It's not only the Overweight: It's the Visceral Fat

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Overweight and obesity (body mass index > 25 kg/m^2) are associated with overall and cause-specific mortality. A recent collaborative analysis of 57 European and North American studies with 894,576 adults showed progressive excess mortality mainly due to vascular diseases [1]. Median survival was reduced by 2–4 years at 30–35 kg/m^2 and by 8–10 years at 40–45 kg/m^2. Like the rest of the world, Israel is experiencing an accelerated increase in obesity as reflected in the MABAT cross-sectional study. In this study obesity prevalence reached 40.4%, with the highest rates observed in Arab women [2]. In the United States, it is well recognized that if obesity trends continue the negative effects will outweigh the benefits gained from declining smoking rates [3]. The enormous burden of the obesity pandemic in terms of health-associated costs of abnormal life expectancy and quality raises crucial questions about treatment priorities. The novel distinction between metabolically "healthy" and "unhealthy" obese subjects may help in such decision-making processes [4].

It is more than 25 years since Per Bjorntorp, a Swedish pioneer in metabolic research, introduced the idea of different patterns of fat distribution. Based on cross-sectional and prospective epidemiologic studies, he suggested a specific relationship between abdominal obesity and metabolic complications [5,6]. Thereafter, the emergence of abdominal obesity as a critical component of the evolving "insulin resistance syndrome," later replaced by "the metabolic syndrome," led to definitions of waist circumference ≥ 102 cm in males or ≥ 88 cm in females, based on the 1998 U.S. National Institutes of Health obesity clinical guidelines. The International Diabetes Federation's definition insists on obesity as an essential component of the diagnosis, with adjustment for different ethnicities [7]. In agreement with this approach, we observed that obesity was the major factor associated with elevated C-reactive protein in subjects with the metabolic syndrome [8]. The separation of the typical gluteo-femoral female fat distribution (pear shape) from the male abdominal fat distribution (apple shape) was quantitated by waist to hip ratios defining acceptable and unacceptable cutoff points for men and women.

These recommended surrogate markers of adiposity (BMI, waist circumference and W:H ratio) are relatively easy to perform but do not reliably distinguish between a large abdomen due to an increase in subcutaneous adipose tissue and visceral fat. Visceral fat is located inside the peritoneal cavity and is composed of ectopic depots residing in mesenteric, epididymal and peri-renal sites requiring special imaging techniques. Liver, muscle and heart are other problematic sites of fat distribution. A cause-effect relationship between the size of the visceral fat and comorbidities is mainly linked to insulin resistance, high triglycerides, low high density lipoprotein, high glucose, high blood pressure, atherogenic lipoprotein patterns, and secretion of pro-inflammatory cytokines [9]. The INTERHEART study emphasized the importance of fat distribution for predicting cardiovascular risk in 27,000 individuals in 52 countries. Markers of abdominal obesity were significantly more important than BMI: subjects with normal range BMI and high W:H ratio had a higher risk than those with a BMI of 30 kg/m^2 but low W:H ratio [10]. The latter has gained much support from biological studies, adding evidence to the epidemiologic association. With an increase in visceral adipose tissue, free fatty acids are easily directed to the liver for enhanced production of glucose, triglycerides and very low density lipoprotein. Moreover, fat cells located in ectopic locations are characterized by severe metabolic derangements, which explain their systemic effects. For instance, glucose transporters were significantly decreased in human omental adipocytes, explaining insulin resistance [11]. Furthermore, visceral fat adipokines were measured in the portal vein of extremely obese subjects during bypass surgery. Portal vein interleukin-6 concentration was substantially increased and correlated strongly with systemic inflammation, as indicated by high CRP levels [12]. Not surprisingly, macrophage infiltration triggering inflammatory molecules and pathways were enhanced in omental versus subcutaneous fat from subjects with obesity (and also in lean subjects) [13,14].

With the evidence suggesting visceral fat as a common denominator of a morbid course of obesity (and metabolic syndrome), the article by Dicker and co-researchers in the current journal is highly relevant [15]. In general, obesity management involves lifestyle modification with

BMI = body mass index
W:H = waist:hip

CRP = C-reactive protein

pharmacotherapy and surgery in selected cases, depending on BMI risk category. An optimal goal is a 10% weight loss over the initial 6–12 month period. Adopting the same lines of treatment in a small case series of obese subjects (BMI 34 ± 3 kg/m^2), a hypocaloric diet and the lipase inhibitor orlistat (Xenical®, Roche, Israel) achieved a modest weight loss of 8.4% with a 15.4% decrease in total abdominal tissue mass, as measured by computed tomography using a 3D program. During 20 weeks follow-up, visceral adipose tissue was reduced by 24.8%, while subcutaneous adipose tissue was reduced by 12% only. The observation that a mean body weight reduction of 8 kg was accompanied by a significant improvement in metabolic risk factors – namely, LDL-cholesterol, triglycerides and fasting blood glucose – is noteworthy. This is novel proof of the preferential response of different adipose sites to a weight-losing regimen (orlistat in this case). Such an effect is necessarily not unique to a specific weight-reducing agent.

When sibutramine (Reductil®) was added, a significant visceral fat loss, measured by CT, with 11% total weight loss, followed [16]. Subjects with abdominal obesity were treated with rimonabant (Acomplia®) in a placebo-controlled prospective design. A cross-sectional area of subcutaneous adipose tissue was reduced by 5.1%, compared to placebo, with a 10.1% reduction in visceral adipose tissue as measured by CT. Liver fat and multiple cardiometabolic risk markers were improved during one year of treatment [17]. Using a different quantitative methodology, abdominal ultrasonography revealed a strong correlation between weight loss achieved by bariatric surgery, the degree of visceral fat loss and the reduction in liver steatosis [18]. Evaluation by magnetic resonance imaging showed a preferential visceral fat loss compared to total and subcutaneous adipose tissue loss in a small group of women after gastric banding [19]. These diverse studies demonstrate the feasibility of visceral fat loss and its analysis in the context of obesity management using different imaging modalities (CT, MRI, ultrasound). Is such an approach practical? The answer is a mixed one: expense and radiation exposure (in the case of CT) argue against. On the other hand, better understanding of "bad" vs. "good" fat patterns and their response to different therapeutic programs should be obtained. Development of a reliable bedside technology to assess deep fat depots is mandatory.

Meanwhile, the important recognition of different patterns of abdominal fat distribution is further supported by the recent Framingham Heart Study, which involved participants aged 52 who were evaluated by CT for fat compartments. More than 40% had visceral obesity that in many cases was not properly classified by BMI and waist circumference [20].

In conclusion, the study by Dicker et al. [15] reinforces our understanding that it is time to improve obesity risk stratification, not only for treatment of obese and overweight patients but also for targeting and measuring visceral fat content for better management of severe obesity-related complications.

LDL = low density lipoprotein

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