Internal and Emergency Medicine (2019) 14:493–494
https://doi.org/10.1007/s11739-019-02074-8

IM - COMMENTARY

Leptin: a marker of renal injury

Sebastio Perrini[1]

Received: 10 March 2019 / Accepted: 12 March 2019 / Published online: 25 March 2019

Leptin, one of the major adipokines, is a pleiotropic hormone whose plasma levels rise with the increase in adipose tissue. Leptin has a dual role as a hormone and a cytokine. As a hormone, it plays a critical role in regulating appetite, growth, energy and bone metabolism. As a cytokine, leptin participates in the enhancement of some pro-inflammatory responses. Increasing leptin concentrations in serum in obese patients significantly contributes to the low-grade inflammatory state that makes those subjects more prone to develop insulin resistance, type 2 diabetes, cardiovascular and autoimmune diseases [1].

Several recent studies have demonstrated that leptin is mainly cleared by the kidney, which is an organ targeted by leptin activities, and patients with end-stage renal diseases exhibit increased plasma leptin concentration [2]. Indeed, it has been shown that leptin-deficient ob/ob mice are protected from renal inflammation and nephrotoxic nephritis. Leptin is involved in the development of glomerulosclerosis through a paracrine TGF-β pathway (between glomerular endothelial and mesangial cells), which promotes the deposition of extracellular matrix and proteinuria [2].

In the Internal and Emergency Medicine Journal, D'Elia and colleagues report the results of an elegantly conducted and analysed study designed to estimate the predictive role of leptin on the decline in renal function occurring in an 8-year follow-up observation of a sample of apparently healthy male adults (The Olivetti Heart Study) [3]. The study included 319 untreated normotensive and not diabetic men without clinical evidence of renal dysfunction at baseline. Elevated serum concentrations of leptin were strongly associated with early renal function loss that starts in patients who have normal renal function. The association was also independently accounting for relevant clinical covariates: age, systolic blood pressure, HOMA index, renal clearance, abdominal circumference and BMI. The main strength of this study is that, unlike previous studies, leptin promotes over time early and late function loss in untreated normotensive and not diabetic men without clinical evidence of renal dysfunction at baseline. The authors suggest a direct effect of leptin in promoting endothelial dysfunction and vascular damage with glomerular endothelial cell proliferation, increased synthesis of collagen and hypertrophy of the mesangium cells. D'Elia and colleagues also argue that high-circulating leptin levels were also significantly associated with increased serum levels of ICAM-1 (soluble intercellular adhesion molecule-1) and VCAM-1 (soluble vascular cell adhesion molecule-1), adhesion molecules markers of endothelial disorder, and reduced arterial compliance in patients with chronic kidney disease [3]. However, the study regarding the specific mechanisms and biomarkers involved in the disease process underlying renal function decline is inconclusive. Indeed, the study leaves one question open. Specifically: how could elevated circulating levels of leptin directly contribute to renal injury? It has been shown that leptin activates a number of signalling pathways that have been previously described as important in promoting cellular damage including MAPK, Wnt/β-catenin and TGFB1 pathway [1]. Along these lines, it is the observation that in cultured HUVECs, leptin increased ICAM-1 production in a dose-dependent manner, and this stimulating effect of leptin on ICAM-1 expression was reversed by MEK inhibitor, PD98059 [4]. Several reports have shown that fibrosis, the histological manifestation of functional decline in the kidney, is associated with an increased expression and activity of Notch and Wnt signalling. Excessive Wnt and Notch expressions prohibit epithelial differentiation and induce fibroblast proliferation and myofibroblastic transdifferentiation that seem to be important for the development of kidney fibrosis and dysfunction [5]. A number of experimental evidences indicate that leptin induces the expressions of Wnt and Notch in several cell lines and that the inhibition of leptin signalling reduces Notch and Wnt expressions and

✉ Sebastio Perrini
sebastio.perrini@uniba.it

[1] Section of Internal Medicine, Endocrinology, Andrology and Metabolic Diseases, General Surgery and Liver Transplantation Unit, Department of Emergency and Organ Transplantation, University of Bari Aldo Moro, Piazza Giulio Cesare, 11, 70124 Bari, Italy

development of aberrant cellular responses [5, 6]. Lastly, in experimental models, leptin in vitro as well as in vivo, infusion stimulates the expression of TGF-β. TGF-β is a major modulator of renal fibrosis and acts through the stimulation of extracellular matrix proteins as well as the inhibition of degradation of these proteins [7].

Although it remains currently unknown whether similar mechanisms are operative in humans, it is possible that enhanced circulating leptin concentrations, particularly in pathophysiological situations such as obesity or diabetes mellitus type 2, may contribute to the renal injury that is often observed in these diseases. We can speculate that leptin, through the above pathways and in concert with other cytokines or vasoactive factors such as Ang II, may foster the development of glomerular pathologies.

The overall pathophysiological changes described by D'Elia and colleagues are still observational, and further studies are certainly necessary in order to understand the underlying mechanisms promoting leptin-induced renal damage in not diabetic men without clinical evidence of renal dysfunction at baseline.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

Statement of human and animal rights The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Informed consent For this type of study formal consent is not required.

References

1. Zhang Y, Chua S (2017) Leptin function and regulation. Compr Physiol 8:351–369
2. La Cava A (2017) Leptin in inflammation and autoimmunity. Cytokine 98:51–58
3. D'Elia L, Manfredi M, Perna L, Iacone R, Russo O, Strazzullo P, Galletti F (2018) Circulating leptin levels predict the decline in renal function with age in a sample of adult men (The Olivetti Heart Study). Intern Emerg Med. https://doi.org/10.1007/s11739-018-1924-9
4. Cha JJ, Hyun YY, Jee YH, Lee MJ, Han KH, Kang YS, Han SY, Cha DR (2013) Plasma concentration of soluble intercellular adhesion molecule-1 (sICAM-1) is elevated in type 2 diabetic patients, and sICAM-1 synthesis is associated with leptin-induced activation of the mitogen-activated protein kinase (MAPK) pathway. Inflammation 201(36):878–887
5. Edeling M, Ragi G, Huang S, Pavenstädt H, Susztak K (2016) Developmental signalling pathways in renal fibrosis: the roles of Notch, Wnt and Hedgehog. Nat Rev Nephrol 12:426–439
6. Harbuzariu A, Rampoldi A, Daley-Brown DS, Candelaria P, Harmon TL, Lipsey CC, Beech DJ, Quarshie A, Ilies GO, Gonzalez-Perez RR (2017) Leptin–Notch signaling axis is involved in pancreatic cancer progression. Oncotarget 8:7740–7752
7. Wolf G, Hamann A, Han DC, Helmchen U, Thaiss F, Ziyadeh FN, Stahl RA (1999) Leptin stimulates proliferation and TGF-beta expression in renal glomerular endothelial cells: potential role in glomerulosclerosis. Kidney Int 56(3):860–872