Serum leptin concentration in heart failure patients: does the literature reflect reality?

We read with interest the recent letter by Bottner et al. published in this Journal[1], in which it was mentioned that leptin is possibly implicated in the wasting associated with severe illness. They reported that patients with severe heart failure had higher serum leptin levels, in comparison to those with less advanced heart failure. However, this is not supported either from their data or from the literature. The patients of Bottner et al. with NYHA stage III are reported to have higher serum leptin levels than those with NYHA stage II. In Fig. 1 of their paper, it appears that significant differences in serum leptin levels are those between NYHA III patients and controls (P<0.005) and NYHA II patients and controls (P<0.05). It is not clear from these data whether the difference between NYHA III and NYHA II is actually significant. The difference in P value noted does not indicate that leptin levels are different between NYHA III and NYHA II patients, as obtaining a significant test result simply demonstrates that it is unlikely that the null hypothesis is true, but it does not provide information on the magnitude of the difference. Moreover, it has been reported that in patients with cachexia associated to lung cancer, circulating serum leptin levels are not elevated[2]. Also, in chronic obstructive pulmonary disease patients, even in the presence of cachexia, circulating leptin is physiologically regulated[3].

Our own data[4] may offer a possible explanation for the apparent discrepancies in the literature[1,5,6] regarding the importance of leptin in heart failure patients. We measured serum leptin levels in 26 men with chronic heart failure stage III and IV, aged 68±2.1 years (mean±SEM). Serum leptin levels were elevated in our patients: 16.1±4.2 ng·ml⁻¹ (mean±SEM). In the most severely affected patients, who had manifestations of cardiac cachexia, according to the definition used by Anker et al.[7], serum leptin levels were decreased by less than half of those without cachexia (10.79±3.93 ng·ml⁻¹ vs 23.24±8.35 ng·ml⁻¹) although significance was not reached (P=0.1). These data contradict Bottner’s findings.

An hypothesis that is yet unproven but which could explain all the apparently contradictory results reported in the literature, is that serum leptin levels do increase in heart failure patients, but when the end stage is reached, there is a tendency for leptin levels to decrease in some patients, specifically in those with cachexia. If all heart failure patients are taken into account, increased and decreased leptin levels merge, yielding not considerably elevated mean values.

As Bottner pointed out, more research must be carried out in order to elucidate the exact role reserved for leptin, among the constellation of factors that are implicated in the pathogenesis of the heart failure syndrome. There are several reports showing alterations in leptin levels in chronic or acute disease[7]. Similar to the patients with cardiac cachexia reported by this group, we found, in critically ill patients with sepsis, who eventually died of the disease, significantly lower leptin levels than in patients who did survive the disease[1].

However, data referring to leptin in disease are not uniform, especially not when comparing different diseases, such as diseases of the lung. Certainly a variety of factors are implicated in the regulation of leptin, many of which are subject to endocrine and metabolic influences themselves, and may therefore directly or indirectly be affected in several disorders. Chronic heart failure constitutes a rather complex syndrome associated with disturbances in several metabolic and endocrine functions, e.g. the sympathetic nervous system[3], or co-factors of the metabolic syndrome, that may in turn influence leptin production and therefore may be responsible for the elevated leptin levels found in these patients. Indeed, Levy et al. found a positive correlation with elevated insulin levels[4].

Our intention was to find out whether or not leptin levels in heart failure patients are related to the elevated activity of the sympathetic nervous system. In contrast to what might have been expected from the fact that leptin expression is suppressed by catecholamines[5], we found an increase in plasma leptin levels[6]. Interestingly, in patients with pheochromocytoma there was also no suppression of leptin levels indicating...

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an impaired regulation of leptin [7]. The finding of elevated leptin levels in cardiac failure patients stage NYHA II or III is supported by Filipatos et al. and others [8]. From their data, however, it appears that leptin levels tend to decrease in cachectic patients with more advanced stages of the disease, which has only recently been confirmed by others [9]. This does not necessarily contradict our observations.

The patients reported in our study presented with normal or slightly elevated body mass index and did not reach the stage of cachexia (BMI ± SEM: 25.8 ± 1.7 kg·m⁻²). The leptin levels indicated (interquartile range) are normalized for the BMI, which should be considered when comparing leptin levels.

A possible explanation for increased leptin levels in less severely affected patients and decreased levels in cachectic end stage heart failure patients may be the predominant decline of muscle mass in milder degrees of the disease, with subsequent reduction of the lean/fat ratio, which is supposed to be responsible for increased leptin production. The further loss of body weight in cachectic patients with advanced disease is due to an additional decline in adipose tissue mass and may thus be associated with a decrease in leptin levels, as has been recently suggested [9].

Whether leptin is implicated in the pathogenetic process of the disease or more likely is affected as part of the several components deranged in the disorder of cardiac failure needs to be further clarified.

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References


[8] Murdoch DR, Rooney E, Dargie HJ, Shapiro D, Morton JJ, McMurray JJ. Irbesartan, and candesartan. A second meta-analysis, based on published comparisons between the various AT₁-receptor blockers and other classes of antihypertensive agents, was also presented. Both of these Merck-sponsored meta-analyses appeared to demonstrate a strong trend in favour of the antihypertensive efficacy of irbesartan and candesartan over that of losartan and valsartan. Moreover, in Table 7 of this paper, all of the studies listed showed comparability vs enalapril, but only irbesartan was comparable to the highest dose of enalapril (40 mg).

Meta-analyses must always be interpreted with caution since they pool data from diverse trials using different study designs and different patient populations. They are best used as hypothesis-generating exercises, to be followed by definitive, prospective, randomized trials. In fact, such blinded, randomized, head-to-head trials demonstrate superior antihypertensive efficacy of the newer AT₁-receptor blockers (irbesartan [12] and candesartan [13]) compared to the maximum recommended once daily dose and the recommended starting dose of losartan, respectively. These clinical trial results should be considered with recently published studies demonstrating that irbesartan provides more complete and more sustained blockade of exogenous angiotensin II than losartan or valsartan in healthy subjects [14,15].

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