REVIEW ARTICLE

Are There Persons Who Are Obese, but Metabolically Healthy?

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The aim of this article was to review the evidence for a metabolically normal subset of the obese and its implications for clinical and research work. The methods included literature review and correspondence with authors. Since 1947, when Vague described a relation between distribution of body fat and the risk factors for cardiovascular disease, much evidence has suggested that early onset of the obesity, hyperplasia of normal adipocytes, and normal quantities of visceral abdominal fat may be associated with a favorable metabolic response in obese subjects. Analyses in 1973 by Keyes and later by Reuben Andres in 1980 suggested that obesity for some was not a risk factor and might even be an asset. Recently, in the study by Bonora et al of the relation between insulin resistance and the 4 main disorders of the metabolic syndrome in the Bruneck epidemiologic study, a subgroup of obese individuals with a normal metabolic response was evident. In a current study by Brochu et al of an obese metabolically normal subgroup of postmenopausal women, visceral abdominal fat estimated by computed tomography (CT) scan and age of onset were significant variables. The obese, metabolically normal subgroup (OBMN) must be taken into consideration in both clinical and research work. Persons with OBMN and their parents may be wrongly blamed because of the obesity. Attempts at weight loss may be counterproductive. The criteria for selection of obese research subjects may favor inclusion of an OBMN subset, which may invalidate statistical analysis. Findings suggesting the OBMN subset include family members with uncomplicated obesity, early onset of the obesity, fasting plasma insulin within normal range, and normal distribution of the excess fat. Hormonal, genetic studies, and prospective studies will help to clarify the significance and underlying mechanisms of this subset.

AN OBESE PERSON, blamed for taking up too much seating space in airplanes recently described her situation in a letter to a well-known newspaper columnist.[1] "I was fat at age 5, and when I was 8 my mother put me on diet pills. All my father's relatives are large people, but my mother was pretty and slim. . . .When my younger sister turned out to be a fat child too, the problems confounded. We were constantly told that no one would ever love us if we didn't lose weight. . . . .I was teased mercilessly at school, and never had a social life as a teenager.

I have joined TOPS (Take off Weight Sensibly) and Weight Watchers, tried every fad diet. . . .I have lost (and gained) hundreds of pounds, and have had my thyroid checked repeatedly. . .I eat moderately, avoid junk food, do not binge, and walk three miles a day. I swim twice a week, take the stairs instead of the elevator, and park my car far away so that I have to walk farther. I am not a glutton."

Obesity has been increasing at a rapid rate over the past century until it has now reached epidemic proportions.[2] Those who are genetically susceptible have gained weight as technology has reduced the need for physical exertion, and hedonic foods high in fat and carbohydrate have become increasingly available. The problem is currently gaining public attention. The New York Times has run a series of reviews of this problem. In considering childhood obesity Karlota[3] describes a 17-year-old Olympic champion weight lifter, 5 feet 9 inches and 300 pounds, who is content with her obesity and raises the question "should parents try to make their fat children thin?"

This review addresses the evidence for a subtype of metabolically normal, healthy obese individuals (OBMN), their evaluation and management, and indications for further research to clarify this question.

EVIDENCE SUGGESTING A METABOLICALLY HEALTHY SUBSET OF OBESE PERSONS

Early Suggestions of a Metabolically Normal Subtype of Obesity

In 1947, Vague[4,5] concluded that android obesity, with upper body predominance and pronounced muscle development, is associated with metabolic and cardiovascular disturbances. In contrast, gynecoid obesity, with predominance of lower body fat, and less muscular development, mainly presents mechanical and aesthetic problems. In 1954 Albrink[6] reported that upper body obesity, based on measurements of skin-fold thickness, was associated with disorders of blood lipids. In 1968 Salans et al[7] reported that adipocyte size varied inversely with their insulin sensitivity, and that obesity with normal sized adipocytes was associated with onset in childhood.[8]

A relation between insulin resistance and the metabolic disorders, diabetes, hypertension, hyperlipidemia, gout, and increased plasminogen activator inhibitor (PAI-1) is now well established.[9,10] The association is now referred to as the metabolic syndrome of insulin resistance. Ruderman et al[11,12] have shown that normal weight individuals may also have insulin resistance and the disorders of the metabolic syndrome. They designated such individuals as metabolically obese normal

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weight (MONW). Hence, in this review, obese persons who are metabolically normal are referred to as the reciprocal, OBMN.

Critical Analyses of the Relation Between Obesity and Metabolic Disorders

In 1973 at the second Fogarty International Conference on Obesity in Perspective, Keyes[13] reported an analysis of the 7 available epidemiologic studies of the relation between overweight and heart attacks. He concluded that "gross obesity is bad", but that much of the propaganda about overweight went beyond scientific justification and resulted in inappropriate therapeutic programs. Shortly after this, Andres[14,15] also reviewed the major population studies of obesity in relation to mortality and suggested that "there are some poorly understood or entirely unknown benefits of mild or moderate obesity" and that "we have to be very cautious in our weight loss goals". In view of this work, we included a "Healthy Obese" subtype in the classification of obesity.[16]

Ferrannini et al[17] have recently analyzed data from the European Group for the Study of Insulin Resistance, which included 1,146 nondiabetic, normotensive, Caucasian men and women, age 18 to 85 Insulin resistance was measured by the hyperinsulinemic/euglycemic clamp technique. They found that in "simple" obesity insulin resistance is not as prevalent as previously thought and that risk for non–insulin-dependent diabetes mellitus (NIDDM) and cardiovascular disease in the 2 groups may differ. They conclude that sensitivity to caloric restriction by dietary or pharmacologic treatment may differ and require different strategies for follow-up and management.

In Italy, the Brunek population-based study of atherosclerosis and its risk factors included 888 subjects randomly selected, ranging in age from 40 to 79. Bonora et al[18] have recently examined the prevalence in this study of subjects with insulin resistance in relation to the 4 main disorders of the metabolic syndrome of insulin resistance, namely impaired glucose tolerance or type 2 diabetes, dyslipidemia, hyperuricemia, and/or hypertension. Obesity was defined as body mass index (BMI) greater than 25. Insulin resistance was estimated by the homeostasis model assessment insulin resistance (HOMA IR) assay of Matthews et al,[19] validated in 85 subjects by correlation with insulin clamp estimates.

As illustrated in Fig 1, there was a clear correlation between the number of metabolic disorders and the percent of individuals with insulin resistance, but it is the column with 0 metabolic disorders that is very relevant to this perspective. A total of 414 (43%) of the subjects were overweight, with a BMI greater than 25, suggesting that the epidemic of obesity includes Italy, as well as the US, and 95 (23%) of these were free of the 4 metabolic disorders. In 45 (57%) of these subjects, insulin resistance was not increased. Thus 11% of the entire group of overweight subjects fitted the criteria of the Obese Metabolically Normal. This percent would have been higher if those of a young age had been included. In contrast, 85 subjects (9.6% of the 888 subjects) had none of the 4 metabolic disorders, but were nevertheless insulin resistant. These may have been in the early stages of the metabolic syndrome, since insulin resistance may precede overt symptoms by 10 to 20 years.[20,21] This provides an opportunity to initiate preventive measures at a time when they can be most effective.

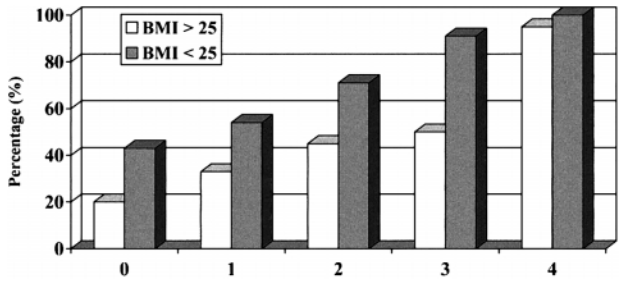

Fig 1. Prevalence of insulin resistance in obese subjects (BMI >25). Relation of the number of metabolic disorders to the percentage of insulin resistance in obese subjects (dark bars) and nonobese subjects (light bars) as defined by BMI. Disorders include impaired glucose tolerance and type 2 diabetes, dyslipidemia, hyperuricemia, and/or hypertension. (Data from Bonora et al.[18])

Brochu et al,[22] at our medical school, recently analyzed the extensive data from 43 sedentary, obese, postmenopausal women, age 50 to 79, who had been subjects from previous research studies. Obesity was defined as body fat greater than 35% estimated by dual energy x-ray absorptiometry. Insulin sensitivity was estimated by the hyperinsulinemic/euglycemic insulin clamp technique. Those with a glucose disposal rate (M-value) less than 8.0 mg/min/kg of lean body mass were classified as abnormal. A total of 26 of the 43 subjects had reduced insulin sensitivity ($P = .0001$) as generally expected in association with obesity, while 17 were obese and metabolically normal. The 2 groups were similar in total body fat mass, subcutaneous fat, as well as waist circumference. Total daily energy expenditure, estimated by the doubly-labeled water technique, resting metabolic rate by indirect calorimetry, and calculated daily physical energy expenditure did not differ signicantly. Increased physical activity is a potent means of reducing or normalizing insulin resistance. Thus, the possibility that the difference in insulin sensitivity was the result of difference in physical activity is ruled out by these measurements. Lean body mass, however, was significantly greater in the metabolically abnormal subjects. By regression analysis, visceral abdominal fat (VAT) measured by computed tomography (CT) scan was inversely related to the insulin sensitivity ($P = .005$). This was not true of the deep layer of the subcutaneous adipose tissue (DSAT), which may affect insulin sensitivity. This is consistent with the finding of Smith and Bray[23] that DSAT did not relate to plasma insulin in women, in contrast to that in men. Early onset of obesity was an independent variable correlating directly with the insulin sensitivity. This is consistent with the recent finding of Muscelli et al[24] that there is a positive association between insulin sensitivity and duration of obesity. In their study, unfortunately, the possibility that longer duration might be explained by a subset of the obese was not considered. As previously described, Salans et al[7] found that adipocyte size varied inversely with their insulin sensitivity, and that obesity with normal-sized adipocytes was associated with onset in childhood.[8] In contrast, Sinaiko et al[25] reports that

weight gain during childhood may be a determinant of cardiovascular disease. Genetic factors must be important here, and a variety of subtypes probably are involved.[26]

IMPORTANCE OF THE OBMN SUBSET IN CLINICAL AND ACADEMIC WORK

In Patient Care

Persons meeting the criteria for OBMN may be analogous to persons who are tall, but not acromegalic. They or their parents should not be blamed for their obesity, and they should not be urged to achieve a "normal" weight. Extreme diets or any of the weight-reducing drugs could have adverse hormonal and other effects and would induce the same adaptive mechanisms to starvation of a person of normal weight.

During the current epidemic of obesity, the overall success rate for losing weight and maintaining the loss is very poor.[2] A healthy obese subset may contribute to this poor record by resisting attempts to reach a supposedly ideal weight and by their strong tendency to regain. This further discourages others attempting to lose weight.

Inadequate Characterization of Subjects in Research

Many epidemiologic and clinical research studies provide limited historical data regarding family history of metabolic disorders, level of physical activity, estimate of insulin resistance, and risk factors. Subjects are often excluded because of one or more of the disorders of the metabolic syndrome of insulin resistance. This, in turn, would increase the proportion of metabolically normal subjects, and if the subset is not identified, may invalidate results of statistical analysis of the data in genetic and other studies.

In Medical Education

For medical students, house staff, fellows, and staff, the experience of fully characterizing patients with obesity and the related disorders may be valuable.

DIAGNOSING THE OBMN SUBSET

The Basic Clinical Workup

This should include (1) a family history of members with obesity of early onset relatively free of the disorders associated with the syndrome of insulin resistance; (2) no evidence of the disorders associated with the metabolic syndrome of insulin resistance; (3) universal distribution of the excess body fat, without visceral abdominal accumulation (obvious "pot belly"); and (4) normal estimate of insulin resistance.

As the computerized clinical record for basic medical workup with efficient collection of data becomes established and generally accepted, inclusion of a diagnostic support system should be useful with respect to OBMN and aid in diagnoses of the disorders associated with obesity. One such program is under development at our school.[27]

Estimation of Insulin Resistance

A practical, relatively inexpensive estimate of insulin resistance would be useful in identifying the OBMN subset. In 1996, the American Diabetes Association (ADA) supported an international Task Force to evaluate the standardization of the insulin assay for epidemiologic and other studies.[28] A host of problems not readily correctible were reported. Even the same assays in different hands produced disparate results. Unfortunately, the evaluation by the ADA task group has not been updated since 1996. Robbins,[29] chair of the 1996 task group, currently advises that caution must be used in comparing the results from an individual with supposed "standards". Today's solid phase automated insulin assays appear to be much more reliable and comparable than those used in the 1996 study, but this is, as yet, unsubstantiated.

Estimates of insulin resistance with 3 levels of practicality are available. (1) The euglycemic/hyperinsulinemic clamp remains the gold standard for measuring insulin sensitivity and glucose production,[30] but this requires overnight admission to a research center, and the stress experienced by the subject may modify the results. (2) Bonora et al[31] have recently reported that the HOMA IR of Matthews et al,[19] requiring only a fasting glucose and fasting plasma insulin measurement, is a practical measure of insulin sensitivity, provided that the assay is sufficiently specific and does not include proinsulin. This is calculated as fasting serum insulin (μU/mL) $\times$ fasting plasma glucose (mmol/L)/22.5. The glucose value does not have to be in the normal range. It is to be hoped that the assay may become standardized and less expensive for use in hospitals and departments of health in the near future. (3) There is now considerable evidence that fasting plasma glucose alone is an adequate indicator of insulin resistance in the general population, provided the plasma glucose is in the normal range.[32] If so, cross-reactivity with proinsulin is unlikely, because this is not increased in normoglycemic insulin-resistant persons.[33]

FUTURE RESEARCH TO CLARIFY MECHANISMS UNDERLYING OBMN

Anatomical Differences Between OBMN and Insulin-Resistant Obese

As previously described, the pioneer studies in Hirsch's laboratory at Rockefeller University[7] indicated that insulin responsiveness was dependent upon adipose cell size. The larger its adipocyte cells, the less insulin sensitive was the tissue.[8] The normal-sized adipocytes were associated with early onset of the obesity. If this is substantiated, biopsy of the superficial layer of subcutaneous adipose tissue with estimation of cell size and number should indicate whether there is hyperplasia of normal-sized adipocytes in those with OBMN.

Genetic Control of the Size of the Subcutaneous and Visceral Adipose Tissue

A knowledge of the genetic mechanisms, which control the size of the adipose tissue masses, might ultimately identify preventive and corrective measures for the obesity of the OBMN subgroup. In the study by Brochu et al,[22] there was a marked difference in the size of the visceral adipose tissue, although the total body fat did not differ significantly. The difference in size of the fat mass between those of lean subjects and that of the OBMN subgroup may also provide a valuable

opportunity to study the genetic control of the size of normal tissues in general. New approaches to explaining the underlying mechanisms are being developed.

Until recently, little was known about the mechanisms required to develop the human embryo from a fertilized egg and to control the size and shape of its components. The 2000 Update of the Human Obesity Gene Map by Perusse et al[34] now lists 250 genes linked or associated with human obesity phenotypes. The investigators warn that some of the loci will turn out to be more important than others, and that many will be proven to be false positive.

The update of the 2000 obesity gene map also includes 15 genes, which are significantly associated with the fat mass or percent of body fat, and 5 genes related to the amount of visceral abdominal fat (VAF). Since the VAF is a major factor in relation to insulin resistance and is of normal size in the OBMN, clarifying its genetic control may be useful in prevention and correction.

Identifying which of the 30,000 genes in the human genome is related to a disorder cannot alone explain the underlying mechanisms, because they mainly serve as recipes for the synthesis of a single protein. Ridley,[35] in his lucid introduction to the human genome, describes how they interact with other genes to produce as many as 300,000 proteins that can then act as building blocks, intracellular messengers, and transporters. Ninety-eight percent of our genes are related to those of a chimpanzee. Many of our genes are in common with genes of the drosophila fruit fly.[36] Some of the genes presumably date from the pre-Cambrian period over 500 million years ago. Thus, the series provides an autobiography of our species. When development of the embryo is initiated, somehow the orientation of the head and tail and of the back and front of the body is identified. The developmental program then starts at the head and prescribes the location, structure, and size of the various tissues. The genes involved are located near the middle of chromosome 12 and are in order corresponding to the sequence in the structuring program. These are known as 'homeotic' genes, and all include a segment known as the homeobox. This produces a protein, which attaches to a strand of DNA, enabling it to switch another gene on and off. All homeotic genes have this capacity as the construction proceeds.

There have been remarkable developments in applying the genetic analysis to medical diagnosis and prevention.[37-39] The recently developed computer chips with large arrays of genes now allow extraordinarily rapid analysis of their association with various conditions.[40] The GeneChip R Test 3 Array (Affymatric, Santa Clara, CA) provides a subset of housekeeping/maintenance genes expressed early in fetal development and in adulthood that may be particularly useful in comparing the OBMN with the insulin-resistant obese.[41]

We cannot expect practical measures for control of obesity to emerge tomorrow from this exciting expansion of knowledge of molecular genetics, but perhaps they are not far off.

Hormonal Factors Affecting Appetite, Energy Balance, and Insulin Resistance

Is the plasma leptin and its response to overfeeding and malnutrition truly metabolically normal in the OBMN? There are many hormonal agents and peptides that affect energy balance and insulin sensitivity.[42] Usually the level in plasma of leptin is increased in obesity. When the adipocyte is overloaded with fat, leptin is released and stimulates its receptor in the hypothalamic paraventricular nucleus to release neuropeptide-Y.[42,43] This, in turn, suppresses appetite and stimulates thyroid function, sympathetic nervous system activity, and thus thermogenesis. All of these effects tend to limit further weight gain.[44] In contrast, during starvation, the concentration of leptin is reduced markedly with a reduction of thyroid activity, decrease in reproductive capacity, and a tendency to store calories as fat.[45] The reaction to starvation may have had survival and evolutionary advantage. Measuring its concentration in the obese, insulin-resistant in comparison with the OBMN subset should be very valuable. It is important, however, to take into consideration its diurnal variation and the relatively brief response to food.

Resistin is a newly discovered hormone,[46] which is secreted by the adipocytes in mice with diet-induced or genetic forms of obesity. Injection of recombinant resistin in normal mice impairs insulin action and glucose tolerance. This may be a link between obesity and diabetes.[47] Circulating insulin concentration is decreased by the antidiabetic drug, rosiglitazone. Resistin may, like leptin, have been selected as an adaptive response to starvation. Comparing the response of the OBMN and insulin-resistant subsets of obesity may also be rewarding.

Prospective Studies

There are, as yet, no prospective studies of persons meeting the criteria for OBMN. Such studies with an adequate initial data base are needed to determine how long the normal insulin sensitivity can be maintained over the life span. At baseline, it should be established that the level of physical activity is not sufficiently above average to explain the normal insulin sensitivity.

CLINICAL CARE OF THE OBESE PERSON WHO MAY BE METABOLICALLY NORMAL

The Need for Follow-Up

If the fasting insulin test and the other findings are normal, it is still possible that the person may be susceptible to the metabolic syndrome of insulin resistance, but has not yet developed the insulin resistance. Also, the apparent subgroup of obese metabolically normal might simply be those in whom increased physical activity and restricted caloric intake have restored insulin sensitivity. An extreme example of this is the Japanese Sumo wrestlers, as described by Matsuzaw.[47] All of them had gross obesity maintained by a 5,000 to 6,000 calorie diet, but they nevertheless fitted the criteria of the obese metabolically normal, and their visceral adipose tissue was normal in amount. On retirement, when they discontinue their program of strenuous training, they developed the metabolic abnormalities of the metabolic syndrome with markedly increased insu-

lin resistance. Whether their visceral adipose tissue increases in size is not stated.

Needless to say, a healthy lifestyle of balanced diet and regular exercise should be encouraged. If insulin resistance does develop, estimates of insulin resistance at regular intervals can serve to evaluate success of more vigorous changes in lifestyle or treatment with drugs.

SUMMARY

There is now considerable evidence that there are individuals who are obese and who nevertheless are metabolically normal (OBMN). Onset of obesity early in childhood, normal visceral adipose tissue, lower triglycerides, and increased high-density lipoprotein (HDL)-cholesterol are significantly correlated in this group. It is important to identify the healthy subgroup: (1) in clinical work to avoid blame and inappropriate treatment; (2) in research studies to avoid confounding statistical analyses; and (3) in medical education to emphasize the need for better characterization of patients. Provided that the fasting plasma glucose is within normal range, measure of fasting plasma insulin alone can provide a practical estimate of insulin resistance in those with normal fasting blood glucose.

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