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The epidemiology of abdominal adiposity

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Chapter 1

General Introduction

BACKGROUND

1. Obesity – definition and classification

Obesity has become a major global public health issue and its prevalence has increased drastically over the last decades among all ages (1,2). The increased availability and consumption of high energy dense foods, containing high levels of saturated fats and refined sugars combined with physical inactivity, have probably led to this rise (2). It is estimated that by 2015 the populations of overweight and obese adults will increase to 2.3 billion and 700 million respectively and that the number of overweight children under the age of five will be over 42 million (2).

Obesity is associated with increased risk of type 2 diabetes, hypertension, cardiovascular disease and breast cancer (3-5) and may significantly impair individuals' quality of life (6). Therefore, this condition and associated complications have a substantial impact on countries health care systems and the economic burden is only likely to increase as the prevalence of overweight and obesity rises. Furthermore, the obesity epidemic is not restricted to developed countries, but it is also affecting developing countries, where this condition often co-exists with undernutrition (2) creating a 'double burden' of disease that threatens to overwhelm the health services of many of these countries (7) .

Table 1: WHO classification of weight status in adults

BMI	Classification
< 18.5	underweight
18.5–24.9	normal weight
25.0–29.9	overweight
30.0–34.9	class I obesity
35.0–39.9	class II obesity
≥ 40.0	class III obesity

Source: Adapted from WHO, 2000

Obesity is clinically defined as a condition of fat accumulation associated with increased morbidity and mortality (2). Body mass index (BMI) is commonly used to classify overweight and obesity in adults (Table 1). It is a simple index of weight-for-height and it is defined as the weight in kilograms divided by the square of the height in metres (kg/m^2). In children, the relationship between BMI and adiposity is age and sex dependent due to changes in body composition during growth (8). Therefore, age and sex-specific BMI cut off values are used and overweight and obesity are commonly classified using the 85th and 95th percentiles cut offs respectively (8, 9). In children under the age of 2 years, overweight is defined by weight-for-length $\geq 95^{th}$ percentiles (9).

2. The importance of fat distribution

Although excess body weight is predictive for total body fat and remains an important indicator of weight-related illness, anatomical distribution of body fat is at least equally if not more significant. Numerous epidemiological studies have demonstrated that increased abdominal adiposity may contribute to the development of the cluster of metabolic risk factors (glucose intolerance, insulin resistance, low concentrations of HDL-cholesterol, elevated triglycerides, hypertension and obesity) (10-13). In the 1940s, Jean Vague already demonstrated that an android or male fat pattern, which consists of greater fat in the upper body region, is related to unfavourable metabolic profile. In contrast, a gynoid or female fat pattern, with relatively greater fat in the hip and thigh areas, is not associated with metabolic complications of obesity (14). Therefore, the accumulation of fat in different body compartments may carry differential metabolic risks (15). In particular, the visceral adipose tissue (VAT) compartment, which is located inside the peritoneal cavity between the abdominal organs, may be a unique pathogenic fat depot (16-18). VAT has been found to be more closely related to obesity-associated pathologies and complications than either total adipose tissue (TAT) or subcutaneous adipose tissue (SCAT) (19, 20). VAT is considered to be more sensitive to lipolytic stimuli than the other adipose tissues (21). Visceral obesity leads to an increase in the production of free fatty acids, which then accumulate in ectopic sites such as the muscle, in the liver and in the pancreas leading to insulin resistance and impaired beta cell function (the two key features in the development of type 2 diabetes). Free fatty acids also provide substrates for hepatic triglycerides production and thus may contribute to dyslipidemia (22). VAT also releases free fatty acids directly into the portal vein and therefore into the liver causing reduced hepatic insulin clearance and increased gluconogenesis in the liver (21, 22). The ratio between different abdominal fat regions, VAT to SCAT, has also been found to be an important indicator of an unfavourable metabolic profile (23). Taksali and colleagues have suggested that individuals with a high proportion of visceral fat relative to abdominal subcutaneous fat have more adverse metabolic profiles compared to those with the opposite phenotype (23).

Although VAT has been found to be the most strongly related fat depot to metabolic disturbances, the role of SCAT in disease risk is still controversial. A recent animal study has demonstrated that subcutaneous fat has a beneficial effect on glucose metabolism when transplanted subcutaneous flank fat from donor mice into subcutaneous or visceral regions of recipient mice (24). However, earlier studies in humans had shown that removal of subcutaneous fat by liposuction does not result in changes of any aspect of metabolic syndrome, but no human studies have yet examined the possible beneficial metabolic effects of subcutaneous fat (25, 26). Other studies in humans, have suggested that in some non-Caucasian populations, abdominal subcutaneous fat might actually have a deleterious role and it might be a significant predictor of adverse metabolic consequences (27-29). Therefore, accurate quantification of both VAT and SCAT mass in large studies and in different settings might help to elucidate the metabolic differences between these two abdominal fat depots.

3. Critical time periods for fat accumulation

Several epidemiological studies have shown that early life factors such as impaired or excess weight change, as well as periods of rapid ‘catch up’ growth, might be important in promoting obesity and associated co-morbidities (30-34). Intrauterine environment and rapid weight gain after birth have been suggested to contribute significantly in programming body composition and growth (35, 36). Foetal growth restriction is known to impact on adipose tissue development *in utero* (37) and low birth weight has been associated with a tendency to store fat centrally (38-40). Furthermore, children who were born small and showed catch up growth in the first 2 years of life had greater percentage body fat and central fat distribution than other children at age five years (41). However, these studies mainly focused on overall adiposity and central adiposity, whereas very few have distinguished between the contributions of visceral and subcutaneous abdominal fat compartments. In the first two years of life, there is substantial increase in total body fat which rises from 12% at 0.5 months to 25.4% at 24 months (42). However, the time course for the development of VAT is poorly defined in the literature and there are no published data that have examined longitudinal changes in VAT and SCAT in the first years of life. Uthaya and colleagues have found that newborns with low birth weight have increased VAT at birth (43). Therefore it would be important to more precisely characterise the timing of the development of this fat compartment in early life; and investigate whether early life factors that have been related to long term obesity and related metabolic complications may be associated with the quantity of visceral fat. Accurate and widely applicable measures of these abdominal fat depots are needed to help answering these key questions.

4. Measurements of abdominal fat distribution

Imaging techniques such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) represent the gold standards for the quantification of visceral and abdominal subcutaneous adipose tissues (44). However, the routine use of these methods is limited in large-scale-population studies and repeated investigations due to ethical and practical constraints, mainly due to burden to participants, analytical cost, limited availability of those instruments for research purposes, poor co-operation when dealing with children and exposure to significant quantity of ionising radiation (CT only) (44-46). Furthermore, these methods are unlikely to be feasible between the ages 3-4 months to 5-6 years as sedation or general anaesthesia is usually required for clinical scans at these ages.

Epidemiological studies generally implement simple anthropometry (e.g. BMI, waist-to-ratio, skinfolds and waist and hip circumference) to evaluate adiposity as they correlate with metabolic markers and imaging estimates (47). However, these measures are poor at discriminating visceral from subcutaneous fat regions (48, 49) and they are often characterized by low accuracy and reproducibility (50, 51). Anthropometry may also not adequately describe ethnic variations of these fat regions. For instance, at the same adiposity, Caucasian adults and children have been found to have higher visceral adipose tissue and lower subcutaneous fat than their Black counterparts (52-58). Furthermore, anthropometric indicators may not capture body composition changes that occur with aging (49). Muscle mass decreases, fat mass increases and becomes more centralised in the abdominal region (49).

Ultrasonography has been suggested to be an alternative method to estimate fat distribution (44, 59-61), it can accurately differentiate subcutaneous from visceral fat compartments and, it has been demonstrated to be a non invasive, reliable and reproducible method for the determination of these fat regions when compared to both CT and MRI techniques (44, 59-61). Therefore, this technique has the potential to be a valuable tool for the assessment of possible risk factors associated with obesity. However, those validation studies were carried out in women, obese adults and patients with diabetes, its validity in different age groups and ethnicity is yet to be proven.

OBJECTIVES OF THIS THESIS:

In this thesis, I therefore assess the validity of ultrasonography to estimate the visceral and subcutaneous abdominal fat compartments in populations covering a wide range of ages. I then apply these measures to examine the role of early life factors that may influence the quantity of these fat depositions.

Specifically, I formulated the following objectives:

1. To investigate the validity and reproducibility of ultrasonography for the measurement of abdominal adiposity in different age groups (during infancy, childhood, adolescence, and in the elderly) and different ethnic populations (Caucasians and Black South Africans).

2. To identify possible early life factors that could influence the quantity of visceral and subcutaneous fat.

OUTLINE OF THE THESIS:

The first part of this thesis (Chapters 2-4 and the first part of Chapter 6) focuses on the validity of ultrasonography to estimate abdominal fat compartments in different populations. In chapter 2, I assessed the validity of ultrasound measures of visceral and subcutaneous abdominal fat in older men and women, compared to MRI. I explored whether the addition of ultrasound measures to conventional anthropometry would increase the accuracy to predict these abdominal fat compartments. It was essential to validate the ultrasound protocol in an adult population as this method was applied in the study described in chapter 5. Chapter 3 tested the accuracy of the prediction equations for estimating VAT and SCAT developed in chapter 2 in South African adolescents using MRI measures as criterion; and derived new prediction models specific for this population. Chapter 4 describes the validation of ultrasonography and anthropometric measures to assess abdominal adiposity in prepubertal children. In chapter 6, I assessed the validity of ultrasound to estimate abdominal adiposity in newborn infants.

In the second part of this thesis, I applied these ultrasound measures to explore the role of early life determinants of the abdominal fat depositions. In particular, in chapter 5, I investigated the associations between birth weight and adult visceral and subcutaneous-abdominal fat using ultrasonography in adults in the population-based Fenland Study. I hypothesized that birth weight might have differential associations with adult visceral and subcutaneous-abdominal fat. Chapter 6 examines the changes in abdominal fat during infancy and identifies associations between early growth parameters and different abdominal fat compartments in the first year of life in the Cambridge Baby Growth Study. I also explored whether early nutrition (e.g. breastfeeding and formula feeding) were related to these abdominal compartments.

Finally, in chapter 7, the main findings are summarised, methodological issues are discussed and implications for future research are addressed.

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