OBESITY – BETWEEN NORMALITY AND PATHOLOGY

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Abstract

There are large amounts of evidence that obesity has many metabolic complications, notably dyslipidemia and metabolic syndrome, which increase the risk of developing type 2 diabetes mellitus and cardiovascular diseases. A unique subgroup of obese individuals, that seems to be protected against obesity related complications, has been identified so that obesity may be not paradigmatically associated with comorbidities. The purpose of this review was to investigate the roles of some metabolic factors, body composition, cardiovascular disease risk in metabolically healthy obese (MHO) individuals, and to emphasize metabolic and clinical characteristics of this subset of obese subjects. MHO individuals, despite their high fat mass, compared with at risk obese subjects, show a normal metabolic profile with remarkably normal to high levels of insulin sensitivity. Compared to "at risk" obese, this subgroup has lower visceral fat mass, that could explain insulin sensitivity, and early onset of obesity. Recent study suggest that MHO subject, also, have a favorable inflammatory profile with less C-reactive protein and IL-6 concentrations. We also analyzed the conclusions of different studies which had as a purpose to determine the role of diet in treatment of MHO subjects. A better understanding of metabolic healthy obesity individuals has important implications for medical education and research.

Obesity as an important public health problem

It is well known that obesity is a heterogeneous disorder with several possible etiologies and that this disorder represents a major public health problem whose prevalence has been rising in developing countries as well as in developed countries [1].

Despite the important impact on public health care system, primary and secondary prevention efforts have failed, till now, to offset the obesity epidemic [2]. This is the reason for public health officials to try mobilizing resources to combat this epidemic by developing more effective and rigurous strategies for treating people who are obese and to prevent the development of obesity and obesity related complications. An important public health goal is to mitigate undesirable weight gain and its effects on metabolic syndrome phenotypes. One of the major challenges in this field is related to the inability of investigators to adequately determine or characterize factors able to distinguish one subtype of obese individual from another. Thus, the identification and eventual treatment of individuals susceptible or at risk to develop metabolic syndrome

should be considered as a step in primary prevention efforts.

Obesity, clinical atherogenic expression of increased adiposity, is widely accepted to be an important risk factor for cardiovascular diseases and metabolic disorders such as diabetes mellitus, high blood pressure, dyslipidemia.[3,4] Also, obesity has been reported to be related to IFG (impaired fasting glucose)[3], insulin resistance, hypertension, levels of total cholesterol and tryglicerides, and low levels of HDL cholesterol[5-7].

Metabolically healthy obese individuals – unique subset of obese

In the 1980s, several researchers [8-10] began to speak about different subtypes of obesity and at the moment it is reported the presence of a subgroup of metabolically healthy obese (MHO) individuals. These subjects appear to be protected or more resistant to the development of metabolic disorders associated with obesity. Despite their large quantities of fat mass, the MHO individuals demonstrate surprising normal to high levels of insulin sensitivity and, very interesting, favourable cardiovascular risk profiles, characterised by normal lipid and inflammation profiles and no sign of high blood pressure(Figure 1)

Figure 1. Metabolic characteristics of metabolically healthy obese and "at risk" obese

Insulin sensitivity of metabolically healthy obese subjects

The prevalence of metabolically healthy obesity is of approximately 20-30% [13]. Ferrannini et al. lead a study in which were performed 1146 hyperinsulinemic/ euglycemic clamp studies in 20 clinical centers from Europe. They reported less insulin resistance in obese subjects than previously thought. This extremely large study emphasize the idea that there are subsets of certain obese subjects with high levels of insulin sensitivity despite their consistent body fat.

Metabolically healthy obese individuals are of interest because they may be a model that may provide insight into the pathogenesis of insulin resistance in humans. Also, they are a potentially clinical challenge in that they may require a different therapeutic strategy.

It is possible that the higher insulin sensitivity may be due to a primary genetic metabolic event such as genetic variations in genes involved in lipid metabolism that contributes to a protective metabolic profile but at the same time influences the early onset of future obesity. Hepatic lipase (LIPC), adiponectin receptor 1 (ADIPORI) and upstream transcription factor 1, that has modulatory effects on hepatic lipase, may be implicated in developing metabolically healthy obesity.[13]

An important question remain about whether there are another metabolic phenotypes that may be particular to the metabolically healthy obese subjects and potentially provides some explanations to their favorable profile. Brochu et al. classified MHO subjects based on a cut-off point for insulin sensitivity using the hyperinsulinemic /euglycemic clamp and at risk obese subjects with impaired insulin sensitivity. The use of the clamp to identify MHO individuals is given the importance of insulin action in the metabolic syndrome. After categorization of these subjects another question appeared: other phenotypes track with the insulin sensitivity values.

A general belief based on different studies, conducted over the past decades, suggests that a high insulin sensitivity is associated with higher muscular mass. Despite limited scientific data to support the idea that muscle mass is associated to insulin sensitivity or insulin resistance, we may sustain this to the fact that muscle mass is the organ of glucose storage and utilization.

Visceral fat area vs. total body fat content

A study from 2004 performed by You et al.[14] reported that the metabolic syndrome was associated with high lean body mass and high visceral fat content in older obese postmenopausal women. On the other hand, Karelis et al. [23] in their study dedicated to inflammatory profile of MHO individuals discovered that lean body mass and visceral content in metabolically healthy obese subjects were significantly lower than at risk subjects. The explanation of investigators is that high lean body mass could be considered as a potential modulator of insulin resistance in sedentary obese postmenopausal women.

There are data suggesting that a lower visceral content, despite high body fat content, and a lower accumulation of fat within ectopic sites may be the response to the favorable

metabolic profile [15, 16]. Lower visceral fat was found in obese insulin-sensitive subjects compared with obese insulin-resistant individuals, despite almost identical waist circumference [13].

In 2002, Examination Committee of Criteria for "Obesity Disease" in Japan[17], reported that non-obese or obese Japanese subjects with normal visceral fat area had a significant decrease in multiple risk factors related to obesity compared with subjects with high visceral fat area. This study suggested that 100 cm^2 of visceral fat area is a reasonable cut-off point as an indicator to risk disorders and complications related to obesity. Depres and Lamarche [18] showed that visceral fat accumulation greater than 130 cm^2 could be associated with a decrease in insulin sensitivity.

We could not speak about visceral fat without reference to liver fat accumulation, knowing the role of fatty liver in the regulation of glucose and lipid metabolism. and lipid metabolism. That is the reason for that the difference in liver fat between phenotypes is of great importance. Therefore, insulin-resistant obese individuals have 54% more fat accumulation in the liver than insulin sensitive obese subjects which increases the risk of atherosclerosis development. [13]

It is of interest for future investigations the examination of adipocytes as a source of potential differences in insulin sensitivity. Larger adipocytes have been associated with insulin resistance so that the measurement of cell size and number in adipose tissue could explain the higher insulin sensitivity observed in metabolically healthy obese subjects.

Inflammatory profile of metabolically healthy obese individuals

Recent studies show that elevated C-reactive protein (CRP) concentrations are associated with insulin resistance [19,20] and, also, cardiovascular disease [21,22]. Karelis et al.[23] reported that metabolically healthy obese individuals had significantly lower levels of C- reactive protein and α-1 antitrypsin compared with at risk subjects. At the same time CRP levels above 3 mg/liter has been shown to increase the risk of cardiovascular disease. Karelis's study showed that MHO women had 92,7% less CRP levels compared with at risk women. C-reactive protein levels seem to be related and to be a marker of lower visceral fat content, which can be due to lower levels of IL-6. Given that the synthesis of CRP by the liver is largely regulated by cytokine IL-6, the lower CRP levels in metabolically healthy obese persons, are partly attributed to their lower levels of IL-6, preferentially produced in visceral adipocytes.

α1 antitrypsin levels were also significantly lower in MHO individuals compared with at risk subjects [23]. It has been shown that high levels of inflammation-sensitive plasma proteins such as α1 antitrypsin are associated with insulin resistance. Moreover, higher levels of α-1 antitrypsin have been associated with an increased risk of myocardial infarction in men with low and high cardiovascular risk.

Gastrointestinal hormones – the role in obesity

Several hormonal factors, particularly ghrelin and leptin, have been reported to be

involved in the regulation of energy homeostasis and body fatness. Ghrelin and leptin may act as messengers between gastrointestinal tract and adipose tissues (from which they are respectively derived) and the central nervous system.

Ghrelin and leptin levels are reported to be involved in the control of appetite and insulin sensitivity, and their dysregulation may be associated with the development of obesity-related disturbances and complications.

It will be of great interest to measure adiposity and gastrointestinal hormones for better understanding of health profiles of metabolically healthy obese individuals, knowing the fact that adipose tissue secretes potent paracrine/ endocrine factors that influence local metabolism and have effects on other metabolic parameters, including satiety, insulin sensitivity, and energy expenditure. All these parameters could influence body composition of MHO subjects. Proteins such leptin, acylation-stimulating protein, adiponectin, resistin, ghrelin could influence adipose and insulin sensitivity. A key issue is whether metabolically healthy obese subjects have a hormonal profile that distinguishes them from at risk individuals or normal healthy individuals. There are studies [24-27] suggesting that stomach-derived ghrelin and adipose tissue-derived adiponectin are inversely related to insulin resistance. But, accumulation of fat seems to down-regulate ghrelin and adiponectins levels. Resistin, leptin, acylation-stimulating protein are reported to be positively correlated with insulin resistance and visceral fat accumulation [28-30].

Concluding, determining the role of adipose tissue and gastrointestinal profiles could underline the pathophysiology of the protective profile of MHO subject.

Cardiovascular risk profile of metabolically healthy obese subjects

MHO individuals appear to have a more favorable cardiovascular risk profile than insulin-resistant obese individuals, but, in the same time, they show early signs of atherosclerosis compared with lean subjects, which could not be explained by alterations in cardiovascular risk factors. Insulin-like growth factor (IGF)-1 may be implicated in early onset of atherosclerosis because low plasma IGF-1 concentrations are associated with type 2 diabetes mellitus, insulin resistance and increased risk of coronary artery disease [31-33].

Maria Adelaide Marini et. al provide evidence that MHO individuals have a metabolic and cardiovascular risk profile that is intermediate between that observed in healthy nonobese women and that of insulin-resistant obese [34]. Waist circumference was the strongest risk factor, associated with carotid intima media thickness (IMT). Tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), secreted from visceral fat , may be responsible for the relationship between central obesity and early onset of atherosclerosis. Plasma IGF-1 were independently associated with carotid IMT, suggesting that low levels of IGF-1 could contribute to early atherosclerosis found in insulin-resistant obese and metabolically healthy obese women. Also, IGF-1 has an important role in endothelial cells stimulating nitric oxide production and, in the same time,

reduced IGF-1 receptor expression have been found in atherosclerotic plaques [35].

There are studies [36] suggesting that obesity without metabolic syndrome is not associated with increased risk for cardiovascular disease development, but it can be an important risk factor among obese patients with metabolic syndrome.

Oflaz et. al have examined vascular endothelial function, measured by flow-mediated dilation, IMT of common carotid, and anthropometic and metabolic parameters in metabolically healthy obese and lean individuals. Intima media thickness of the common carotid was significantly higher and flow-mediated dilation was significantly lower in MHO individuals despite their favorable metabolic profile. Neither lipid profile, insulin sensitivity, blood pressure, neither anthropometric parameters could not explain the flow-mediated dilation or IMT in the MHO and lean individuals.

We believe in the statement of Karelis that a prudent approach would be that MHO subjects are at lower risk than at risk obese individuals, but at a higher risk than the general population.

What about diet? Are there advantages for MHO subjects?

As we have seen before, metabolically healty obese individuals seem to have a very favorable metabolic profile. This is the reason for that one may even question the need to aggressively treat MHO individuals. Another important question, still unresolved, is whether metabolically healthy subjects would gain any metabolic benefit from weight loss.

There are studies suggesting that weight loss improves insulin sensitivity and metabolic disorders. In the same time these studies show a reduced risk of developing type 2 diabetes mellitus in MHO individuals after weight loss [37]. Other intervention studies have demonstrated that weight loss by energy – restricted diets reduces some markers of inflammation, like C-reactive protein, interleukin-6 and tumor necrosis factor-α. So weight control is recommended for reducing cardiovascular risk and systemic inflammation. Nicklas et al.[38] shows that weight loss has a direct effect on adipose tissue, which increases the production of anti-inflammatory mediators such as IL-10 and IL-1 receptor antagonist, and, in the same time, decreases the production of proinflammatory mediators (Il-6, TNF-α).

On the other hand, in the study of Karelis [39], a diet-induced 5-10% reduction in body weight in obese insulin-resistant women showed unsignificantly improvement in insulin sensitivity. It, also, suggest that a subgroup of insulin-sensitive obese women was resistant to dietary treatment, which may even had a small negative effect. It was examined indirect calorimetry data, which showed insignificant changes in the respiratory quotient that suggest the improvement in insulin sensitivity in at-risk patients without changes in fasting oxidative substrate disposal.

Usually it is forbidden for obese patients to drink alcohol as a restrictive method of diet approach. But, it was discovered that moderate alcohol intake, compared with non-drinking, was associated with lower prevalence of metabolic disorders, since benefits on lipid and glucose metabolism [40].

Physical exercise may be a more appropriate lifestyle intervention for metabolically healthy obese individuals. Physical training was effective in improving whole body insulin sensitivity by 16-49%, with no difference between insulin-sensitive and insulin-resistant subjects [41-43]. It may be possible, for metabolically healthy obese individuals, to be more responsive to physical exercise than to diet restraint.

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