Obesity Paradox
A paradox contradicting itself

MY NOSE WILL GROW NOW!
First introduced

• For the first time Gruberg and colleagues published in 2002 their study on 9,633 consecutive patients who underwent percutaneous coronary intervention (PCI)

• Patients were divided into three groups according to BMI: normal, BMI between 18.5 and 24.9 (n = 1,923); overweight, BMI between 25 and 30 (n = 4,813); and obese, BMI >30 (n = 2,897).

• Despite similar angiographic success rates among the three groups, normal BMI patients had a higher incidence of major in-hospital complications, including cardiac death (p = 0.001). At one-year follow-up, overall mortality rates were significantly higher for normal BMI patients compared with overweight or obese patients (p < 0.0001).

paradoxical findings

• In epidemiological studies, For characterization of the relative risks (RRs) of mortality and morbidity, the rates in underweight (BMI <18.5 kg/m$^2$), overweight (25 to <30 kg/m$^2$), class I obesity (30 to <35 kg/m$^2$), class II obesity (35 to <40 kg/m$^2$), and class III obesity (BMI >40 kg/m$^2$) are compared with those in normal-weight subjects (18.5 to <25 kg/m$^2$).

• A plot of the RR of mortality against BMI follows a U-shaped, or J-shaped, curve with the minimum mortality close to a BMI of 25 kg/m$^2$. Mortality increases as BMI increases above 25 kg/m$^2$ and as BMI decreases below 25 kg/m$^2$.

• During the past decade, there is increasing evidence that patients, especially elderly, with several chronic diseases and elevated BMI may demonstrate lower all-cause and cardiovascular mortality compared with patients of normal weight.

Hainer et al. Obesity Paradox Does Exist. DIABETES CARE, VOLUME 36, SUPPLEMENT 2, AUGUST 2013
The Obesity Paradox: Fact or Fiction?

- They reviewed the studies who revealed protective effects of obesity on Heart Failure. Though they claimed the obese patients may have been healthier and deleterious effects of cachexia, not the salutary ones of obesity has caused the situation, they concluded a “U-shaped” outcome curve according to BMI for patients with HF may actually exist, in which mortality is greatest in cachectic patients; lower in normal, overweight, and mildly obese patients; but higher again in more severely obese patients.

Habbu et al. The American Journal of Cardiology, 2006
Wang T. The Obesity Paradox in Heart Failure, Weighing the Evidence
j am college of cardiol, 2014

It has been proposed that obese patients have greater “metabolic reserve,” making them better able to tolerate HF’s catabolic effects. Some experimental data, for example, suggest that elevated lipoproteins can be protective, binding endotoxins and other inflammatory mediators that are elevated in disorders such as HF. Patients who are obese by BMI can still be “metabolically healthy” and vice versa*. Other factors, including fat distribution, degree of systemic inflammation, fitness level, and insulin resistance, maintain comparable or greater influences on metabolic health, and a number of studies are examining these features in patients with HF. All need more research.


Metabolically obese normal weight and phenotypically obese metabolically normal youths: the CASPIAN Study.
Kelishadi R et al
patients with atrial fibrillation and heart failure

- Over 2000 patients, shows that obese or overweight have better survival when compared with normal weight or underweight in Chinese AF and HF patients. It may be due to better metabolic reserve to meet the catabolic state of HF.

In surgical intensive care patients with peritonitis

- 286 Pts. Short-term (28 days) but not long term (5 y) outcomes (length of stay, discharge, mortality) were improved in the obese.

Pulmonary hypertension patients

- 100 Pts, Obesity was significantly associated with lower mortality in both pre-capillary and disproportional post-capillary PH patients. It seems that in PH, similarly to other chronic clinical cardiovascular disease states, there may be a protective effect of obesity, compatible with the “obesity paradox”

Zafrir et al. Respiratory Medicine (2013) 107, 139e146
The obesity paradox in acute coronary syndrome: a meta-analysis

- 26 studies and 218,532 patients with ACS were included
- The obesity paradox in patients with ACS has been confirmed. Although it seems to be clear and quite obvious, outcomes should be interpreted with caution. It is remarkable that obese patients had more often diabetes mellitus and/or hypertension, but they were younger and had less bleeding complications, which could have influence on their survival
Obesity Paradox Does Exist

VOJTECH HAINER et al. DIABETES CARE, VOLUME 36, SUPPLEMENT 2, AUGUST 2013
Cardiac diseases, Peripheral arterial disease, Stroke, Thromboembolism, Postoperative after cardiac surgery, T2M, critically ill, COPD, hemodialysis, osteoporosis: protected by increased body weight

Obesity Paradox Does Not Exist

EBERHARD STANDL et al. DIABETES CARE, VOLUME 36, SUPPLEMENT 2, AUGUST 2013
Obesity paradox should not prevent doctors and patients from proper lifestyle management, can be explained by covariates
ST-elevation myocardial infarction: 6,938 in-hospital patients, The odds for in-hospital mortality were significantly lower for obese class I (OR 0.56; 95% CI 0.35–0.91) and significantly higher for underweight patients (OR 2.72; 95% CI 1.14–6.48) compared to the normal weight group and odds ratios showed a U-shaped distribution.

Witassek et al. Swiss Med Wkly. 2014;144:w13986
Acute First-Ever Stroke

2785 patients, Based on BMI estimation, obese and overweight stroke patients have significantly better early and long-term (10-year mortality) survival rates compared to those with normal BMI

Vemmos et al. *Stroke*. 2011;42:30-36

- adiposopathy describes a “disease” wherein pathogenic enlargement of fat cells and fat organ results in anatomic/functional abnormalities leading to adverse clinical consequences.
- anatomic obesity paradox suggests that abdominal adipose tissue distribution is paradoxically more pathologic than the peripheral adipose tissue distribution.
- physiologic obesity paradox Despite an increased amount of body fat in lipomatosi, patients with benign multiple symmetrical lipomatosis do not have an increased risk of hyperglycemia or dyslipidemia.
- demographic obesity paradox women lower, Asians higher risk.
- therapeutic obesity paradox, adding functional fat can improve metabolic diseases that, paradoxically, are usually due to having too much body fat My journal club\obesity paradox\PDFs\Bays.pdf.
- The CVD event and/or intervention obesity paradox refers to more favorable outcomes observed among patients with overweight or obesity who experience a CVD event because of being thin is due to severe illnesses (e.g., chronic heart or lung disease, cancer), or because the thinner individuals smoke cigarettes more, or because of heightened physical fitness or awareness of potential CVD Risk and treatments in obese.
Should patients with chronic disease be told to gain weight? The obesity paradox and selection bias

• In summary, the obesity paradox may be partly explained by selection on a baseline variable (e.g., diabetes) affected by prior exposure (body weight before baseline). Because results from observational studies in which the start of follow-up and exposure do not coincide should be interpreted with care, the obesity paradox provides little evidence that chronic disease patients should gain weight.

• doi:10.1016/j.amjmed.2014.10.043
  lajous et al
Another aspect of adiposity: white-brown adipocyte plasticity

• White adipose cells in mammals have the ability to store and release energy in the form of lipids (for long term fasting) large spherical shape, one large cytoplasmic lipid droplet, secrete hormones and several cytokines.

• Brown adipocytes dissipate energy for thermogenesis, highly regulated by the sympathetic nervous system to maintain body temperature when mammals are exposed to temperatures below thermoneutrality, activated by sympathetic nerves acting on beta3-adrenoceptors especially when shivering.

• It is named “adipose organ’ to describe the general functional and plastic properties that are shared by most of its depots.

• BAT has a denser network of capillaries and more numerous parenchymal fibres than WAT.

Smorlesi et al. obesity reviews (2012) 13 (Suppl. 2), 83–96
The transdifferentiation theory

in specific physiologic conditions (chronic cold exposure), white adipocytes transform into brown adipocytes to supply the thermogenic needs, and conversely, brown adipocytes transform into white adipocytes when the energy balance is positive and the adipose organ requires increased Storage capacity
during pregnancy, lactation or postlactation states in females, white adipocytes seem to have the ability to convert into milk-secreting epithelial cells metabolically active
The newborn has BAT. brown adipocytes are present also in adult humans and are detectable by positron emission tomography (PET)
Cold exposure and physical activity induce browning of the adipose organ via several molecular mechanisms

The beta-adrenergic signaling cascade includes the activation of cAMP, protein kinase A (PKA) and p38MAPK; thus, sensitizers or activators of these pathways, such as the R1-alpha subunit of cAMP-dependent PKA and the transcription factor FoxC2 which are enriched in fat tissue of humans and mice, could also be implicated in the white-to-brown fat conversion.
Clinical Importance

• White-to-brown transdifferentiation is of medical interest, because the brown phenotype of the adipose organ is associated to obesity resistance, and drugs inducing this phenotype suppress murine obesity and related disorders.
Basic findings: exercise pil?

FNDC5 (fibronectin domain-containing [protein] 5) was initially discovered and characterized by two groups in 2002. In 2011 FNDC5 burst into prominence as the parent of irisin, a small protein containing the fibronectin type III domain. Irisin was proposed to be secreted by skeletal muscle cells in response to exercise, and to circulate to fat tissue where it induced a transition to brown fat. Since brown fat results in dissipation of energy, this pathway is of considerable interest for metabolism and obesity.
In French words


• Very recently, the concept of "beigeing", defined as the occurrence of thermogenic brown adipocytes in white adipose tissue, has emerged, leading to the identification, by Bruce Spiegelman's group, of a new muscular hormone, called irisin, which is able to stimulate the "beigeing". This finding should convey toward the discovery of new mutations involved in the pathogenesis of obesity and lipodystrophies, and should be translated into innovative therapeutic perspectives.
Histopathology of the obese adipose organ

- WAT of obese mice and humans expresses high levels of a cytokine that is thought to be not only a classic product of macrophages but is also produced by adipocytes: tumor necrosis factor alpha (TNF alpha). This cytokine is hypothesized to have a role in insulin resistance (TNF-α inhibits insulin-stimulated tyrosine phosphorylation of both IR (insulin receptor) and IRS (insulin receptor substrate)-1, and downregulates the insulin-sensitive glucose transporter GLUT-4). Salicylate is inhibitory to this process.

- Thus, insulin resistance was thought to be the result of TNF alpha (and other cytokines) production by increased amounts of hypertrophic adipocytes, which is typical of the obese condition.
Histopathology ...

• In 2003, two independent laboratories showed that the adipose tissue of obese animals and humans is infiltrated by macrophages to remove remnants of dead adipocytes, inducing a chronic low-grade inflammation. They also showed that macrophage infiltration is positively correlated to the size of adipocytes and is coincident with the appearance of insulin resistance. Furthermore, they showed that most cytokines involved with insulin resistance are produced by cells residing in the heavy population, including macrophages, and not in the mature adipocyte fraction.
visceral adipocytes are more fragile and reach a critical size that triggers death, termed the ‘critical death size’ (CDS), earlier than subcutaneous adipocytes.

One possible explanation of the differences in size, expandability and, consequently, CDS, is that visceral adipocytes may be brown adipocytes that have been converted to white adipocytes.

It could offer an explanation of the well-known higher morbidity potential of visceral fat.
From excess adiposity to insulin resistance: The role of free fatty acids

Fig. 2. The binding of insulin to the α-subunit of the insulin receptor activates autophosphorylation reactions whereby the intracellular part of the insulin receptor (β-subunit) becomes tyrosine-phosphorylated by the protein kinase activity of these same receptors. A phosphorylation cascade follows, initiating a protein phosphorylation cascade. The phosphorylation of IRS-1 and -2 leads to binding and activation of phosphatidylinositol 3-kinase (PI3K), which converts phosphatidylinositol 3,4 bisphosphate [PI(3,4)P2] to phosphatidylinositol 3,4,5 trisphosphate [PI(3,4,5)P3]. These nucleotides act as anchors, binding protein kinases to the plasma membrane and activating them. [PI(3,4,5)P3] bound to the plasma membrane associates with phosphoinositide-dependent kinase-1 (PDK-1), and this leads to phosphorylation and activation of protein kinase B, otherwise known as Akt. Activated Akt is thought to initiate many of the metabolic actions of insulin in the adipose tissue, the muscle, the liver and the pancreas.
Fig. 3. Fatty acids, in their activated form (fatty acyl-CoAs), are metabolized primarily via one of two pathways, oxidation or storage. When fatty acid flux exceeds the capacity of these pathways, as it occurs in obesity, fatty acids and intermediates of fatty acid metabolism [linoleic acid, diacylglycerol (DAG), phosphatidic acid (PA), lysophosphatidic acid (LPA), ceramide] accumulate and activate protein kinase C-theta (PKC-θ), which becomes phosphorylated. Phosphorylated PKC-θ starts a downstream activation of two serine-kinases, the c-JUN NH2-terminal kinase (JNK), and the inhibitor kappaB kinase (IKK). JNK and IKK associate with IRS-1, promoting its serine-phosphorylation (serine312 in humans, serine307 in rodents). The serine phosphorylation is responsible for IRS-1 blocking and the occurrence of insulin resistance by interrupting insulin receptor/IRS interaction and promoting IRS-1 protein degradation.
Visceral adipose tissue and subcutaneous AT

- The visceral adipose tissue (VAT) is localized primarily as intra-abdominal depots around the intestine, the mesentery, the omentum and peri-renal areas, and drains directly to the liver through the portal circulation. Although the complex pathophysiology of VAT has not been completely elucidated, it is known that VAT adipocytes are more metabolically active, more sensitive to lipolysis and more insulin-resistant than the subcutaneous adipose tissue (SCAT).
- Conversely, SCAT is more avid in the absorption of circulating free fatty acids (FFA), in triglyceride synthesis and in the storage of lipids in fat cells. VAT metabolic activity is regulated by its peculiar physiochemical components, i.e., the presence of a greater number of glucocorticoid receptors and β-adrenoceptors, and a lower number of insulin receptors.
- The critical death size of visceral adipocytes is smaller than that of subcutaneous adipocytes, likely accounting for the greater morbidity related to visceral fat.
Deleted in Breast Cancer 1 (DCB1) (protein) limits adipose tissue fat accumulation and plays a key role in the development of metabolic syndrome phenotype.

-- Diabetes. 2014 Jul 22. pii: DB_140192. [Epub ahead of print]

Escande et al.

- many lines of evidence suggest that obesity may develop as a protective mechanism against tissue damage during caloric surplus, and it is only when the maximum fat accumulation capacity is reached and fatty acid spillover occurs into to peripheral tissues, that metabolic diseases develop.

-- Nin et al


Deleted in breast cancer 1 (DBC1) protein regulates hepatic gluconeogenesis.
Thanks for your attention