated or untreated dyslipidaemia or hypertension while the RIO-Lipids trial observed obese or overweight patients with untreated dyslipidaemia such as

elevated triglycerides or total cholesterol:HDL ratio. In the RIO Diabetes, a group of 1047 diabetic patients (BMI 27-40) receiving metformin or sulphonylurea were followed-up to evaluate the effect of rimonabant not only on reduction of weight and waist circumference but also on HbA1C. In the RIO NA trial patients were re randomised after a year to carry on treatment with rimonabant or receive placebo. In all trials, after 1 year, rimonabant significantly ($P<0.001$) reduced weight and waist circumference to a greater extent than placebo; mean weight loss was -6.5kg and a decrease in abdominal circumference of -6.4cm was observed (pooled data RIO-NA, RIO-EU and RIO-Lipids). The same dose of rimonabant also effected a reduction in triglyceride level and increase in HDL levels. In the RIO Diabetes study, a significantly greater percentage of patients also achieved the clinically significant end-point of HbA1c<6.5% as compared to those receiving placebo (42.9% vs 20.8%; $p<0.001$). Rimonabant 20mg daily also resulted in an increase of plasma adiponectin of 57.7% (repeated measurements method). Statistical analysis showed that these changes were partly independent of weight loss alone and attributable to a direct effect of rimonabant through its blocking action on the CB_1 receptor.

Rimonabant was generally well tolerated, the most frequent adverse effect resulting in discontinuation were depression, anxiety and nausea. In conclusion, selective CB_1 receptor blockade with rimonabant decreases waist circumference and body weight and thus as shown earlier, modifies the metabolic risk factors in high risk obese or overweight individuals[22].

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