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Editorial

# Obesity

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## Introduction

According to current knowledge, no single definition exists for "obesity", nor for "overweight". However, it is commonly accepted that a body mass index (BMI = kg/m$^2$) greater than 27 corresponds to a state of being overweight while a BMI greater than 30 indicates true obesity. Using these criteria, the rate of obesity is about 12% for both sexes in the US, 9% for men and 12% for women in Canada, and about 5% for men and 7% for women in Europe. When less restrictive criteria are adopted (defining the overweight person as one who weights 20% more than his or her ideal weight), 18% of the male Italian population and 35% of the female Italian population can be considered obese. Thus, the phenomenon of obesity constitutes a considerable social problem.

"Morbid obesity", defined as a BMI >40, or a weight excess greater than 100% of ideal weight, is associated with reduced average life expectancy, liver disorders, respiratory problems and locomotive disorders.

Type 2 diabetes mellitus is frequently associated with obesity. Epidemiological studies have shown that in some racially homogenous populations, such as Pima Indians, indigenous Fijians, and American blacks, obesity and diabetes appear to be genetically determined. Studies conducted on experimental animals (mice) have led to the isolation of the gene responsible for obesity in the *ob* locus. In fact, obese mice have been obtained through cross-breeding experiments. The *ob* locus codes the synthesis of the OB protein, called Leptin, which has a molecular weight of 16 kD. This protein, administered parenterally to obese leptin-deficient mice, causes both a reduction in food consumption and an increase in energy output. The protein produced by the *ob* gene thus acts by regulating the deposition and reabsorption of fat in adipose tissues. This protein has also been isolated in humans, although its role seems to be less crucial, since it acts together with numerous other hormonal substances and neurotransmitters.

Obesity is also associated with cardiovascular diseases. Body fat distributed mainly in the abdominal region (waist/hip > 0.91) is associated with an increased risk of type 2 diabetes and cardiovascular diseases.

Obesity, type 2 diabetes hypertension and cardiovascular diseases are widely diffused in Western populations and present a common pathogenic pathway. The prevalence of these metabolic disorders increases with age in a directly proportional manner: in subjects over the age of 70, the prevalence of these disorders reaches epidemic levels.

Although opinions of researchers working in this field differ, many scientists have hypothesized that type 2 diabetes, arterial hypertension, cardiovascular diseases and dyslipidemia represent different phenotypic expressions of the same biochemical defect: *insulin resistance*. In order to clarify the concept of "insulin-resistance", one must first understand the mechanism of action of insulin at the cellular level. For the sake of simplicity, the mechanism of action of insulin can be divided into three levels:

- the first level includes the initial events related to the activity of tyrosine kinase of receptor;
- the second level includes the chain of chemical reactions related to the phosphorylation or dephosphorylation of serine, reac-

tions that revolve around an enzyme called "MAP" (mitogen-activated protein/microtubule associated protein kinase);

- the third and last level consists of the final biological effect of the insulin cascade that includes the intracellular transport of glucose, glycogenosynthesis, lipid synthesis, *etc*. Resistance to the action of insulin may depend on the secretion of an anomalous insulin molecule, on an insulin receptor defect or on a post-receptor defect.

In recent years, however, the most compelling hypothesis is that insulin resistance is derived from an intracellular metabolic disorder, occurring in Randle's cycle or the "glucose fatty acid cycle". The triglycerides stored in adipose tissues are hydrolyzed into fatty acids and glycerol by the hormone-sensitive enzyme, lipoprotein lipase (LPL), which is inhibited by insulin. Increased lipolysis in adipose tissues, which occurs in obesity, leads to an increase in blood free fatty acids (FFA) levels. FFA are then transported into the plasma by albumin and are oxidized in the skeletal and cardiac muscles. The increase in FFA oxidation induces, on the contrary, an inhibition of glucose oxidation.

This inhibition is mediated by an increase in acetyl-CoA/CoA and NADH/NAD ratios, secondary to β-oxidation of FFA, and by higher intracellular concentrations of citrate, which act by inhibiting anaerobic glycolysis and the activation of glucose through a reduction in esokinase activity, in phosphofructokinase (PFK) and in the pyruvate dehydrogenase (PDH) complex.

Thus, a profound metabolic alteration causes, is associated with, or results from obesity in almost all cases. Conditions exist, however, for which, at the clinical and thus the therapeutic level, altered lipid and glucose metabolism do not take on primary practical importance, with respect to other consequences, such as respiratory insufficiency, hepatic or gastro-intestinal disease, certain immunological disorders, major osteo-articular diseases, and last but not least in terms of practical importance, the psychological implications of esthetics.

## A. Obesity, Type 2 Diabetes and Insulin Resistance

Insulin sensitivity in non-diabetic subjects decreases with an increase in body weight, such that a weight increase of more than 35-40% with respect to ideal weight is associated with a reduction in insulin sensitivity of about 30-40%.

Insulin resistance mainly affects skeletal muscles and involves both oxidative and non-oxidative processes of glucose metabolism. The organism reacts to increased insulin resistance by secreting larger amounts of insulin at the pancreatic level.

## B. Arterial Hypertension, Cardiovascular Diseases and Insulin Resistance

It has been known for many years that the rate of arterial hypertension is higher among obese and diabetic individuals. On the other hand, physical exercise and weight loss lead to an increase in insulin sensitivity and the simultaneous improvement in blood pressure values in both obese and diabetic subjects. Furthermore, an improvement in insulin sensitivity and the consequent reduction of the high concentrations of plasmatic insulin are closely related to the decrease in systolic and diastolic blood pressure values of non-diabetic obese subjects.

Studies conducted using euglycemic hyperinsulinemic clamp in young normal-weight subjects with essential hypertension, showed that tissue uptake of glucose was reduced by 30-40% with respect to control values, and that the degree of insulin resistance was closely related to the increase in pressure values. On the contrary, glucose oxidation, measured using indirect calorimetry, was not reduced, indicating that alterations in glucose metabolism are not entirely caused by a defect in glycogenosynthesis.

It is also known that normal-weight non-diabetic subjects with essential hypertension have hyperinsulinemia. De Fronzo *et al*[1] and Skott *et al*[2] evaluated urinary sodium excretion during euglycemic hyperinsulinemic clamp in young healthy volunteers. During the 30 to 60 minutes following a physiological increase in plasmatic insulin concentrations, a reduction in renal sodium excretion was recorded, which reached a minimum of about 50% of the initial excretion rate. Using micropuncture and microperfusion techniques, the antinatriuretic effects of insulin were shown to be exerted at both the proximal and distal regions of the nephron. Insulin concentrations within the range of 30-40 mU/ml suppressed this antinatriuretic effect.

A second mechanism through which insulin causes hypertension involves the stimulation of the sympathetic nervous system. Rowe *et al*[3] have shown that insulin causes an increase in plasma levels of noradrenaline, while hyperglycemia has no effect on these levels. The increase in plasma concentration of noradrenaline is significantly related to an increase in heart rate and blood pressure values. The activity of the sympathetic nervous system can influence blood pressure through an increase in heart beat (increased myocardial contractility and heart rate), in cardiopulmonary blood volume (contraction of smooth muscles of the major blood vessels), in peripheral resistance and in renal reabsorption of sodium (direct stimulation of sodium reabsorption by the renal tubules, renal vasoconstriction and stimulation of renin secretion) with expanded fluid volume in the extracellular compartment.

In some disorders, such as type 2 diabetes, essential hypertension, obesity and old age, insulin resistance constitutes the primary metabolic disorder: cells respond to insulin resistance through an increase in insulin secretion. The resulting hyperinsulinemia causes two important effects:

- an increase in renal reabsorption of sodium which leads to an increase in the volume of extracellular fluids and to hypertension;
- the stimulation of the sympathetic nervous system that causes hypertension through various mechanisms (increased sodium reabsorption with a consequent increase in blood mass, peripheral vasoconstriction, increased heart beat). The stimulation of the sympathetic nervous system can induce or worsen pre-existent insulin resistance, causing feedback, which perpetuates both the insulin resistance and the hypertension.

Hyperinsulinemia can modify the activity of many cellular pumps found on the cell membranes, including those on arteriolar smooth muscle cells. Thus, sodium accumulation occurs that, in turn, leads to increased sensitivity of arteriolar smooth muscle cells to the pressor effects of noradrenaline and angiotensin II. $Na^+$-$K^+$-ATPase is an insulin-regulated enzyme that plays a fundamental role in the regulation of intracellular electrolyte concentration. Another cellular pump that may be considered important in the pathogenesis of essential hypertension is the $Na^+$-$H^+$ pump that is considered equivalent to the $Na^+$ transport system. In fact, insulin stimulates sodium-proton exchange in skeletal muscle cells and in adipocytes. This pump is also involved in $Ca^{2+}$ ion exchange and plays an important role in maintaining cellular pH.

Hyperinsulinemia increases $Na^+$-$H^+$ exchange, thus increasing intracellular pH. The intracellular accumulation of $Ca^{2+}$ increases the sensitivity of vessel smooth muscles to the pressor effects of noradrenaline, angiotensin and NaCl load.

The clinical complications of atherosclerosis are the major cause of mortality in civilized countries. Epidemiological data gathered from three vast independent perspective studies conducted in different institutions suggest that hyperinsulinemia constitutes an independent risk factor in cardiovascular diseases (CHD).

The main effect of insulin on the arteries can be summarized as follows:

- proliferation of smooth muscle cells;
- increased synthesis and low activity of low-density lipoprotein receptors; increased formation and reduced regression of lipid plaques;
- stimulation of connective tissue synthesis;
- stimulation of growth factors.

Crutz *et al*[4] have shown that the chronic infusion of insulin in the femoral artery of dogs causes a notable proliferation of intima and the accumulation of cholesterol and FFA at the insulin infusion site, while no effects are seen in the controlateral femoral artery.

Further studies have shown that the addition of insulin to a culture medium of smooth muscle cells stimulates the proliferation of these cells.

Insulin is not only a substance that promotes cell growth, but it also stimulates proliferation through various factors including IGF-1, and thus contributes to the process of atherosclerosis.

Finally, recent studies confirm this hypothesis, demonstrating that higher plasma levels of insulin, obtained both after fasting and after stimulation, were associated with a higher risk of mortality due to cardiovascular incidents.

## C. Clinical Perspective of Obesity Related Pathologies

**1.** Respiratory failure

It is not our intention to discuss such a specific argument in this forum. We shall limit ourselves to stating that, in cases of severe obesity, there is a higher rate of restrictive respiratory insufficiency, and to a lesser degree, Pickwick's syndrome.

**2.** Gastro-intestinal disorders

The principal form of liver damage present in obesity, especially when associated with type 2B and IV hyperlipemia, is hepatosteatosis. This presents with the traditional semiotic signs of hepatomegalia (with antero-inferior margin of the round liver) and with sever and diffused subcutaneous dystrophy, evolving into hepatic fibrosis and, in extreme cases, portal hypertension. In practical medicine, the most reliable diagnostic exam is eco-tomography, which shows a 'shiny' liver, in which steatosis appears in "spots".

Biochemically, the only indication is cholestasis and the most reliable exam consists of the elevation of the GT levels. Whenever a true elevation of the hepatocytonecrosis index occurs, hepatitis (viral or drug-based) or alcohol abuse should be suspected.

At the gastro-intestinal level, the major problem caused by obesity is abdominal "obstruction", and thus the consequent motility and transport disorders, such as constipation, intestinal bacterial contamination and GBRD.

Constipation is particularly accentuated during weight loss diets. Intestinal bacterial infection depends on the ileocecal transit time and duodenal-gastro-esophageal reflux can become particularly problematic due to *helicobacter pylori* gastric infection, which commonly may be associated with obesity.

Thus, the practicing physician should be reminded that there are other risk factors in addition to these, including ischemic cardiopathy. There is a special form of chronic recurrent pancreatitis, related to excess weight with type 2B and IV hyperlipidemia. This is one of the major causes of cholesterolemic stones of the bile ducts found in these patients.

**3.** Immunological disorders

Only those disorders resulting treatment for obesity by jejunum-ileum by-pass surgery shall be mentioned. These include not only modifications of humoral and cellular-mediated immunity due to reduced immunoglobulin production (IgA species) of the intestinal wall and of the morphology and function of the ileum, but also metabolic alterations, such as modified reabsorption of biliary salts (with gallbladder stones) and calcium (with oxalic renal calculi) and deficiency syndromes due to the onset of intestinal bacterial contamination caused by "fistula" and "staunching".

**4.** Osteo-arthropathy

In addition to that reported in the paragraph on jejunum-ileum by-pass, it should be pointed out that the malabsorption of liposoluble vitamins (e.g. vitamin D), in particular, causes osteoporosis. Both the pathological conditions, polyarthritis and osteoporosis, are aggravated by continued states of excess body weight and by the deficiency and immunological pathologies mentioned above.

**5.** Esthetics

It is important to remember that body weight may have psychological implications. Essentially, these include a distorted self-image with bouts of depression and altered ego.

### References


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