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DIABETES + INSULIN RESISTANCE (M RUTTER, SECTION EDITOR)

Understanding the Obesity Paradox in Type 2 Diabetes Mellitus

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Abstract The term "obesity paradox" corresponds to the research observation that overweight or obese patients may counterintuitively have a survival benefit once a disease is established. This appears also true in type 2 diabetes mellitus, where it has been shown that being overweight or obese is associated with better survival. The reasons behind this paradox remain unclear but likely derive from an intricate relationship between insulin resistance, fat storage, and inflammatory responses in type 2 diabetes. In this review, we look at what the potential mechanisms may be underlying this paradox.

Keywords Type 2 diabetes mellitus · Obesity · Overweight · Insulin resistance · Obesity paradox · Body mass index

Introduction

According to the World Health Organization report in 2008, over 1.4 billion adults were overweight and over half a billion were obese, and overall, obesity is associated with early mortality accounting for 3.4 million excess deaths each year. It is also noted that being overweight or obese is linked to a greater proportion of excess deaths worldwide than being underweight [1]. Obesity has a significant impact on health and well-being and is also associated with various comorbidities including type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, fatty liver, obstructive sleep apnea, cardiovascular disease, renal disease, increased risk for several cancers, poor mental health and well-being, and reduced quality of life.

The incidence of T2DM is increasing in parallel with obesity and approximately 347 million people have diabetes worldwide, and by 2030, diabetes will be the seventh leading cause of death. Diabetes is associated with microvascular (nephropathy, retinopathy, and neuropathy) and macrovascular complications through stroke, ischemic heart disease, and peripheral vascular disease [1].

The term "obesity paradox" corresponds to the research observation that overweight or obese patients may have a survival benefit once a disease is established. It was first described in 1999 in overweight and obese people undergoing hemodialysis for end-stage renal disease [2] and has subsequently been found in those with heart failure [3], hypertension [4], myocardial infarction [5], and peripheral artery disease [6].

Further evidence has arisen from a study we performed in patients with T2DM where comorbidities and cancer were taken in account that showed in patients with T2DM, being overweight or obese, compared to being normal weight, was associated with a higher risk of non-fatal cardiovascular events, but was not associated with an increased mortality. Indeed, the body mass index (BMI) associated with the best survival was shifted from the conventional "normal weight" (18.5–25 kg/m^2) to the "overweight" (25–30 kg/m^2) BMI category [7].

T2DM induced by the "metabolic stress" of obesity may be a fundamentally different problem from T2DM that develops in the absence of obesity [8]. Patients with T2DM who are obese may reverse their diabetes phenotype with weight loss

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[9]. Those with a greater genetic susceptibility to T2DM may be more likely to develop T2DM at a lower BMI "stress" and might also be at greater risk of the development of early complications of T2DM and consequently may have a poorer prognosis [10].

Attention is also shifting from that of being "weight centric" to that of the general fitness of patients; obesity may be an inexact surrogate for the subject's level of fitness [11•]. In a general population, exercise capacity on a treadmill has been shown to predict cardiovascular events better than BMI, and in men with T2DM, those who were overweight or mildly obese but physically fit were less likely to have cardiovascular events than those of normal weight but physically unfit [12, 13].

There are several other possible explanations for the obesity paradox. Patients with T2DM and a low BMI might have higher tobacco and alcohol consumption, contributing both a lower BMI and conferring an adverse prognosis through increased cardiovascular risk [14, 15]. Another possible explanation is that obese patients may be more likely to be screened earlier for diabetes leading to earlier diagnosis and the benefit of earlier intervention. Being overweight might provide a metabolic reserve in older patients, protecting against frailty, malnutrition, and osteoporosis [16, 17]. Age-related sarcopenia may be a more important medical problem than obesity [18, 19].

T2DM and the Relationship to Obesity

The incidence of type 2 diabetes is increasing in parallel with obesity, and the majority of patients with T2DM are overweight or obese as classified with a BMI greater than 25 kg/m^2. Only approximately 15 % of patients with T2DM are of normal weight (BMI 18–5–25 kg/m^2) [20, 21]. Therefore, despite the apparent reduced survival of normal-weight patients with diabetes, this represents a relatively small percentage of the population. However, the controversy still remains: why do overweight and obese patients survive longer? The answer may be found in a fundamental issue that has not been fully resolved yet: what exactly is T2DM? T2DM is a complex disorder that is likely to have many genetic and environmental causes rather than having a single causative etiology leading to a chronic, progressive metabolic disease characterized by the presence of chronic hyperglycemia [22]. It was rare before the twentieth century, and its epidemic was systematically described by Joslin who linked it to obesity [23]. In the 1930s, Himsworth deduced that "there were insulin sensitive patients whose diabetes was due to insulin deficiency and insulin insensitive patients whose diabetes was due to resistance to insulin" [24].

Anthropometric studies "to define the diabetic phenotype in the 1940s noted that patients attending a New York diabetic clinic were slender if young and more adipose when the disease presented in later life" [25]. John Lister in 1951 "combined anthropometry with Himsworth's insulin sensitivity test and noted the distinctive phenotype of the older insulin-insensitive patients, whom he referred to as type 2," in contrast to the less distinctive type 1 patients [26]. The terminology did not catch on until the 1970s. In fact, "the concept of type 1 diabetes as an immune-mediated disease emerged over the period from 1974 to 1976 and showed many of the features of a classic paradigm shift" [27].

> Although Harley, a British physician, commented in 1866 that "there are at least two distinct forms of the disease [diabetes] requiring diametrically opposing forms of treatment," the French physician Lancereaux is generally credited with making the distinction between fat and thin diabetes: "diabete gras" and "diabete maigre" [28, 29].

Interestingly, since then, in principle, the treatment has not dramatically changed. Clinicians sorted their patients according to the triad of age of onset, perceived requirement for insulin, and body mass, just as they do to this day. However, historically, there has been a substantial overlap between the two forms of diabetes that has likely contributed to the obesity paradox with those patients having absolute or relative insulin requirements being associated with lower weight levels and higher mortality risk.

T2DM Physiopathology

It is widely accepted that T2DM is a disease whose course is primarily characterized by insulin resistance and decline in β-cell function. Hence, controlling the hyperglycemia is the main treatment for T2DM with a combination of diet and lifestyle, drugs that enhance peripheral insulin sensitivity (Metformin as first line), or drugs that may increase insulin secretion or action on peripheral tissue, finally leading to therapy with exogenous insulin.

However, the mechanisms leading to this metabolic dysfunction have not been clearly defined as yet. Historically, overweight and obesity have been considered the main risk factors to develop T2DM [30].

It is now recognized that T2DM is not due to simple obesity though it is still not clear what the initiation of the process is for the development of T2DM and whether T2DM is the cause or result of that weight gain. Likely, it is a complex interaction between genes and the environment, and identifying the initial insult by identifying those triggers for the initial obesity and insulin resistance have implications for both prevention and treatment [31].

To understand that, it must be taken into account that the diet is an environmental and behavioral factor that plays a fundamental role in the development of T2DM. The Pima Indians population gives an interesting epidemiological example. They are one of the ethnic groups with the highest incidence of T2DM. However, until the traditional Pima diet of grains, squash, melons, and legumes, supplemented by gathered desert plants, had not evolved to a more American diet, T2DM was uncommon. Previous observations suggested that diabetes was either rare or largely unrecognized among Pimas around the 1900s [32, 33]. "At that time, increasing settlement of the area by people of European derivation led to diversion of the Pimas' water supply and disruption of their agriculture" [33]. "The loss of water resulted in curtailment of subsistence farming and led to fundamental changes in their way of life" leading to shift their diet to American standards [34]. Likely, this change triggered the development of T2DM in the population.

Therefore, understanding the complexity between genetics and diet in this population has been a key goal over the past few decades. However, despite several studies, a clear picture of genetic and environment interaction has yet to be described [35].

Insulin Resistance, Evolutionary Perspective

From an evolutionary point of view, human survival has been enabled by the ability to withstand starvation in times of famine by storing excess energy as fat. This ability has enhanced the capacity to fight off infection by mounting a pro-inflammatory immune response and the ability to cope with physical threats by an adaptive stress response [36]. "The excess energy needed in these situations is provided by mobilization of stored energy substrates. The requirement for energy storage is essentially served by the anabolic actions of insulin. Following food intake, insulin secretion by pancreatic β cells facilitates the storage of glucose as glycogen in the liver and skeletal muscles, and the deposition of fatty acids in the form of triglycerides (TGs) in adipose tissues. The stored energy can then be mobilized during fasting, infection, trauma, or stress, by the action of catabolic hormones or factors with anti-insulin effects" [37].

The negative regulation of insulin signaling could be considered "as a physiologic adaptive mechanism that is activated whenever the organism needs to switch from an anabolic to a catabolic or an insulin resistance state and mobilize energy, primarily in the form of glucose released from the liver and free fatty acids released from adipocytes, to support vital metabolic processes". Therefore, "in this state, insulin-dependent glucose uptake in muscle and adipose tissue is inhibited while hepatic glucose production and adipocyte lipolysis are disinhibited" [38•].

Modern man has inherited the same mechanism for fat storage but lives in a different environment characterized by continuous exposure to "high-energy food intake and low physical activity. Modern lifestyle favors positive energy balance that, in the long term, creates the need for surplus fat storage. When the capacity for safe lipid storage in adipose tissue is exceeded, then lipid overflow to non-adipose tissues occurs" such as muscle and liver. This is more likely to occur in individuals with dysfunctional adipose tissue associated with central obesity [38•]. Therefore, theoretically, the capacity of safe lipid storage may represent a paradoxical beneficial adaptive evolutionary process in the context of the sedentary modern lifestyle. In fact, those who cannot safely store the excessive energy intake may appear superficially healthier by not gaining weight, however, may be more exposed to the detrimental effect of a failure of safe fat deposition.

Obesity Paradox, Insulin Resistance, and Inflammation

Increasing evidence has implicated insulin-resistant conditions of T2DM, glucose intolerance, and metabolic syndrome with chronic activation of the acute inflammatory response [39]. The hypothesis is that the chronic low-grade inflammation and activation of the immune system that occurs in T2DM may be because of the presence of one or more specific triggers like overnutrition or altered nutrition [40]. The pattern of modern life (high calorific food availability and sedentary lifestyle) is associated with an imbalance between high-energy intake and energy expenditure. The amount of energy that exceeds the adipose tissue storage limits tends to accumulate in locations not classically associated with adipose tissue storage (ectopic) fat such as muscle and liver [41].

It is unclear why ectopic fat deposition occurs in some individuals but not others, but a number of potential mechanisms have been proposed. One hypothesis suggests that, in states of positive energy balance, excess free fatty acids are initially stored subcutaneously, but once that capacity is reached, storage shifts to ectopic sites, including the viscera, heart, peripheral muscles, and vasculature [42, 43]. This failure of the subcutaneous tissue to store additional free fatty acids is believed to result from a failure of proliferation and differentiation of adipocytes leading to subcutaneous adipose hypertrophy as opposed to hyperplasia [43, 44]. Consistent with this theory, the degree of subcutaneous abdominal adipose cell hypertrophy has been shown to predict the development of type 2 diabetes mellitus [44].

Alternatively, there is the concept of "metabolically benign obesity" [45]. It is now well known that there are people who are classified as obese according to their BMI; however, they show signs of having metabolically benign obesity that has lower visceral, liver, and muscle

fat content than those BMI-matched "insulin-resistant obese people. This finding suggests that metabolically healthy but obese people have a better ability to trap free fatty acids in adipose tissues" [46]. However, it is unclear why these subjects express a favorable metabolic profile, and it is likely that a combination of environmental (i.e., diet components, fitness) and genetic factors produces a "healthier" obesity profile.

Individuals who are not able to "safely" store free fatty acid in adipose tissue may chronically induce the innate immune system (i.e., activation of macrophages, dendritic cells, Kupffer cells in the liver) to clear free fatty acid from the circulation. These inflammatory cells may then act as dysfunctional adipocytes producing adipokines and cytokines. In addition, stressed (hypertrophied) adipocytes attract immune cells (among which are macrophages) into the interstitial vascular tissue [47]. "Eventually, however, a positive feedback cycle is formed in which activated macrophages recruit more immune cells and a state of chronic inflammation is induced. Some of the cytokines and adipokines produced interfere with adipocyte differentiation," and others induce insulin resistance through modified intracellular insulin signaling mechanisms. "Some, like TNF-α and IL-6, impair adipocyte differentiation, reduce lipid accumulation, and increase adipocyte lipolysis" [48].

The cause for adipose tissue dysfunction and ectopic fat storage is unknown. Blüher recently proposed a model in which genetic, environmental, and behavioral factors are involved in excess energy intake. The inability to store excess calories in "healthy" subcutaneous fat depots may initiate several mechanisms including adipocyte hypertrophy, autophagy, and inflammation that are activated either in sequence or in parallel, ultimately leading to adipose tissue dysfunction [49•]. However, "little is known about the genetic factors determining of adipocyte number, differences in body fat distribution, or their association with metabolic disorders" [49].

There is experimental evidence that "fat distribution rather than BMI and total fat mass underlie the risk for metabolic diseases in obese individuals. Significant reduction in subcutaneous fat mass by liposuction does not improve circulating metabolic and inflammatory parameters" [50]. "Whereas reduction of visceral fat mass by omentectomy in addition to gastric banding has significant beneficial and long-term effects on measures of glucose metabolism and insulin sensitivity in obese individuals" [51, 52]. Interestingly, an experimental study in rodents showed that increasing subcutaneous adipose tissue, by performing a fat mass transplantation, had positive metabolic effects in rodents, with improved glycemic control and insulin resistance [53].

Therefore, it appears that "increased adipose tissue mass and higher risk for obesity-related disorders are not necessarily directly related to fat mass. Adipose tissue dysfunction and ectopic fat accumulation seem to be important factors determining the individual risk to develop metabolic and cardiovascular comorbidities of obesity" and directly related to chronic inflammation.

Conclusion

The obesity paradox in T2DM implies that overweight and obese subjects benefit from enhanced survival. The mechanisms are still unclear and possibly multifactorial, with interplay between imbalance in energy intake and expenditure, genetic predisposition in storing fat safely, and chronic induction of the inflammatory response. What is clear is that the estimation of fat mass with BMI does not properly reflect an increased risk of adverse events.

Compliance with Ethics Guidelines

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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