

# Body fat distribution and insulin resistance



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Obesity is defined as an excess accumulation of body fat associated with increased fat cell size and number. Obesity is a common and serious medical problem worldwide, especially in industrialised countries, but the prevalence of obesity is also increasing in developing countries such as South Africa.<sup>1</sup> One of the key factors accounting for this may be increased urbanisation.<sup>2</sup> The movement of populations from rural to urban areas is associated with major changes in lifestyle, particularly the increased availability of calorie-dense foods and drinks. Although obesity is associated with social stigma in Western countries, public opinion of obesity and overweight in the Middle East and Africa is different, being associated more with health and wealth.

Obesity occurs when energy intake is greater than energy expenditure. The surplus energy will be stored as fat in the adipose tissue. In the last decade there has been a plethora of data relating to the fact that adipose cells are not just a storage depot for excess calories; rather they are metabolically active tissue. Leptin, and more recently a number of additional hormones, growth factors and cytokines,<sup>3</sup> have been reported to be secreted by adipocytes and to have paracrine as well as endocrine effects on a variety of target tissues. It is also known that the different fat depots in the body have different metabolic activities and this may relate to their differential effects on insulin sensitivity.

## Measurement of body fat distribution

The technology revolution has offered many new techniques to measure body fat distribution in humans. Some of those techniques are able to distinguish between visceral fat and other fat depots. The most accurate estimates of abdominal visceral fat can be obtained by using imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI).<sup>4</sup> Dual-energy X-ray absorptiometry (DEXA) is another imaging technique that can be used to measure total body fat and abdominal fat.<sup>5</sup> Frequency of measurements is limited owing to cost, and with CT, exposure to radiation.<sup>4,6</sup>

The simplest and most commonly used indicators of body fat distribution are waist-to-hip ratio (WHR) and waist circumference (WC). WHR is considered to be a robust measure of metabolic risk in many population studies. However, many scientists in the field prefer WC because of its simplicity of measurement and its strong correlation with visceral fat distribution.<sup>7</sup> WC is also more strongly associated with metabolic function in children<sup>8</sup> and adults<sup>9</sup> than WHR. Furthermore, a high WHR value may be attributed to increased visceral fat and decreased gluteal muscle mass.<sup>10</sup>

## Fat distribution

Many factors are involved in the control of body fat distribution, with gender, age and ethnicity considered to be the most important factors.<sup>11</sup> When fat is located predominantly in the upper body this pattern has been termed android, central, male or upper-body segment, and is found frequently in men.<sup>12</sup> When fat tissue accumulates predominantly in the lower body it is termed gynoid and this pattern is found more frequently in women.<sup>12</sup> It is known that women have more fat than men even when matched for body mass index (BMI).<sup>13,14</sup> This sex difference is caused by greater subcutaneous adipose tissue in females.<sup>15</sup> This gender difference is already observed in the first year of life and even prenatally.<sup>16</sup> Studies<sup>17,18</sup> have also shown that elderly individuals tend to accumulate excess abdominal fat.

The importance of fat distribution has been gaining much attention because of the relationship between the accumulation of fat in the abdominal region and an elevated risk of many diseases such as hypertension,<sup>19,20</sup> type 2 diabetes mellitus,<sup>21,22</sup> cardiovascular disease,<sup>23,24</sup> stroke<sup>20</sup> and breast cancer.<sup>25,26</sup>

The importance of fat distribution was first highlighted in the 1940s when Jean Vague<sup>27</sup> noticed that subjects with an android body type have an increased risk of developing certain diseases compared with subjects with gynoid body fat distribution.<sup>27</sup> In 1983 Krotkiewski *et al.*<sup>28</sup> predicted that visceral fat may be of particular importance for metabolic aberrations because of its unique position and relationship to the portal circulation.

## Aetiology of abdominal obesity-related insulin resistance

Insulin resistance is the impaired ability of insulin to control hepatic glucose production and to enhance glucose clearance in target tissues.<sup>29</sup> Insulin resistance also leads to the impairment of other biological actions of insulin, including its effect on lipid and protein metabolism, vascular endothelial function and gene expression. The cellular demand for insulin increases as cells become more insulin resistant. The body can overcome this by secreting more insulin from the pancreatic beta cells and by reducing hepatic clearance of insulin. This increased demand on the beta cells may lead to progressive loss of beta cell function, secondary to exhaustion of their secretory capacity. This combination of insulin resistance and beta cell dysfunction characterises type 2 diabetes mellitus.

The metabolic syndrome is a grouping together of metabolic abnormalities in subjects who often display abdominal obesity. These subjects are often dyslipidaemic, insulin-resistant, have raised fasting glucose levels and are hypertensive. It has been suggested that insulin resistance is the primary aetiological factor for the metabolic syndrome,<sup>30</sup> and a number of factors have been implicated in the aetiology of insulin resistance arising from abdominal obesity.

Different fat depots vary in their responsiveness to hormones that regulate lipolysis, with the visceral depot being less responsive to the antilipolytic action of insulin.<sup>31</sup> The resulting high rate of free fatty acid (FFA) turnover in the visceral fat depot has an important physiological consequence, because of the direct link between the visceral depot and the liver through the portal vein.<sup>32</sup> The delivery of FFA into the portal circulation by the visceral fat depot may lead to increased triglyceride and glucose synthesis and reduced hepatic clearance of insulin.<sup>32</sup> Therefore, it has been hypothesised that the FFAs released from the visceral adipose depot are important factors contributing to the relationship between visceral fat and reduced insulin sensitivity. However, a recent study<sup>33</sup> has shown that the visceral adipose depot contributes only 5% of the FFAs present in the portal circulation in lean subjects and 20% in obese subjects,<sup>33</sup> suggesting that other factors may be more important in contributing to the insulin resistance associated with the visceral adipose depot.

Another possible cause of the reduced insulin sensitivity observed in subjects with increased abdominal girth is the cytokine, tumour necrosis factor alpha (TNF $\alpha$ ). This molecule is an adipocyte secretory product that may play a role as a mediator of insulin resistance in infection, tumour cachexia and obesity. This cytokine is also present at higher concentrations in subjects with abdominal obesity.<sup>34</sup> Studies of cultured cells have demonstrated that TNF $\alpha$  causes decreased expression of the insulin-sensitive glucose transporter 4 (GLUT4), the

protein largely responsible for glucose uptake into insulin-sensitive tissues such as fat and skeletal muscle.<sup>35</sup> TNF $\alpha$  also inhibits activity of the intracellular signalling pathway that is stimulated by the binding of insulin to its receptor.<sup>35</sup>

Adipocytes secrete a number of other cytokines including interleukin (IL)-6, IL-8 and IL-18. IL-6 is known to be secreted at higher levels from visceral than subcutaneous adipocytes<sup>36</sup> but its involvement in the aetiology of insulin resistance has recently been questioned.<sup>37</sup> IL-8 production has also been shown to be higher in visceral than subcutaneous adipocytes<sup>38</sup> and serum concentrations correlate positively with measures of insulin resistance.<sup>39</sup> The cytokine IL-18 has also been shown to correlate positively with both the level of visceral adiposity and insulin resistance.<sup>40,41</sup>

## Ethnicity and body fat distribution

A number of studies have shown that body fat distribution varies from population to population. Thus, South Asians in the UK were found to have a greater level of abdominal fat than Europeans,<sup>42</sup> and Asian Indians in the USA were found to have high body fat levels relative to BMI and muscle mass.<sup>43</sup> These differences have also been observed in newborn Indian subjects.<sup>44</sup> Such differences in body fat distribution were found to be associated with high blood pressure, high triglyceride and lower high-density lipoprotein (HDL) cholesterol levels and high fasting and post-oral glucose insulin levels. Studies in South Africa have also demonstrated higher WHRS in Indian than African subjects.<sup>45</sup> Investigations in both the USA<sup>46</sup> and South Africa<sup>47</sup> have shown that the visceral fat depot is smaller in black than white subjects matched for BMI and this may explain the less atherogenic lipid profile observed in the black South African population.<sup>48</sup> However, the former population group is more insulin resistant than the white population.<sup>49</sup> This suggests that either visceral fat plays no role in the aetiology of insulin resistance or that visceral fat in black subjects is more effective at influencing insulin sensitivity than in white subjects. A study<sup>50</sup> has now shown that WHR in black South African females is positively associated with fasting serum triglyceride levels and insulin resistance.

## Visceral versus subcutaneous abdominal fat

More than other patterns, increased absolute intra-abdominal fat has been linked to an increased risk of developing certain diseases.<sup>51</sup> However, abdominal adipose tissue comprises both visceral and subcutaneous fat, and there is some controversy regarding the relative contribution of each of these depots to the aetiology of

the metabolic dysfunction observed in abdominally obese subjects. Relationships have been observed between insulin sensitivity and the level of abdominal subcutaneous fat.<sup>52,53</sup> However, a recent study<sup>54</sup> has shown that removal of subcutaneous abdominal fat by liposuction has no effect on insulin sensitivity or fasting serum lipid levels and many researchers report that visceral adipose tissue is the stronger determinant of insulin resistance.<sup>55-57</sup> Another recent study,<sup>58</sup> however, has shown that both visceral and subcutaneous abdominal fat levels are related to insulin sensitivity. These discrepant results may be due to the fact that there is no definition of what constitutes visceral or subcutaneous adipose depots.<sup>59</sup> Indeed, it has been suggested that the subcutaneous abdominal adipose depot be regarded as two compartments, the superficial and the deep, separated by the fascia superficialis. The size of the deep subcutaneous depot has been shown to correlate strongly with the level of insulin resistance<sup>60</sup> and to have a higher lipolytic rate than the superficial subcutaneous abdominal fat depot.<sup>61</sup> Such studies suggest that the visceral fat depot, in combination with the deep subcutaneous depot, both contribute to insulin resistance.

## Conclusions

Abdominal obesity is associated with reduced insulin sensitivity and is one of the defining characteristics of the metabolic syndrome. The mechanism by which increased fat deposition in the abdomen may lead to insulin resistance is not fully known; however increased FFA and cytokine production have been implicated in this process. The relative contribution of visceral and subcutaneous adipose tissue to insulin resistance is a matter of great debate, however the division of the subcutaneous depot into deep and superficial layers may provide a mechanism by which the true involvement of the subcutaneous abdominal depot in the aetiology of insulin resistance can be investigated. Future studies to determine the control mechanisms involved in abdominal fat accumulation may provide novel forms of treatment for type 2 diabetes and the other chronic disorders associated with visceral obesity. Genetic studies have already demonstrated that up to 50% of the variance in abdominal fat mass is accounted for by genetic factors,<sup>62</sup> suggesting that the development of therapies targeting visceral fat accumulation may not be out of reach.

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