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Review

Should visceral fat be reduced to increase longevity?

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ABSTRACT

Several epidemiologic studies have implicated visceral fat as a major risk factor for insulin resistance, type 2 diabetes mellitus, cardiovascular disease, stroke, metabolic syndrome and death. Utilizing novel models of visceral obesity, numerous studies have demonstrated that the relationship between visceral fat and longevity is causal while the accrual of subcutaneous fat does not appear to play an important role in the etiology of disease risk. Specific recommended intake levels vary based on a number of factors, including current weight, activity levels, and weight loss goals. It is discussed the need of reducing the visceral fat as a potential treatment strategy to prevent or delay age-related diseases and to increase longevity.

Contents

Abbreviations: T2DM, type 2 diabetes; CVD, cardiovascular disease; MetS, metabolic syndrome; BMI, body mass index; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; CR, calorie restriction; GH, growth hormone; 11β HSD-1, 11β hydroxysteroid dehydrogenase type 1; MCP-1, monocyte chemoattractant protein-1.

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1. Introduction

The prevalence of overweight (body mass index > 25) and obesity (body mass index > 30) has reached epidemic proportions in most of the developed world. Obesity increases the risk for several co-morbidities including type 2 diabetes (T2DM) (Monzillo et al., 2003), stroke (States et al., 2009), cardiovascular disease (CVD) (Tarantino et al., 2012), and metabolic syndrome (MetS) (Tarantino et al., 2009), the further expression of which is hepatic steatosis. The risks associated with obesity have been extended to cancer (Calle et al., 2003; Donohoe et al., 2011) including, prostate (Freedland and Platz, 2007), breast (Protani et al., 2010), liver (Kawai et al., 2011), kidney (Renehan et al., 2008), colon (Dignam et al., 2006), ovarian (Bandera et al., 2009), and endometrial cancers (Chia et al., 2007).

2. Visceral fat and disease risk

The fundamental cause of obesity is a long-term imbalance in energy intake and expenditure (i.e., positive energy balance) leading to the increased body mass including the accumulation of subcutaneous and visceral fat. Although general obesity is an important risk factor for many diseases, several human studies have demonstrated that visceral fat accrual, which is the fat located in the viscera, as most strongly related to many health conditions, including CVD, insulin resistance and T2DM (Carr et al., 2004). The mechanism(s) linking visceral fat with the MetS is not entirely clear, but it has been suggested to involve its anatomical location, leading to a 'portal' effect of greater free fatty acids (FFA) and glycerol release (Cohen-Mansfield and Perach, 2011). Evidence has shown that adipose tissue is an active endocrine organ, capable of secreting many cytokines, often referred to as adipokines, that can promote inflammation and interfere with insulin action (Harwood, 2012). Furthermore, some studies have shown that subcutaneous and visceral fat are biologically distinct, with visceral fat demonstrating far greater pro-inflammatory characteristics than subcutaneous fat. In the remainder of this review, we will discuss (1) the epidemiologic and surgical data in humans linking visceral fat and not subcutaneous fat to disease, (2) epidemiological and experimental data in humans linking visceral fat accretion to mortality risk and lifespan, and (3) treatment strategies aimed at reducing disease risk by depleting visceral fat stores.

3. Epidemiologic studies

The ability to prevent or delay the onset of disease is a critical determinant of lifespan. Some diseases are not treatable or preventable and have an inheritable component of risk. However, the leading causes of death and co-morbidities in humans, including CVD, stroke and T2DM are age-related conditions that can be largely prevented or delayed by lifestyle interventions (Selwyn, 2007). Epidemiologic studies have revealed that a common yet preventable risk factor for these diseases is the accumulation of visceral fat, which is a hallmark of aging in humans (Tchkonia et al., 2010). Using either waist circumference and/or waist-to-hip ratio as a proxy of abdominal obesity, numerous studies have found that visceral fat is a stronger risk factor for insulin resistance, T2DM (Jenum et al., 2012), CVD (Foster et al., 2011a), stroke (Walker et al., 1996) and heart failure (Nicklas et al., 2006) than body mass index (BMI) or other fat depots.

Contemporary clinical and epidemiological studies from China, Japan and Korea indicate that fatty liver is more often associated with visceral fat than with alcoholism (although the latter remains important!) (Finelli and Tarantino, 2012a).

However, the hazards of abdominal obesity are not only limited to metabolic disorders, but also to cognitive decline (Anstey et al., 2011), Alzheimer's disease (Naderali et al., 2009) and disability (Vincent et al., 2010).

4. Liposuction of subcutaneous fat

Several studies have reported on the metabolic consequences of surgically removing large quantities of subcutaneous fat by liposuction. The general premise of these studies is that absolute fat mass is the most important contributor to obesity-related complications such that large-scale removal of abdominal subcutaneous fat should improve several metabolic parameters including insulin sensitivity. Results from these studies have been contradictory, some of them showing beneficial effects of liposuction on insulin sensitivity (Benatti et al., 2011; Mohammed et al., 2008; Saleh et al., 2009; Hong et al., 2006) but others not (Foster et al., 2010, 2011b,c). Moreover, only one study reported an improvement in the blood lipid profile, but not in insulin sensitivity (Benatti et al., 2011). It has been suggested that the conflicting nature of these studies is due to several uncontrolled confounders including the way that insulin sensitivity was assessed, failure to match properly for baseline parameters, poor control of behavior confounders after the procedure and the removal of varying amounts of subcutaneous fat (Klein et al., 2004).

A study by Klein et al. (2004) attempted to definitively address the potential of liposuction as a tool to treat obesity-related metabolic disorders by controlling for the aforementioned confounders. In a study consisting of 15 obese patients (8 non-diabetic controls and 7 T2DM patients) with similar BMI, several metabolic parameters were assessed before and 10–12 weeks after having ~10.5 kg of subcutaneous abdominal fat removed. Utilizing the euglycemic–hyperinsulinemic clamp procedure, they found that liposuction did not significantly alter insulin action in muscle, liver, or adipose tissue, or plasma levels of C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), adiponectin, glucose, insulin, blood lipids and blood pressure. Therefore, surgically removing large quantities of subcutaneous abdominal fat does not appear to be sufficient to improve metabolic parameters, and suggests that subcutaneous fat is not an important component of obesity-related metabolic disorders in humans.

5. Visceral fat and mortality risk

Several studies have reported that obesity, generally defined as a BMI > 30, increases the risk of disease specific and all-cause mortality (Davey Smith et al., 2009; Ryan, 2010; Bender et al., 1999; Wong et al., 2011) and reduces life expectancy (Finkelstein et al., 2010). Obesity has not only been linked to a reduced life expectancy but also to accelerated aging as demonstrated by obese women having telomeres that were 240 bp shorter lean women of a similar age (Valdes et al., 2005).

Since abdominal obesity, assessed by waist circumference or the waist-to-hip ratio in large population studies, has emerged as a stronger predictor of disease risk than BMI, studies have begun assessing the mortality risk posed by abdominal obesity (Boggs et al., 2011; Price et al., 2006; Berrington de Gonzalez et al., 2010). Wannamethee et al. (2007) found that a particularly high waist circumference (>102 cm), waist-to-hip ratio (top quartile), and a composite of waist circumference and sarcopenia were the strongest predictor of mortality in men. Another large cohort study in Europe reported that general (BMI) and abdominal adiposity (waist circumference; waist-to-hip ratio) are both strong predictors of mortality risk but that the importance of abdominal obesity

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