

Leptin: a cardiovascular perspective

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Abstract

The development of obesity, as well as resultant type 2 diabetes, hypertension and cardiovascular disease, is causing concern in South Africa. Following the discovery of leptin in 1994, hopes were raised that the manipulation of the leptin axis might yield successful therapy for obesity. Although hope still remains, the role of leptin is more complex than was first envisaged. Strong evidence indicates that there is an important role for leptin in obesity-related hypertension, although the net effects of hyperleptinaemia on cardiovascular pathophysiology remain complex and are not clearly understood. Therefore, the cardiovascular side-effects of leptin as a possible anti-obesity drug deserve greater attention.

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Introduction

Within the realms of noncommunicable disease development in South Africa, obesity is a disease that causes concern. This especially holds true for type 2 diabetes and cardiovascular diseases. Disheartened obese individuals who are unsuccessful with weight management might consider anti-obesity treatment, such as leptin. In this review paper, we will attempt to describe the adipocytokine, leptin, and especially its actions on the cardiovascular system.

The discovery of leptin

Leptin, which is a 16 kDa hormone, was first identified in 1994.^{1,2} What made this discovery significant was that leptin is mainly synthesised and secreted by subcutaneous white adipose cells. This gave rise to the notion that adipose tissue is an endocrine organ. Since leptin is mainly secreted by adipose tissue, serum leptin levels are directly proportional to adipocyte mass.³⁻⁵ Leptin has a central role in energy homeostasis.⁶ It stimulates energy expenditure and inhibits appetite via the hypothalamus.^{7,8} Originally, these were the properties that raised the hopes of the public and industry that it might play a possible role in weight loss therapy.

Leptin and obesity

The importance of leptin in regulating the appetite and in energy expenditure was clearly demonstrated by individuals with congenital leptin deficiency who expressed severe hyperphagia (from the age of four months) and subsequent obesity.^{9,10} Within these severely obese individuals, hormone replacement

therapy represented the first, rationally based and effective treatment of human obesity.¹¹ The treatment consisted of daily subcutaneous injections of recombinant human leptin, and was expected to have beneficial effects on appetite, adipose mass and hyperinsulinaemia.¹² However, congenital leptin deficiency is a rare human genetic syndrome.¹³

Today, the obese population is not characterised by leptin deficiency, but is hyperleptinaemic, which is indicative of a leptin-resistant state.⁷ These elevated circulating leptin concentrations clearly fail to return body adiposity to within the lean range.¹⁴ Therefore, the ability of exogenous leptin to reduce food intake and body weight in the face of replete adipose stores (especially in obese individuals), seemed to be even more limited.¹⁵ Exogenous leptin doses produce a circulating leptin level more than 10 times that of normal levels, and result in only a small mean decrease in the body weight of obese subjects.¹⁶

The poor efficacy of leptin to promote leanness in obese individuals and the hyperleptinaemic state of obese subjects gave rise to the notion of functional leptin resistance. This term is loosely based on and comparable with the concept of insulin resistance in type 2 diabetes.¹⁴ It is of utmost importance to understand the possible mechanisms behind leptin resistance in order to determine the causes of obesity and to identify potential mechanisms that could be targeted for therapy.

The more effective role of exogenous leptin administration was demonstrated, which was based on results that indicated a relative leptin deficiency in the post-obese state.^{7,17,18} After weight loss, obese

individuals indicated a steep decrease in serum leptin that was disproportional to changes in adiposity.⁷ This resulted in an increased appetite and decreased energy expenditure, with consequential weight gain. More recently, it was shown that exogenous leptin administration in weight-reduced obese subjects resulted in improved satiation.¹⁹

To summarise, the existing evidence on recombinant leptin therapy suggests that relatively high doses of exogenous leptin result in only a small decrease in the body weight of obese individuals.^{14-16,20} This is understandable in the case of a leptin-resistant condition in obese individuals.

The metabolic functions of leptin

It is not the main purpose of this paper to unravel the metabolic effects of leptin, which are quite wide-ranging. In short, leptin is an important regulator of insulin action. This is demonstrated by leptin-deficient and leptin-resistant conditions, which are both characterised by insulin-resistant glucose metabolism.^{21,22} Also, in subjects with leptin deficiency, leptin administration improves insulin sensitivity.⁶ Insulin, in turn, stimulates leptin secretion by adipocytes.²³ This so-called adipoinsular axis functions as a hormonal regulatory feedback loop under normal physiological conditions.²⁴⁻²⁶ The physiological regulation of body

weight by leptin seems to be disturbed (leptin resistance) in overweight or obese individuals. At the level of the pancreatic β -cell, leptin resistance may contribute to dysregulation of the adipoinsular axis and result in hyperinsulinemia, and ultimately the development of type 2 diabetes mellitus.²⁷

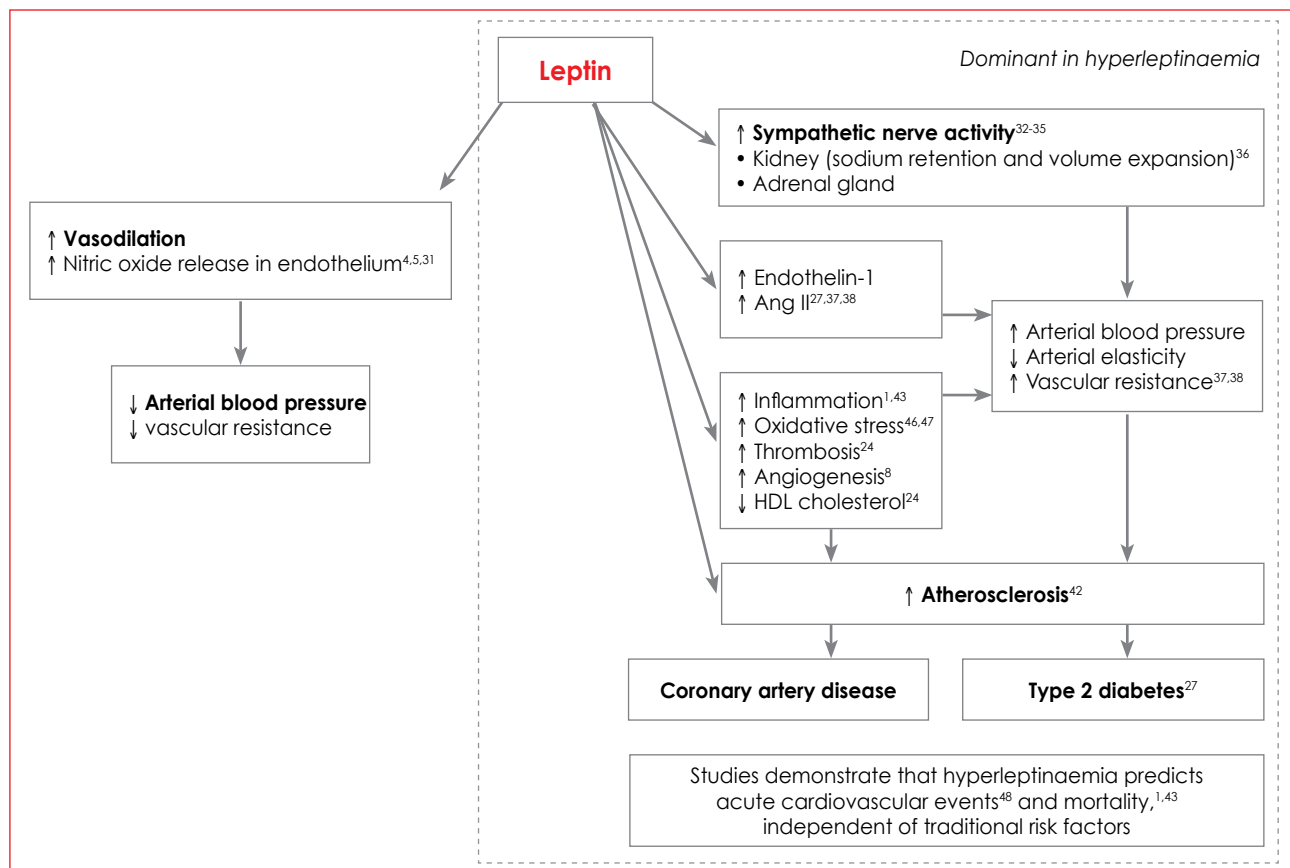
Apart from its effects on insulin, leptin seems to have various beneficial effects under normoglycaemic conditions, including hepatic glucose production and lipid metabolism.¹⁴ However, under hyperleptinaemic or hyperglycaemic conditions, these functions are disrupted, as in the obese leptin-resistant state.¹⁴

The biological functions of leptin are far-reaching, and even include providing support to reproductive competence, immune function and bone biology.^{14,28-30}

Leptin and the cardiovascular system

Apart from the central functions that involve energy metabolism and homeostasis, leptin may also exert actions that relate to cardiovascular homeostasis directly.

The actions within the cardiovascular system to maintain normal blood pressure seem to be balanced (Figure 1) in lean individuals with normoglycaemia and leptin sensitivity. These actions refer to blood pressure-lowering mechanisms (via vasodilation, by promoting



Ang II: angiotensin II, HDL cholesterol = high-density lipoprotein cholesterol

Figure 1: The cardiovascular actions of leptin

nitric oxide release from the endothelium),^{4,5,31} but also to mechanisms that increase blood pressure. These pressor actions mainly refer to the elevating sympathetic drive³²⁻³⁴ via the corticotrophin-releasing factor.³⁵ Elevated renal sympathetic nerve activity results in sodium retention, volume expansion, and blood pressure elevation.³⁶ Leptin also promotes the release of vasoconstrictive substances, such as angiotensin II and endothelin-1,^{24,37,38} thereby increasing blood pressure.

However, in obese hyperleptinaemic or leptin-resistant conditions, the homeostatic control of blood pressure is impaired. Although leptin resistance refers to the condition of diminished cellular and metabolic responsiveness to leptin,¹⁴ a condition of partial or selective leptin resistance seems to exist. Selective resistance is thought to occur mainly in central neural signalling pathways downstream of the leptin receptor.^{22,44} Thus, the metabolic effects of leptin, which result from the arcuate nucleus, are impaired, whereas the sympathoexcitatory effects are maintained.⁴⁵ This limits the effectiveness of leptin in the treatment of common human obesity.⁴⁶ Consequently, much research has been devoted to finding the mechanisms and treatment of partial leptin resistance in human obesity.^{22,44}

Apart from its described pressor and depressor actions, leptin also affects atherogenesis,^{24,39,42} angiogenesis⁸ and thrombosis,⁴⁷ via direct and indirect mechanisms. At the vascular level, leptin seems to potentiate the secretion of various inflammatory markers (C-reactive protein, tumour necrosis factor and interleukin 2 and 6),¹ and stimulates the migration and proliferation of smooth muscle cells.⁴⁸ In obese conditions, leptin may also increase oxidative stress through multiple mechanisms.^{40,41}

When taking these wide-ranging cardiovascular actions of leptin into consideration, it is no wonder that numerous clinical studies have shown that hyperleptinaemia predicts acute cardiovascular events and restenosis after coronary injury and cerebral stroke, independent of traditional risk factors.^{43,47,49}

The role of ethnicity and gender on the cardiovascular effects of leptin

Healthy women have substantially higher leptin levels than men.²⁴ This was also demonstrated in black and white South African populations.⁵⁰ With regards to gender, it is unclear what the underlying mechanisms are. They may be due to differential fat distribution or different gender-related hormonal influences.^{51,52} Clear ethnic differences, with regard to the concentrations, as well as their association with cardiovascular measurements, were also described in the South African context (Figure 2). Our group and others have found that lean and overweight black women have

higher serum leptin concentrations than age- and obesity-matched white women.^{53,54} These higher leptin levels were accompanied by elevated blood pressure. However, when a comparison was made between obese black and white women, leptin levels were similar.⁵⁵ In addition to the ethnic differential leptin levels in pre-obese conditions, we also observed much stronger associations between leptin and various areas of fat deposition, namely body fat percentage, waist circumference, and skin-fold thicknesses of the iliac crest.⁵⁶ Thus, although black women exhibit higher leptin levels, their leptin concentrations are more weakly associated with obesity indices than those of white women. It is challenging to explain this observation, but it may be possible that certain tissues of black women, such as the stomach, ovaries, or skeletal muscle, may be more active in producing leptin independently of adipose tissue.⁵⁷

When investigating the links of leptin with blood pressure in obese women, we found that leptin in obese hypertensive black women is associated with systolic blood pressure and low arterial compliance. This was not evident in obese, but normotensive black women.⁶¹ Contrarily, obese white women who had similar leptin levels to obese African women had favourable associations of leptin with cardiovascular function.⁵³ This ethnic discrepancy is difficult to explain, but indicates an ethnic vulnerability which should be noted.

Cardiac changes are also a well-known consequence of obesity-related hypertension. Norton et al have described that adiposity-induced increases in left ventricular mass reflected an enhanced effect of blood pressure on left ventricular growth, which is an effect that may be mediated by leptin.⁵⁶

With regard to cardiometabolic consequences, we found that elevated leptin concentrations in both black and white women increased their odds of having the metabolic syndrome by six- to eightfold.^{10,64} Based on the various actions of leptin discussed before, this elevated risk could be explained by the detrimental effects of obesity, but also by the various metabolic and cardiovascular effects of hyperleptinaemia.

Apart from the link between leptin and blood pressure, we investigated whether leptin is also associated with subclinical atherosclerosis in black and white school teachers. Surprisingly, we found a significant and independent association between leptin and carotid cross-sectional wall area, which was independent of obesity, ethnicity and gender. This provides evidence of the atherogenic effects of leptin beyond blood pressure.⁵⁰

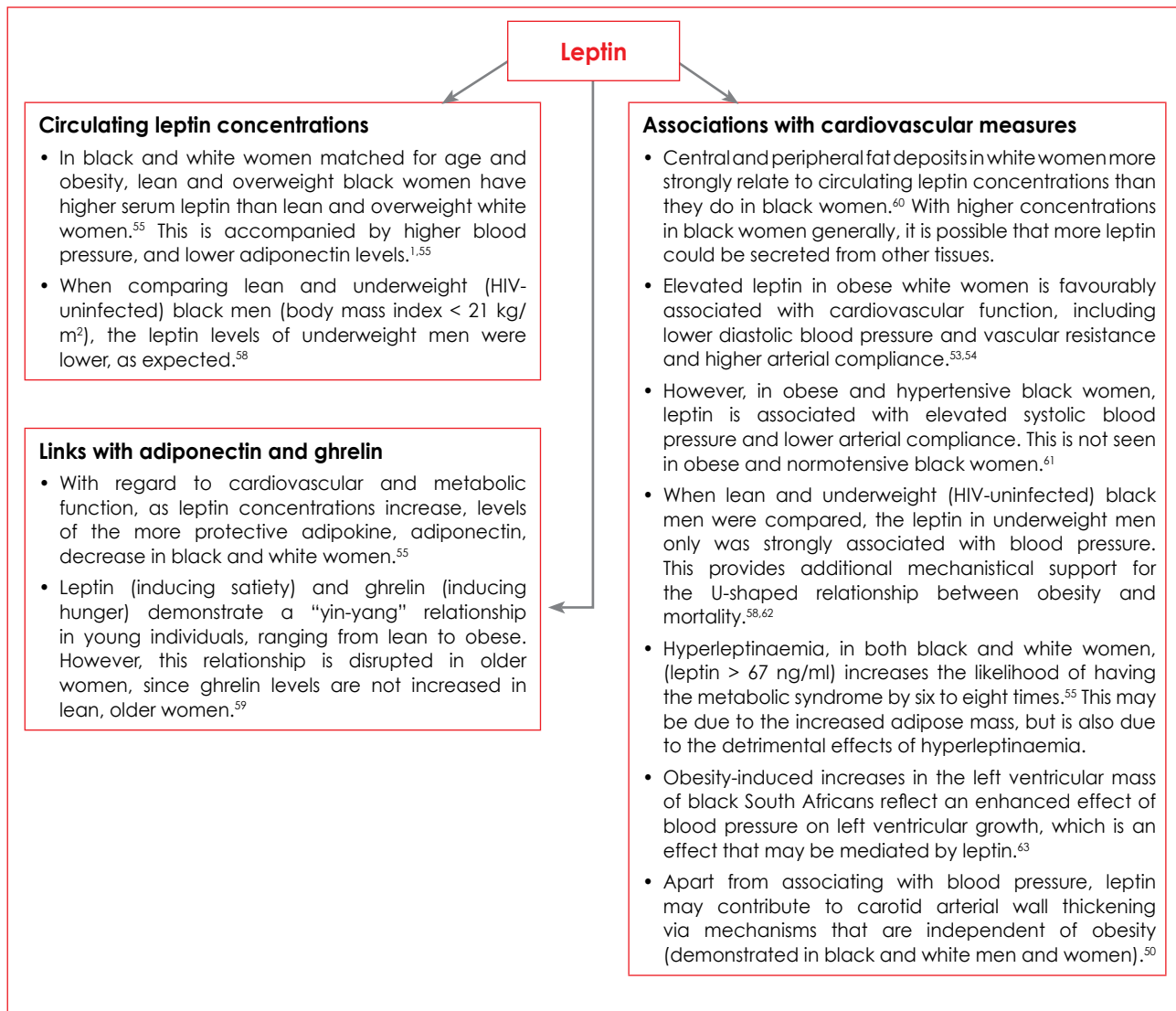


Figure 2: The cardiovascular actions of leptin in black and white South Africans

On the other side of the obesity spectrum, it is well-known that a U-shaped curve exists between body mass index and mortality.⁶² We found supporting evidence for this phenomenon in underweight (human immunodeficiency virus-uninfected) black men who exhibited strong positive relationships between blood pressure and leptin levels.⁵⁸ Since hypertension is not uncommon in lean and underweight black men, this finding may add mechanistic support to understand this phenomenon.

Conclusion

Consideration should be given to leptin and its significant actions, particularly within the cardiovascular system. Since the net effects of leptin on cardiovascular pathophysiology remain complex and are not clearly understood, careful evidence-based decisions should be made when considering exogenous leptin administration.

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