Obesity paradox
Marcello Camici*, Fabio Galetta, Ferdinando Franzoni and Angelo Carpi
Department of Clinical and Experimental Medicine, Pisa University, Italy

Abstract
Several studies verify and emphasize the obesity paradox but they do not offer any evident explanation for the paradox. Obesity paradox explanation by pathogenetic action mechanisms of parathyroid hormone-related protein and calcitonin gene-related peptide is evaluated. The vasodilatant action of these peptides has been taken into consideration in decreasing the peripheral arterial vascular tone during obesity in response to the obesity-increased renin-angiotensin-aldosterone and sympathetic system activity.

Introduction
The original description of obesity paradox was published using data >1300 patients with chronic kidney disease undergoing haemodialysis where first was observed the overweight may help to reduce the high mortality and morbidity in haemodialysis patients. This conclusion then was observed in other chronic diseases such as obstructive pulmonary disease, chronic heart failure, stroke, coronary artery disease as well as in patients with critical illness.

Obesity affects the cardiovascular system through multiple actions and mechanisms [1]. Although obesity has been implicated as one of the major risk factors for hypertension, heart failure and coronary artery disease evidence from clinical cohorts of patients with established cardiovascular diseases indicates an obesity paradox because overweight and obese patients tend to have a more favorable short- and long-term prognosis. Despite an higher prevalence of hypertension in obesity, recent data have shown an obesity paradox. Uretsky et al., [2] investigated the effects of obesity on cardiovascular outcomes in 22576 treated hypertensive patients with coronary artery disease. During 2-year follow up, all cause mortality was 30% lower in overweight and obese patients, despite less effective blood control compared with the normal weight group. A previous study also showed decreased stroke risk and total mortality among overweight patients compared with lean patients [3]. Similarly another major hypertensive study showed a U-shaped relationship between all cause and non-cardiovascular mortality and body mass index meaning excess mortality at both extremes of body mass index [4]. In another study of 800 elderly hypertensive patients, total mortality and cardiovascular and non-cardiovascular major events were highest in those with leanest body mass index quintile [5]. The association between body mass index and major events was U-shaped, whereas non-cardiovascular mortality decreased with increasing body mass index.

In aggregate, these studies suggest that although obesity may be a powerful risk factor of hypertension and left ventricular hypertrophy, obese hypertensive patients may paradoxically have a better prognosis, possibly because of having lower systemic vascular resistance and plasma renin activity compared with more lean hypertensive patients [6].

More recently other studies have not shown the obesity paradox using better indices of obesity than body mass index such as waist circumference and waist to hip ratio [7]. Combining body mass index with measures of central obesity may help to reduce the high mortality and morbidity in haemodialysis patients. This conclusion then was observed in other chronic diseases such as obstructive pulmonary disease, chronic heart failure, stroke, coronary artery disease as well as in patients with critical illness.

Obesity paradox
Several studies have reported increasing prevalence of low 25(OH)D in obesity: overweight it is considered a risk factor for vitamin D deficiency [10-12]. In obesity the mean serum level of 1,25(OH)D3 (calcitriol) and 25(OH)D3 (calcidiol) are lower than in non-obese subjects while the serum level of immunoreactive parathormone (iPTH) is higher than in non-obese subjects [10,13].

The mechanism for vitamin D deficiency in obesity is unknown. It has been suggested a decreased bioavailability of 25(OH)D
because of increased sequestration in adipose tissue (vitamin D is fat soluble) [10]. Alternatively it has been proposed that being enhanced the production of active vitamin D metabolite 1,25(OH)D its high concentration exert negative feedback control on the hepatic synthesis of 25 (OH)D [11]. It has been suggested that the metabolic clearance of vitamin D may increase in obesity people possibly by enhanced uptake by adipose tissue [10]. The higher serum PTH levels (subclinical hyperparathyroidism) despite the normal total and ionized serum calcium is directly linked to the obesity-vitamin D deficiency.

It has been observed that in primary cultures of bovine parathyroid cells the 25 (OH)D suppresses PTH synthesis and secretion by bovine parathyroid cells possibly by direct activation of vitamin D receptor (VDR) so it has been suggested a decreased feedback inhibition in obesity [14,15]. The regulation of parathyroid hormone secretion and synthesis is linked to variations in serum calcium which is mediated by G-protein coupled, calcium-sensing receptors on parathyroid cells (rapid regulation of PTH secretion) whereas alterations in the stability of mRNA-encoding PTH by miRNA-binding proteins occur in response to prolonged changes in serum calcium (long-term regulation of PTH secretion). Independent of changes in intestinal calcium absorption and serum calcium, 1,25 (OH)D also represses the transcription of PTH by associating with the vitamin D receptor which heterodimerizes with retinoic acid X receptors to bind vitamin D response elements with the PTH gene. Additionally 1,25 (OH)D regulates the expression of calcium-sensing receptors to indirectly alter PTH secretion on parathyroid cells [14-18].

So, the chronic vitamin D deficiency such as in obesity leads to subclinical secondary hyperparathyroidism [19]: there is an inverse relationship between serum 25(OH) vitamin D levels and serum parathyroid hormone levels [20].

In the obesity as in the primary hyperparathyroidism, the chronic plasma elevated concentration of PTH has biological effects in the heart and peripheral circulation where acts as vasodilator [21]. PTH stimulates the vascular smooth muscle cell by binding to the PTH/PTH related peptide (PTHrP) receptor and thus increases the intracellular cAMP levels and reduces the influx of calcium. This is believed to explain the vasodilating properties of PTH found in vitro as well as in vivo. The PTHrP has been observed significantly increased in plasma of patients with type 2 diabetes and obesity (BMI 29+1.9 kg/m²) [22].

The PTH is a circulating hormone that carries signals from a calcium sensor in the parathyroid glands to remote target tissues while the PTHrP is a local messenger within tissues: yet they share a receptor [23].

PTHrP and its receptors are both expressed widely in the central nervous [24]. The protein protects neurons against glutamate-induced excitotoxicity in cerebellar granular cells. This form of excitotoxicity results from the activation of voltage-dependent calcium channels by glutamate receptors of the kainite class. The activation of voltage dependent calcium channels markedly increases the expression of PTHrP [25] which in turn inhibits the entry of calcium and promotes the survival of neurons.

PTHrP is secreted by a variety of smooth-muscle beds [26], in which it is released in response to mechanical stretching [27] and in response to vasoconstrictors such as angiotensin II (28) It acts as a smooth-muscle dilator by binding to its receptor PTHR1 the same receptor that may be stimulated by PTH also [29,30] This process sets up the circuitry for a short-loop feedback system in which PTHrP responds to stretching by relaxing smooth muscle locally. In keeping with this hypothesis, transgenic mice that express PTHrP in vascular smooth muscle have low blood pressure [31]. Does PTHrP/PTHrIR system account for the obesity paradox by reducing the peripheral vascular resistance in response to the vasoconstrictors stimuli present in obesity such as the increased renin angiotensin aldosterone system activation?

**Obesity and calcitonin gene related peptide (CGRP)**

Elevated plasma levels of CGRP have been found in human obesity [32]. Where could be a molecular link in the pathophysiology of migraine following the obesity [33,34]: in animal studies CGRP shows a functional role in cerebrovascular regulation [35]. CGRP may alleviate arterial vasoconstriction following subarachnoid hemorrhage and thus protect the brain from vasospasm and subsequent ischemia [36]. In peripheral vascular arterial system also the CGRP has a potent vasodilator action as in animals as in humans [37]. CGRP is a 37 aminoacid neuropeptide derived from alternative processing of the calcitonin gene [38]. This peptide is located in the central nervous system and in peripheral sensory fibers that innervate the blood vessels and the viscera [39]. It is recognized that CGRP is an extremely potent endothelium-independent vasodilator both in vivo [40] and in vitro [41]. Receptors specific for CGRP are present on the vascular smooth muscles cell membrane and CGRP is known to stimulate cAMP in this tissue [42]. The CGRP receptor is a relatively unique G protein receptor coupled that is a multimter of Receptor Activity Modifying Protein (RAMP1-2) and Receptor Component Protein (RCP) [43]. It was also demonstrated that CGRP is capable of activating K channels of vascular smooth muscle which results in vasodilatation secondary to membrane hyperpolarization [44]. CGRP has various actions on the human cardiovascular system such as control of peripheral vascular tone, potent vasorelaxation, increase in rate and force of contraction of heart.

CGRP is a major transmitter in capsaicin-sensitive sensory nerves: sensory nerve terminals of capsaicin-sensitive C-and A- delta fibers release CGRP by chemical, thermal and mechanical stimuli. Various factors such as glucocorticoids, nerve growth factor, vascular wall tension and sympathetic nervous system at the local level modulate CGRP release so the plasma level measurement of CGRP is a marker of sensory nerve activity [45]. In ischemic cardiac preconditioning CGRP plays an important role in mediation of preconditioning state that has a protective effect on cardiac ischemia [46]. Nitroglycerin activates sensory nerve fibers to release CGRP and the cardiovascular effects of nitroglycerin (vasorelaxation and cardioprotection) are partly mediated by endogenous CGRP [47]. Very little is known about the role of CGRP in obesity where it has been demonstrated that is implicated in the pathophysiology of the migraine.

It plausible to speculate that this neuropeptide could play a role as neuromodulator of neurogenic inflammation during obesity where is present a state of low grade systemic inflammation and sympathetic hyperactivity [48]. In animal study, plasma levels of CGRP are found to be elevated in pre-obese Zucker rats prior to the onset of severe obesity [45]. This raises the possibility of CGRP having a role in the development of obesity instead of being elevated as a consequence of the low grade inflammation state of obesity. Nonetheless, further studies are required to conclude that. Does elevated CGRP plasma levels account for the obesity paradox by reducing peripheral vascular arterial tone in response to the vasoconstrictor stimuli present in obesity such as the increased sympathetic nervous system tone?
Obesity paradox in large-scale studies (Table 1)

The message derived from small-to large scale studies is uniform and suggest that an optimal BMI with lowest risk of death is in the overweight or even in obese categories. We analyze a large scale-studies about obesity paradox. In acute heart failure ADHERE Scientific Advisory Committee [49] shows a decreased mortality from 5% to 2.2% per BMI quartiles whereas in chronic heart failure higher BMI is associated with lower mortality risk [50].

In stroke [51] obese and overweight patients have significantly higher survival when compared to patients with normal BMI in early (1 week and 1 month) and long-term (10 years). In coronary artery disease and hypertension [2], obese and overweight patients have hazard risk better and thin patients worse compared to normal weight subjects as reference.

In percutaneous coronary intervention [52] patients with BMI 27, 5-30 Kg/mq have lowest adjusted hazard risk for death. In coronary artery bypass grafting [53] patients with BMI of 33 kg/mq have lowest relative risk for 30-day mortality and patients with BMI under 22 Kg/mq have significantly higher relative risk for death. Medical therapy for acute coronary syndromes [54] in patients with modest overweight has the lowest risk of mortality.

In chronic kidney disease [55] after adjustment for available surrogates of nutritional status a better survival is independently associated to higher BMI. In intensive care unit [56] a lower 60-day in hospital mortality is present in overweight and obese patients.

In chronic obstructive pulmonary disease with acute exacerbations [57] an adjusted model shows that BMI per 1 Kg/mq unit increase is associated with 5% less chance of death (HR 0.95, 95% CI 0.93-0.97) and obese (HR 0.83, 95% CI 0.69-0.99) patients have lower 60-day in hospital mortality.

Higher BMI is independently associated with better survival after adjustment for available surrogates of nutritional status and inflammation [66]. In chronic obstructive pulmonary disease with stable disease [58] adjusted relative risk for death in overweight vs normal is higher.

Discussion

Reverse epidemiology is a term for a medical hypothesis which olds that obesity may be protective and associated with greater survival in regard to the cardiovascular risk. The paradox was first described in 1999 in overweight and moderately obese patients undergoing hemodialysis and has subsequently been found in those with heart failure muscle. PTHrP is a cardiovascular regulatory peptide involved in the control of vascular tone as vasodilatator. In vascular smooth, PTHrP can operate in both a paracrine or autocrine pathway via the PTH-1R in the regulation of vascular tone. What are the physiological and cellular mechanisms relating to obesity-over expression of PTHrP in vascular smooth muscle to blood pressure and regional hemodynamics? In this context, the reports of Clemens et al. [59,60] provide convincing evidence that PTHrP, endogenously produced by the smooth muscle alters blood pressure homeostasis in conscious animals. Indeed, both transgenic mice lines, overexpressing PTHrP or its receptor in smooth muscle, are hypertensive despite the numerous compensatory mechanisms that would be expected to blunt such phenotype. Further studies are needed on the second intracellular messengers elicited by ligand the PTHrP-1R such as cAMP/PKA system and NO/cGMP system. In addition to the local vascular wall vasoregulatory role of PTHrP discussed by Clemens and co-workers [59,60], Nagao et al. [61] have demonstrated that intracerebroventricular injection of PTHrP in rats produces an increase in blood pressure accompanied by a decrease in heart rate. These actions were abolished by pretreatment with an alpha-blocker suggesting that PTHrP present in the brain may be implicated in the central regulation of blood pressure through sympathetic activation.

CGRP is a neuropeptide involved in the neuromodulation of vascular tone as vasodilatator.

CGRP interacts with its receptor to produce cardiovascular effects such as positive inotropic actions and vasorelaxation. May this explain the obesity paradox in regard to the acute coronary syndromes?

We remember that nitroglycerin activates sensory nerve fibers to release CGRP and the cardiovascular effects of nitroglycerin (vasorelaxation and cardioprotection) are partly mediated by endogenous CGRP [62]; understanding the physiological role of CGRP in various tissues is evolving [63]. In human obesity the plasma CGRP level is significantly increased vs normal weight control and after weight loss CGRP concentration remains unchanged: only high fat meal intake and not high carbohydrate meal intake is associated with increased CGRP secretion [64]. After a high fat meal in obese patients the glucose-dependent insulinotropic polypeptide (GIP) induces CGRP expression in human adipocytes: there phore elevated CGRP levels in obesity might result from GIP-induced CGRP release in adipose tissue and might be triggered by an high fat diet [65]. Furthermore CGRP is expressed and released from adipose tissue during sepsis and systemic inflammation [66] and from adipocytes treated with inflammatory cytokines in vitro [67].

<table>
<thead>
<tr>
<th>Condition</th>
<th>Principal Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute heart failure</td>
<td>In hospital mortality decreases from 5% to 2.2% per BMI quartiles. The mortality OR for obese, overweight, underweight vs healthy weight is 0.74 (95% CI 0.68-0.81), 0.83 (95% CI 0.76-0.90) and 1.34 (95% CI 1.15-1.58), respectively</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>Higher BMI associated with lower mortality risk: adjusted HR for all-cause death for obese or overweight vs healthy weight patients is 0.81 (95% CI 0.72-0.92) and 0.88 (95% CI 0.80-0.96) respectively</td>
</tr>
<tr>
<td>Stroke</td>
<td>Obese and overweight patients have significantly higher early (1 week and 1 month) and long-term (10 years) survival when compared in patients with BMI (p=0.01 for all)</td>
</tr>
<tr>
<td>Coronary artery disease and hypertension</td>
<td>With normal weight subjects as reference, overweight and obese patients have better (HR 0.52-0.66, p&lt;0.001) and thin patients have worse survival (HR 1.85, p&lt;0.001)</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>Patients with BMI 27.5-30 Kg/mq have lowest adjusted HR for death (0.59,95% CI 0.39-0.79)</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>Lowest RR for 30-day mortality in patients with BMI of 33 Kg/mq, patients with BMI &lt;22 Kg/mq have significantly higher RR for death</td>
</tr>
<tr>
<td>Acute coronary syndromes and medical therapy</td>
<td>Medical therapy treated patients with modest overweight (BMI 26.5-28 Kg/mq) have the lowest risk of mortality (HR 0.52, 95% CI 0.34-0.80)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>Higher BMI is independently associated with better survival after adjustment for available surrogates of nutritional status and inflammation</td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>Overweight (HR 0.86, 95% CI 0.74-0.99) and obese (HR 0.83,95% CI 0.69-0.99) patients have lower 60-day in hospital mortality</td>
</tr>
<tr>
<td>COPD exacerbations</td>
<td>In an adjusted model, BMI per 1 Kg/mq unit increase is associated with 5% less chance of death (HR 0.95, 95% CI 0.93-0.97)</td>
</tr>
<tr>
<td>COPD stable disease</td>
<td>Adjusted RR for death in overweight vs normal weight patients is 1.64(95% CI 1.20-2.23) in men and 1.42 (95% CI 1.07-1.89) in women</td>
</tr>
</tbody>
</table>

Table 1. Obesity paradox in large-scale studies.
Finally very recently Flegal KM and others [68], by a systematic review and meta-analysis estimates the association of all-cause mortality with overweight and obesity using standard body mass index categories and shows that relative to normal weight, both obesity (all grades) and grades 2 and 3 obesity are associated with significantly higher all-cause mortality. Grade 1 obesity overall is not associated with higher mortality and overweight is associated with significantly lower all-cause mortality.

Any evident explanation for the paradox but possible explanations have included benefits of higher metabolic reserves, cardioprotective metabolic effects of increased body fat, earlier presentation of heavier patients, greater likelihood of receiving optimal medical treatment.

Two arguments have been put forth to account for the existence of the obesity paradox. First argument is that the obesity paradox is a consequence of one or several confounding factors present in the obese populations for example the BMI that does not directly distinguish between adipose and lean tissue or central and peripheral adiposity. Second argument argues that the explanation has to be found in the biology of the obese phenotype itself because of the obese people has been distinguished in two phenotypes-obese people described as metabolically healthy but obese, having uncomplicated obesity, or having metabolically benign obesity and obese people described as metabolically unhealthy, having complicated obesity, or having metabolically malignant obesity.

More in particular we are going by any pathogenetic mechanism that could explain why obesity should protect against mortality in subjects with chronic obstructive disease to some explanations in chronic kidney disease such as a more stable hemodynamic status in obese individuals, higher concentrations of tumor necrosis factor alpha receptors and/or adipokines in obesity that can oppose proinflammatory cytokines, neurohormonalstability of obesity, endotoxin-lipoprotein interaction, time discrepancies among competitive risk factors (overnutrition vs. undernutrition) and the overwhelming effect of the malnutrition-inflammation complex on traditional cardiovascular risks.

References
7. Czernichow S, Kengne AP, Stamatakis E, Hamer M, Batty GD (2011) Body mass index, waist circumference and waist-hip ratio: who is the better discriminator of cardiovascular disease mortality risk?: evidence from an individual-participant meta-analysis of 82 864 participants from nine cohort studies. Obes Rev: 12: 680-687. [Crossref]
of parathyroid hormone-related protein (PTHrP) to vascular smooth muscle in transgenic mice lowers blood pressure and alters vascular contractility. Endocrinology 140: 1815-1825. [Crossref]


60. Quan J, Lorenz JN, Maeda S, Sutliff RL, Weber C, et al. (1999) Reduced blood pressure and increased sensitivity of the vasculature to parathyroid hormone-related protein (PTHrP) in transgenic mice overexpressing the PTHrP receptor in vascular smooth muscle. Endocrinology 140: 1826-1833. [Crossref]


68. Flegel KM, Kit BK, Orpana H, Graubard BL (2013) Association of all-cause mortality with overweight and obesity using standard body mass index categories. JAMA 309: 71-81. [Crossref]