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Metabolic complications of obesity: inflated or inflamed?

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Abstract

Adipose tissue dysfunction rather than excess adipose tissue mass (defined as obesity) is mechanistically related to development of metabolic diseases traditionally linked to obesity: metabolic syndrome, type 2 diabetes and cardiovascular disease. Inflammation of adipose tissue seems to be an important manifestation of adipose tissue dysfunction and closely relates to insulin resistance, the mediator of obesity-related morbidity. However, it is not completely clear whether inflammation in adipose tissue leads to first, local, and then systemic insulin resistance or insulin resistance leads to adipose tissue inflammation, which, in turn, increases insulin resistance. These questions can only be answered by studying models of insulin resistance, independent of obesity. The conceptual shift from adipose tissue mass to adipose tissue function will have significant diagnostic and therapeutic implications. Our efforts in establishing markers to identify "at risk" population and finding newer therapeutic agents must focus on adipose tissue dysfunction and not on obesity alone.

Keywords: Inflammation; Adipose tissue; Type 2 diabetes; Insulin resistance; South Asians

1. Introduction

Obesity is steadily increasing in prevalence in United States and other developed and rapidly developing nations with an unprecedented increase in childhood obesity as well. The US statistics shows that one in five Americans is obese. Various insurance company data suggest that obese individuals are more likely to use health care facility than nonobese individuals in the same age range. Obesity is observed to be the major culprit for growing prevalence of type 2 diabetes in epidemic proportions globally (WHO). Current prevalent view is that obesity leads to insulin resistance, which, in turn, promotes development of type 2 diabetes, dyslipidemia and related cardiovascular disease (Reaven, 1988). However, the popular notion regarding the metabolic risks and death associated with obesity is ambivalent. The Center for Disease Control (CDC) data regarding obesity and death (Mokdad, Marks, Stroup, & Gerberding, 2004), which were needed to be revised (Mokdad, Marks, Stroup, & Gerberding, 2005) due to controversy about the statistical bias, do not help the public perception on obesity either. Furthermore, it is becoming increasingly evident that there are significant ethnic differences in susceptibility to metabolic complications of obesity, particularly type 2 diabetes (NHANES, 1999-2000). In fact, World Health Organization and the international diabetes foundation (IDF) now suggests lower cutoff for body mass index (BMI) and waist circumference for ethnic groups like Asians, who are more susceptible to diabetes and cardiovascular disease, than for persons of European descent (Caucasians) (International diabetes foundation; WHO).

Metabolic changes mediating increased morbidity and mortality risk in obesity is determined by functional changes in adipose tissue of obese people. Increasing evidence demonstrates that adipose tissue functions as an endocrine

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organ and is involved in regulation of various metabolic pathways. In this review, we will evaluate some of the evidence to support the need for a conceptual shift from fat "quantity" to adipose tissue "function" in the evaluation of metabolic implications of obesity.

2. Is obesity risk overinflated?

A simple and visual definition of obesity is excessive body fat. However, in epidemiological literature, marker of obesity is BMI (weight in kg/height in m^2). Over the past decade, a large body of literature, both epidemiological and cross sectional, has accumulated, underlying the correlation between obesity and increased mortality due to cardiovascular disease. Even a modest increase in body weight is thought to result in a four-fold increase in the risk of cardiovascular disease in both men and women. The surgeon general announced the cutoff of BMI >30 as obese and >25 and <30 as overweight. Many celebrities from Hollywood and in the field of sports fell in overweight or obese category with these BMI definitions due to higher muscle mass and, thus, higher total body weight, and this has caused disbelief in public opinion regarding risk of obesity.

The studies linking obesity and increased mortality as well as beneficial effects of weight loss are not conclusive and have many confounding variables like physical inactivity, low socioeconomic status and low education levels, to name a few. Furthermore, the association between BMI and mortality appears to be highly age-dependent in a study that showed a steady decline in mortality due to obesity with age until about 74 years, after which there appears to be no correlation between BMI and mortality (Stevens et al., 1998).

The distribution of adipose tissue is important when considering the risk of obesity. Cardiovascular and metabolic risk is more closely associated with truncal obesity. The literature is full of references to so-called visceral fat, which, in many instances, means waist circumference and also includes abdominal subcutaneous fat. Several investigators have demonstrated that truncal subcutaneous adipose tissue is a strong predictor of insulin resistance (Abate, Garg, Peshock, Stray-Gundersen, & Grundy, 1995; Klein, 2004). One clinical method to assess for upper body or truncal obesity is measuring waist circumference. Waist circumference is a predictor of both subcutaneous and visceral adipose tissue quantity. Adult Treatment Panel III (ATP III) guidelines (Table 1) have defined that a waist circumference of >40 in. in men and >35 in. in women to be considered as truncal obesity (National Cholesterol Education Program (NCEP), 2002). These cutoffs are largely derived from data pertaining to Caucasians and do not seem to apply to Asians. Lower cutoffs are suggested for other ethnic groups like Asians and Europeans by IDF (International diabetes foundation). However, different cutoffs for waist circumference for different ethnicities lead to more complicated algorithms in our multicultural society and appears to not have the necessary impact in identifying people at risk by medical community in the fields.

3. Are all obese people metabolically unhealthy?

When we focus on obesity as expression of fat mass, we are not taking into account a large body of literature, which supports the notion that not all obese individuals have similar metabolic risks. One of the major factors playing an important role is lifestyle. It is evident that physical inactivity plays a major role in accumulation of fat. Therefore, data reported on obesity do not routinely correct for physical activity. One recent epidemiological study has reported that among the obese women, those who had 3.5 h or more of physical activity per week had decreased relative risk of mortality, compared to obese and inactive women, but did not reach the level of risk seen in the lean inactive women (Hu et al., 2004). In this study, weight and exercise patterns were self-reported. Various well-planned studies have shown that active obese individuals have lower morbidity and mortality than normal-weight individuals who are sedentary. One study measured all parameters of obesity as well as fitness in detail and showed that a lean unfit individual has higher risk of mortality than an obese fit individual (Wei et al., 1999). Similarly, adiposity does not lead to attenuated response to physical activity and fitness.

Some recent studies have shown that cardiovascular risk among obese subjects varies substantially, depending upon the level of other risk factors associated with obesity. These risk factors are abnormalities of glucose metabolism, dyslipidemia as well as hypertension. The constellation of features seen as complications of obesity is termed as *metabolic syndrome* (Table 1). However, the prevalence of metabolic syndrome, benchmark of increased cardiovascular risk, is also not uniformly high in obese subjects. The CDC data shows that with increasing prevalence of obesity, there is an increase in the prevalence of type 2 diabetes (National Institute of Diabetes and Digestive and Kidney Diseases, 2004). However, only about 12% of US adult patients with BMI ≥27 kg/m^2 have type 2 diabetes mellitus. Conversely, 67% of US patients diagnosed with type 2 diabetes mellitus have a BMI ≥27 kg/m^2, while 46% have a BMI ≥30 kg/m^2 (National Institute of Diabetes and Digestive and Kidney

Table 1
ATP III definition of metabolic syndrome

Three of the following in any combination	
Abdominal obesity (waist circumference)	
Men	>40 in.
Women	>35 in.
Triglycerides	>150 mg/dl
HDL cholesterol	
Men	<40 mg/dl
Women	<50 mg/dl
Blood pressure	>130/85 mmHg
Fasting glucose	>100 mg/dl