Leptin and Transplantation: Pieces are Still Missing in the Puzzle

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Leptin (from the Greek word *leptos* meaning "thin") is a 16 kD protein, which is the product of the *obese* (Ob) gene secreted primarily from adipocytes [1,2]. Its role in regulating food intake and energy expenditure has been well established, and it has become increasingly clear that it possesses other physiologic functions by which it influences neuroendocrine, reproductive, hemopoietic and metabolic control pathways, albeit by mechanisms that have yet to be elucidated [3]. These manifold capabilities distinguish this hormone as being one of special interest in almost all disciplines of medicine.

In the current issue of *IMAJ*, Kagan et al. [4] report on the characteristics of leptin secretion and its relationship to serum insulin and cortisol in patients following heart, liver and kidney transplantation. All the patients received immunosuppressive therapy consisting of prednisone, azathioprine, cyclosporine, or tacrolimus. No significant differences in serum leptin concentrations were observed between the three groups of transplanted patients. This study also supports previous works by showing that serum leptin concentrations are significantly higher in women than in men, and that they correlate with the body mass index [5,6]. In addition to BMI and gender, cortisol and insulin were the other important independent determinants of serum leptin concentration levels in their patients, as was also observed in other studies [6–8].

This work by Kagan and colleagues elicits several novel conundrums regarding the interaction between leptin and metabolic, hormonal and immune responses, the significance of which has remained elusive since this hormone was first identified.

Leptin and the kidney

The first enigma concerns a potential link between leptin and the kidney, particularly the long-term consequences of hyperleptinemia following renal transplantation. The kidney is known to be the principal site of elimination of circulating leptin in healthy subjects [9]. Moreover, a number of studies have shown leptin levels to be elevated in patients with chronic renal failure, both before and during peritoneal or hemodialysis [10]. Consequently, reversal of renal failure could be expected to have effected a *reduction* in leptin levels. Kagan et al., however, demonstrated *elevated* leptin serum concentrations in kidney transplant recipients. The authors postulate that leptin overproduction rather than the shortage of leptin degradation by the kidney would be the more likely explanation of hyperleptinemia in these patients. It should also be considered that altered body composition may have contributed to the hyperleptinemia observed in their post-transplant patients: solid organ transplantation usually results in significant weight gain [11–14], with most of the post-transplant weight gain representing an increase in fat mass [12,15]. Although Kagan's team did compare the leptin levels of patients with those in healthy controls at several time points following transplantation, had they accumulated such data before, shortly after and during the years following transplantation, their argument would have been considerably strengthened

Even more intriguing, however, is the fact that leptin has been implicated in detrimental renal effects by several investigators [16,17]. Wolf and co-workers [16] recently reported that leptin stimulates glomerular endothelial cell proliferation *in vitro* and *in vivo*, and that leptin administration in rats caused proteinuria and glomerular mesangial matrix expansion. This raises an important question about the effect of leptin on kidney function: could the chronic stimulation of glomerular cells by leptin contribute to glomerular remodeling and decreased kidney function? [17].

Thus, by showing that leptin secretion is increased following transplantation, this study has elicited further implications regarding its function in a transplanted organ. Moreover, if future studies reveal that leptin metabolism in end-stage renal disease is a detrimental factor, it follows that interventions to reduce leptin accumulation should be implemented [17].

Leptin and the cardiovascular system

The second mystery surrounds the effect of leptin on cardiovascular function. Cardiovascular disease is now the leading cause of long-term morbidity and mortality in kidney transplant recipients. The etiology of cardiovascular disease in the transplanted population is multifactorial: some of the immunosuppressive drugs may play a key role by causing or exacerbating hypertension, hyperlipidemia, and glucose intolerance. These cardiovascular risk factors are aggravated even more by the increase in body weight that occurs in the vast majority of patients after renal transplantation [14].

The effect of leptin on the heart may further contribute to cardiovascular morbidity. It has been shown to increase heart rate and blood pressure through sympathetic nervous system activity [18]. Moreover, fasting plasma leptin levels are associated with increased myocardial wall thickness, independent of body composition and blood pressure levels. Nickola et al. [19] have recently

BMI = body mass index

demonstrated that leptin depresses ventricular myocyte shortening and intracellular calcium transients, leading to depression of cardiac cell contraction. Thus, higher leptin levels following transplantation may affect not only the kidney, but the heart as well.

Leptin and the liver

The third riddle has to do with the effect of leptin on the liver. Several lines of evidence have suggested a possible link between leptin and hepatic fibrosis: leptin augments both inflammatory and profibrogenic responses in the liver, and it has been postulated that hyperleptinemia enhances up-regulation of transforming growth factor beta-1, leading to activation of stellate cells, whereupon the fibrogenic response in the liver is augmented [20]. Leptin has also recently been suggested to play a role in the pathogenesis of hepatic steatosis [21]. We now have a variation of the same theme as mentioned above: higher leptin levels following transplantation may affect not only the kidney and heart, but the liver as well.

Leptin and the immune system

Last but not least is the question of leptin's role as an immune modulator and its interaction with immunosuppression following transplantation. Both the structure of this hormone and that of its receptor suggest that a leptin might be classified as a cytokine [22]. Leptin has structural similarities to the long-chain helical cytokine family, which includes interleukin 6 and 11, ciliary neurotrophic factor, granulocyte colony-stimulating factor, and leukemia inhibitory factor; and it participates in both innate and acquired immunity. The host lymphocyte plays the central role in the immune response to transplanted allografts, possessing the specific capability to differentiate "self" from "non-self." Leptin regulates T cell responses, polarizing Th cells toward a Th1 phenotype, induces the production of pro-inflammatory cytokines (e.g., IL-2 and interferon gamma), and suppresses IL-4 production in activated T cells [23]. In addition, it modulates phagocytosis and cytokine production by macrophages and stimulates hematopoiesis of murine cells [24]. Thus, the significance of the role played by hyperleptinemia in immunomodulation following transplantation clearly warrants further exploration.

Conclusion

While Kagan and team's work provides substantial evidence that leptin levels are elevated in transplanted patients, the picture is still incomplete. The endocrine, immune and adipose systems are linked via an elaborate system made up of an array of cytokines and neuropeptides. The cross-talk between those systems may be of prime importance in the period following transplantation, and further studies are needed to delineate the pathophysiologic significance and wider ramifications of leptin secretion following transplantation. If it emerges that leptin metabolism following transplantation is maladaptive, interventions to reduce the accumulation of leptin secretions could become part of the protocol for transplant patient management.

IL = interleukin

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