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Editorial:

LEPTIN, OBESITY AND CONTROL OF BREATHING : THE NEW AVENTURES OF MR PICKWICK

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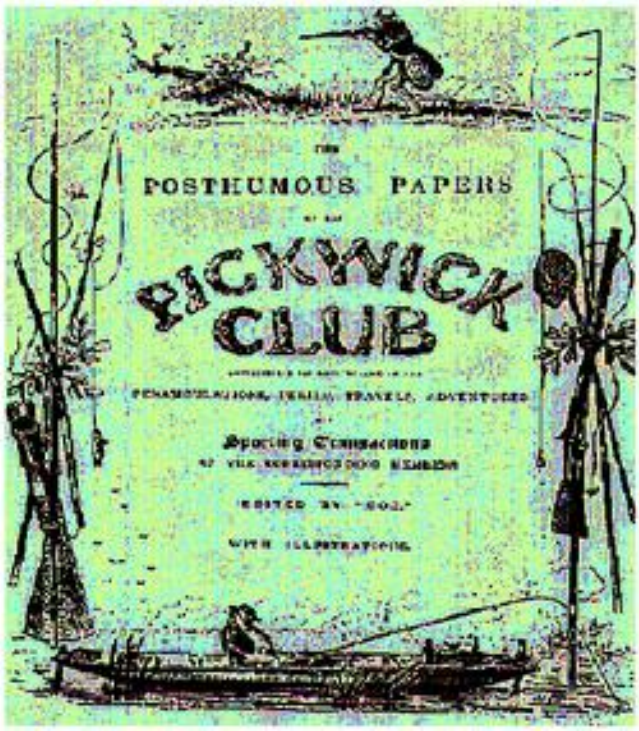
".... and on the box sat a fat and re-faced boy, in a state of somnolency....the fat boy rose, opened his eyes, swallowed a hugh piece of pie he had been in the act of masticating when he fell asleep....Joe-dams the boy he's gone to sleep again."
The posthumous paper of the Pickwick Club, Charles Dickens 1836

Spanish version

There are just two decades that respiratory disorders linked to obesity began to take an important place in medical publications. Nevetheless, fiction literature has largely anticipate (once again...) science: already in 1836, Charles Dickens drew in his novel "The posthumous paper of the Pickwick Club"[1] what would be, certainly, the best characterization of an obese subject with respiratory disorders.



Front wrapper from «The posthumous paper of the Pickwick Club» by Charles Dickens and drawn of Joe

It was necessary to wait more than 150 years so that Bickelmann et al[2]found a patophysiological explanation to the "phenotype" of Joe, "this fat red-faced boy, that snores as his wait at table, becomes easily asleep and then stop to breath", when they described apneas and alveolar hypoventilation in these subjects.

The link between obesity and respiratory failure is not fortuitous. Obesity, well known as a cardiovascular risk factor is also a "respiratory" risk factor. The respiratory consequences of obesity aggravated if patient suffers also of sleep apnea or COPD, may explain the occurence of life-threatening respiratory failure.

Moreover, in our modern society with 20-30% of the adult population be diagnosed with obesity, with a growing prevalence of this condition [3], [4] we can easily understand the more and more important place of obesity within the causes of respiratory failure.

Even though respiratory impact of obesity is evident[5] pathophysiological mechanims that may explain the developpement of hypercapnia in the obese population are nowadays no clear. Leptin, a recently described protein, may put some light in this darkness.

Leptin (from the greek leptos: thin) is an endogene proteine described as an adipose-derived hormone. Leptin receptors are founded in the hipothalamus and several physiological actions were described for this hormone 6,7. Amongst them, it must be underlined its role in the angiogenesis, in vascular tone regulation and autonomous nervous system control, in pituitary-adrenal axis supression and also a potential role in the hypothalamic amenorrhea syndrome. But its main action seems to be its participation in the metabolic regulation of body weight. In this context, circulating plasma leptin levels reflect the amount of energy storage and increases exponentially with increasing fat mass8. This hormons may acts then as a negative feed-back system by activating specific receptors associated with apetite supression and increased energy expenditure [6], [7]. Amongst them, it must be underlined its role in the angiogenesis, in vascular tone regulation and autonomous nervous system control, in pituitary-adrenal axis supression and also a potential role in the hypothalamic amenorrhea syndrome. But its main action seems to be its participation in the metabolic regulation of body weight. In this context, circulating plasma leptin levels reflect the amount of energy storage and increases exponentially with increasing fat mass[8]. This hormons may acts then as a negative feed-back system by activating specific receptors associated with apetite supression and increased energy expenditure[6].

Recent investigations suggested also, a responsability of leptin in control of breathing, in particular in the obese population.

First evidences of this relationship were suggested by studies in animal odels which lack the gene responsible for production of leptin. These animals show marked abnormalities in breathing control that lead to chronic respiratory failure. This breathing control dysfunction is aggravated during sleep, mainly during REM period. Event though these animals developped also obesity as a consequence of leptin deficiency, respiratory dysfunction appeared earlier and seems to be independent of that[9]. On the other hand, even though obesity superimposed-increase in thoraco-abdominal mechanical load may aggravate by itself the ventilatory failure, these animals show also some modifications in myosine heavy chain composition that lead diaphragme less resistant to fatigue developpement. This may explain, at less partially, the typical reduction in total lung capacity and compliance found in obesity and the propensity of this population to develop hypercapnia[10]. These modifications didn't appear in animals free of leptin pathway abnormalities and in which obesity was induced artificially. Finally, these abnormalities, which are characteristics in the human of the so called obesity hypoventilation syndrome (OHS), reversed after leptin replacement therapy[10].

It seems fascinating to extend this hypothesis to the human, so that leptin may acts by stimulating ventilatoy drive in response to an increase in the ventilatory load, typical of obesity and that, in this context, leptin deficiency may lead to OHS. Then, if obesity is considered as a necessary but no as a sufficient condition to hypoventilate, a deficiency of this hormone may explain the abnormal ventilatory comportment in the obese subgroup that develop hypercapnia. Nevertheless, in the human being the situation seems to be more complex: if in the animal model, a narrow correlation exists between leptin low levels and propension to obesity and ventilatory failure, in the human, this relationship is variable. Generally, leptin deficiency in human obesity is extremely rare and on the contrary, circulating leptin levels are high. We could characterize then, human obesity as a true leptin-resistant state[11]. Given that leptin ventilatory effects were mediated by its hypothalamic recceptors, we could speculate that this leptin-resistant state may be explained by two differente mechanims: first to an impaired transport across the blood-brain barrier and second to an impairement in central leptin signaling (i.e down-regulation of leptin receptors)[12]. Supporting the first hypothesis, it has been demonstrated leptin-specific binding sites in the

choroid plexus[13] that may act as leptin carriers through the blood-brain barrier. In this context, it was also showed a negative correlation between the CSF/serum leptin ratio and body mass index (BMI)[14], This finding suggest that leptin enters the brain by a saturable transport system. As the capacity of leptin transport is lower in obese individuals, this may provide an explanation to leptin resistance.

Some published evidences reinforce the relationship between leptin and ventilatory comportment in obesity:

- Circulating leptin levels is a better predictor of OHS than BMI itself[15] and those independently of apnea hypopnea index
- Non invasive ventilation (NIV) used regularly, reduces serum leptin levels in OHS. In this context, reversal of hypoventilation obtained by NIV, may reduce the "need" of high leptin levels to fight against the increased ventilatory load in obesity[16]

This suggest that CNS-leptin levels may act to mantain alveolar ventilation to compensate for the increased ventilatory load in obesity, and that abnormalities in the leptin metabolic pathway may explain whether, at same ventilatory load, some obese hypoventilate but others not.

Obstructive sleep apnea (OSA) is another respiratory condition associated to obesity. Prevalence of obesity in OSA population varies from 40 to 70% according to different authors[17]. There are also several evidences concerning the relationship between leptin and OSA. Among them, it must be underlined:

- Intermittent hypoxia, that characterizes sleep apnea, is a main determinant of circulating leptin levels and those independently of the degree of obesity[18], [19]
- OSA patients have higher leptin levels than non-OSA ones when compared relative to BMI[20] Moreover leptin levels correlate with severity of OSA mesured by apnea hypopnea index[21]
- High leptin levels seems to favor increased visceral fat accumulation. One of the main characteristics of visceral obesity is the increased deposition of fat or soft tissue in the neck and upper airway region. This may predispose the subject to upper airway collapse, that characterizes OSA[21]. For case, it must be emphasized that obesity type (i.e centripetal obesity) and, in particular, neck circumference predicted better presence of OSA that BMI itself [22].
- CPAP therapy in OSA reduces circulating leptin levels[23] I was also described that regular use of CPAP may lead to a reduction in visceral fat deposition in OSA patients [24].

Furthermore, OSA is one of the main determinants of hypoventilation in obese individuals[25]. In this way, leptin levels, were significtively higher in hypercapnic OSA when compared to no hypercapnic ones and those independently of BMI[26].

All these findings reinforced the importance of leptin-pathway abnormalities (and in particular of a leptin-resistant state) in the pathophysiology of the two most relevant obesity-associated respiratory diseases, and the probable role of these abnormalities as a link between these two conditions (i.e by promoting hypercapnia in OSA patients)

These complex interactions lead to envisage a sort of vicious cercle in which leptin plays a role crucial (Figure 1)

Then, we can propose the hypothesis that obese humans may be at risk for developping respiratory abnormalities in two specific situations: the rare cases of patients with "true" leptin deficiency (with low plasma and CSF leptin levels) and the much more frequent scenario of those with a leptin-resistant state (with plasma levels high but CSF levels proportionately low)

In conclusion, besides of its known role in regulating body weight and energy expenditure, leptin seems to have miscellaneous effects on respiratory function in obesity. Its stimulatory action on respiratory control center seems to be a protective mechanism against respiratory complications in obesity. The leptin-resistant state, that characterize a particular subgroup of obese patients, seems to play an important role in known obese-associated ventilatory disorders such as OSA and OHS. These findings open a fascinating way: the future potential of using soluble leptin analogues (that may penetrate the CSF barrier), in the management of obesity-associated respiratory disorders. If this hypothesis will be confirmed, scientists will advance the first victory against the imaginative fictions sustained by the followers of the Pickwick's Club father.

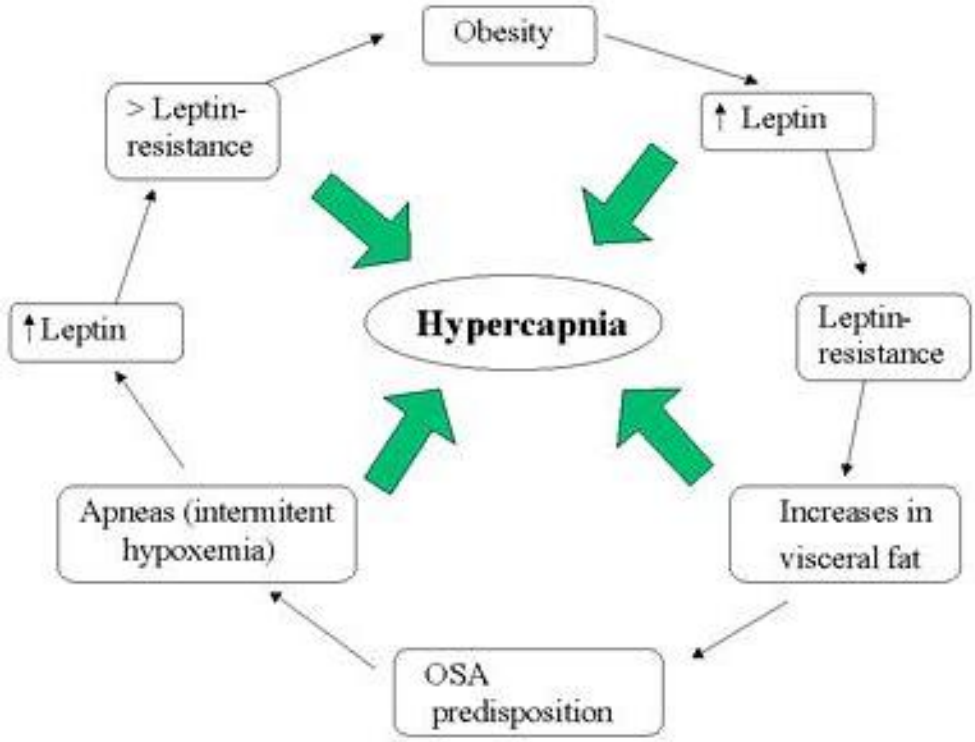


Figure 1: Obesity and respiratory disturbances: leptin's place

REFERENCES

1.- Dickens C. The posthumous paper of the Pickwick Club. London: Chapman and Hall, 1836

2.- Bickelmann AG, Burwell CS, Robin ED, et al. Extreme obesity associated with alveolar hypoventilation; a Pickwickian syndrome. Am J Med 1956; 21:811-818

3.- Fry J, Finley W. The prevalence and costs of obesity in the EU. Proc Nutr Soc 2005; 64:359-362

4.- Hedley AA, Ogden CL, Johnson CL, et al. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999-2002. Jama 2004; 291:2847-2850

5.- Rabec C, Merati M, Baudouin N, et al. Management of obesity and respiratory insufficiency. The value of dual-level pressure nasal ventilation. Rev Mal Respir 1998; 15:269-278

6.- Mantzoros CS. The role of leptin in human obesity and disease: a review of current evidence. Ann Intern Med 1999; 130:671-680

7.- O'Donnell CP, Tankersley CG, Polotsky VP, et al. Leptin, obesity, and respiratory function. Respir Physiol 2000; 119:163-170

8.- Considine RV, Sinha MK, Heiman ML, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 1996; 334:292-295

9.- Tankersley C, Kleeberger S, Russ B, et al. Modified control of breathing in genetically obese (ob/ob) mice. J Appl Physiol 1996; 81:716-723

10.- Tankersley CG, O'Donnell C, Daood MJ, et al. Leptin attenuates respiratory complications associated with the obese phenotype. J Appl Physiol 1998; 85:2261-2269

11.- Atwood CW. Sleep-related hypoventilation: the evolving role of leptin. Chest 2005; 128:1079-1081

12.- Polotsky VY, Wilson JA, Smaldone MC, et al. Female gender exacerbates respiratory depression in leptin-deficient obesity. Am J Respir Crit Care Med 2001; 164:1470-1475

13.- Malik KF, Young WS, 3rd. Localization of binding sites in the central nervous system for leptin (OB protein) in normal, obese (ob/ob), and diabetic (db/db) C57BL/6J mice. Endocrinology 1996; 137:1497-1500

14.- Caro JF, Kolaczynski JW, Nyce MR, et al. Decreased cerebrospinal-fluid/serum leptin ratio in obesity: a possible mechanism for leptin resistance. Lancet 1996; 348:159-161

15.- Phipps PR, Starritt E, Caterson I, et al. Association of serum leptin with hypoventilation in human obesity. Thorax 2002; 57:75-76

16.- Yee BJ, Cheung J, Phipps P, et al. Treatment of Obesity Hypoventilation Syndrome and Serum Leptin. Respiration 2005

17.- Laaban JP, Cassuto D, Orvoen-Frija E, et al. Respiratory complications of massive obesity. Rev Prat 1992; 42:469-476

18.- Polotsky VY, Li J, Punjabi NM, et al. Intermittent hypoxia increases insulin resistance in genetically obese mice. J Physiol 2003; 552:253-264

19.- Sanner BM, Kollhosser P, Buechner N, et al. Influence of treatment on leptin levels in patients with obstructive sleep apnoea. Eur Respir J 2004; 23:601-604

20.- Tatsumi K, Kasahara Y, Kurosu K, et al. Sleep oxygen desaturation and circulating leptin in obstructive sleep apnea-hypopnea syndrome. Chest 2005; 127:716-721

21.- Ulukavak Ciftci T, Kokturk O, Bukan N, et al. Leptin and ghrelin levels in patients with obstructive sleep apnea syndrome. Respiration 2005; 72:395-401

22.- Young T, Palta M, Dempsey J, et al. The Occurrence of Sleep-Disordered Breathing among Middle-Aged Adults. N Engl J Med 1993; 328:1230-1235

23.- Ip MSM, Lam KSL, Ho C-m, et al. Serum Leptin and Vascular Risk Factors in Obstructive Sleep Apnea. Chest 2000; 118:580-586

24.- Chin K, Shimizu K, Nakamura T, et al. Changes in Intra-Abdominal Visceral Fat and Serum Leptin Levels in Patients With Obstructive Sleep Apnea Syndrome Following Nasal Continuous Positive Airway Pressure Therapy. Circulation 1999; 100:706-712

25.- Jeannin L, Rabec C. La fonction respiratoire de l'obèse. Rev Prat 1997; 11:35-38

26.- Shimura R, Tatsumi K, Nakamura A, et al. Fat Accumulation, Leptin, and Hypercapnia in Obstructive Sleep Apnea-Hypopnea Syndrome. Chest 2005; 127:543-549