LINKS BETWEEN RENIN-ANGIOTENSIN SYSTEM GENETIC POLYMORPHISMS AND LEPTIN SECRETION IN OBESE HEART FAILURE PATIENTS

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Abstract

Chronic heart failure (CHF) and obesity are two conditions frequently associated and which, despite all the advances made in their management in the recent years, their prevalence continues to rise. Obese patients present unique challenges in the diagnosis of CHF and also therapeutic particularities. The genetic differences may be a possible explanation for the fact that some people, irrespective of their lifestyle and common classical cardiovascular risk factors, are more susceptible to develop heart failure. Moreover, the adipose tissue, a huge endocrine organ which secretes adipokines, is also a well-established source of all renin-angiotensin-aldosterone system components, being strongly involved in the pathogenesis of CHF. That is why this review will explore the possible links between the RAS genetic polymorphisms and leptin secretion in obese HF patients, trying to bring a more precise understanding of this relationship, which will undoubtedly facilitate a more appropriate treatment of HF in obese patients. We also try to explain the possible incriminated mechanisms, and plausible biological explanations for the relationship between RAS genetic polymorphisms and adipokines secretion in obese heart failure patients.

Key words: chronic heart failure, obesity, renin-angiotensin system, genetic polymorphisms, leptin.

INTRODUCTION

Heart failure is a progressively debilitating disease, with a climbing prevalence, currently being encountered at a rate of 1-2% of the population in developed countries, despite all existing treatments (1). The presence of obesity in heart failure patients is frequently observed in clinical practice and these two conditions are representing alarming public health problems (2).

Undoubtedly, obesity is a major cardiovascular risk factor, which also brings an additional challenge in

the diagnosis of heart failure. This is due to the fact that usually patients with obesity present dyspnea, oedema, a decreased exercise capacity, but also low acoustic echocardiographic images which limit the diagnostic accuracy (1). Another particularity is that obese patients have lower natriuretic peptides' levels, which are important diagnostic and prognostic biomarkers in heart failure (2).

The “obesity paradox” phenomenon in heart failure

Obese heart failure patients seem to have a better prognosis than normal weight subjects - the so-called “obesity paradox”, phenomenon which is seen in other chronic diseases, too (1, 2). The relationship between the body mass index (BMI) and the prognosis of cardiovascular patients has been a controversial for a long time. But, recent studies strongly suggest a favourable prognostic of heart failure in patients with obesity, even though the exact mechanism is yet not completely understood. It remains to be fully demonstrated that obesity has a true protective effect, being of major importance in choosing the best treatment strategy. From our point of view, the main mechanistic hypotheses explaining a better outcome in obese patients with heart failure is the balance between the anabolic and catabolic burden. A low BMI in heart failure is associated with the so-called “malnutrition-inflammation complex syndrome”, with TNF- α and cytokine activation and hypoalbuminaemia, being of extremely poor prognosis (3). That is why the guidelines do not recommend a weight loss in heart failure patients with a body mass index (BMI) <35 kg/m², but only in those with a BMI 35- 45 kg/m² (1).

Particularities of heart failure in obese patients

Commonly, obese individuals develop heart failure with preserved ejection fraction. Recent studies

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have shown that obesity, especially the visceral adiposity, induces subclinical diastolic dysfunction, this association being independent of the presence of other traditional cardiovascular risk factors. They suggest that early cardiomyocyte hypertrophy and interstitial matrix expansion may precede organ-level pathology. Long-term obese subjects present a cardiometabolic profile, including left ventricle hypertrophy, diastolic dysfunction, and increased vascular stiffness, which finally lead to heart failure (4). Alternatively, obesity can directly affect myocardial structure and function by increasing the circulatory volume and cardiac output, but also by having a local effect. The association of obesity and heart failure involves abnormal metabolic, inflammatory, neurological and neurohormonal changes, and moreover the synthesis of various adipocyte cytokines - the most important being adiponectin and leptin (5).

The role of adipokines in heart failure development

The adipose tissue also acts as an endocrine

organ, with a huge contribution in regulating metabolism and immune responses. The adipocytes secrete a large number of adipokines, such as adiponectin, leptin, angiotensinogen, TNF- α , IL-6, MCP-1, plasminogen activator inhibitor (PAI-1), resistin, visfatin, omentin. Some of them are closely related to the cardiovascular system. Therefore, leptin, angiotensinogen, TNF- α , IL-6, MCP-1 and plasminogen activator inhibitor (PAI-1), resistin, visfatin are closely related to inflammation and atherosclerosis, while adiponectin and omentin seem to have anti-inflammatory and anti-atherogenic effects (5).

The existing link between adiposity and heart failure can be partially mediated by the secretion of adipokines. Several authors suggested leptin, a highly specific to human adipose cells cytokine, as being one of the most promising links.

Higher plasma leptin levels are associated with increased BMI and the majority of obese individuals are hyperleptinemic, due to a state of leptin resistance. The notion of “leptin resistance” in obesity is well-known

Figure 1. The association between obesity and heart failure is complex, involving a large number of interacting factors: metabolic, inflammatory (IL-6), neurohormonal changes with increased sympathetic tone, high leptin, visfatin and resistin levels. The fat deposits may have a direct role in the pathogenesis of coronary atherosclerosis and also the adipose tissue is a large endocrine organ, secreting all of the above adipokines and all of the RAS components. Genetic polymorphisms, such as INDEL mutation of the angiotensin converting enzyme, the angiotensinogen M235T and AT1 A1166C mutations have several implications in heart failure development and response to treatment.

and it is analogous to the insulin resistance found in patients with type 2 diabetes mellitus, moreover they frequently coexist in obese patients. This concept derives from the fact that the majority of obese individuals are not leptin deficient, but actually present high leptin concentrations. Even though, data is lacking regarding leptin's peripheral effects in obese patients, leptin has important implications in activating several immune cells implicated in atherosclerosis, such as T lymphocytes, monocytes and macrophages. (6). There has been an intense interest in the adipose tissue's role in the development and evolution of heart failure. But, studies in this area of research are still bringing controversial results. There are long-term prospective studies which show that higher baseline leptin levels are associated with an increased risk of heart failure in individuals without coronary artery disease, after adjustment for multiple risk factors, including body mass index (7). Also, some studies show that leptin is responsible for mitogenic effects, cardiomyocyte fatty acid loading, reduction of the cardiomyocyte contraction and progression of coronary artery calcification independently of other cardiovascular risk factors (6). Hyperleptinemia is associated with endothelial dysfunction, oxidative stress, hypertrophy and proliferation of vascular smooth muscle cells (8). Moreover, leptin itself represents a pro-inflammatory cytokine, knowing that atherosclerosis is viewed as an inflammatory disease. On the other hand, directly correlating plasma leptin levels to ischaemic events, independently of traditional risk factors remains controversial. There are small studies positively correlating plasma levels of leptin with cardiac ischemic disease (9). On the other hand, other studies found no association between high plasma leptin levels and atherogenesis. Higher levels of leptin may represent only a counter – regulatory response (10). There is strong data correlating hyperleptinemia found in obese patients with a favorable prognosis in heart failure, by neutralizing the direct myocardial harmful effects of other pro-inflammatory adipokines, as listed above (11-13). Also, recent data describes leptin's protective cardiovascular effects by regulating the non-esterified FFAs oxidation by the peripheral tissues, in this way preventing ectopic fat accumulation in peripheral organs, such as the heart, skeletal muscles or kidneys. Consequently, it prevents ceramides secretion from the ectopic adipose tissue, which are known as cytotoxic lipids leading to cardiomyocytes apoptosis and progression of heart failure (14).

Sex discrepancies in serum leptin levels exist.

Studies show higher plasma leptin levels and leptin receptor (ObR) expression in females compared with males after adjusting for age, BMI, and body fat percentage, indicating that female adipocytes produce more leptin per gram of adipose mass. Also, leptin levels inversely correlate with the waist-hip ratio, which is lower in women compared with men. As subcutaneous adipose tissue predominates in women, this may be responsible for higher rise in leptin levels with increasing BMI compared with men counterparts (15).

Genetic polymorphisms of renin-angiotensin-aldosterone system in obese adults with heart failure

It is well known that the renin-angiotensin-aldosterone system (RAS) plays a crucial role in the heart failure's pathogenesis. The cleavage of AGT, in the presence of renin, generates ANG I, which in turn, is the substrate for ACE (a kininase II enzyme) to obtain angiotensin II (ANG II). A link between the RAS and adipokines has already been demonstrated. Furthermore, a topic of particular importance regards the possible links between the RAS genetic modifications and the presence of obesity in heart failure patients. On the other hand, heart failure is a progressively debilitating condition and despite the broad array of treatment, a significant heterogeneity exists in the benefits of the current treatment and genetic differences may be a possible explanation for the fact that some people, irrespective of their lifestyle and common classical cardiovascular risk factors, are more susceptible to develop left ventricular dysfunction. It is also clear that the response to treatment is strongly influenced by the presence of different genetic mutations. Therefore, a special attention is given to the RAS components genes polymorphisms, such as angiotensinogen (AGT), angiotensin converting enzyme (ACE), angiotensin (ANG) receptors (AT1 and AT2), and aldosterone synthesis genes (2), especially in heart failure patients. Body fat and body weight could be influenced by the stimulation or inhibition of the ANG II production, indirectly linking RAS to obesity. A genetic ACE polymorphism was firstly described by Rigat *et al.* in 1990, who defined the INDEL mutation as either the presence (insertion, I) or absence (deletion, D) of a 287-bp insert in intron 16 of the gene on chromosome 17q23 (dbSNP rs1799752) (16). Afterwards, this INDEL mutation has been proposed as a genetic marker for many diseases, such as cardiovascular events or obesity-related complications. In the past decade, studies have successfully reported a strong relation

between the D allele or DD genotype and overweight/obesity (17).

Central actions of leptin on neurons and astrocytes are well-known, being responsible for metabolic regulation effects. Recent studies have shown leptin's effects on stimulating AGT expression in the brain or other peripheral tissues. AGT expression is correlated with the density of leptin receptors. Thus, it is conceivable that transcriptional control of AGT within selected cell types, to control metabolic function, may be done through second-messenger systems that are directly activated by leptin (18).

Leptin is also known to regulate activity of the forkhead transcription factor 1 (FOXO1), which is highly expressed in insulin sensitive tissues, including the adipose tissue (18). FOXO1 found in the liver has been shown to positively regulate AGT and ANG plasma levels. Hyperleptinemia may lead to an overexpression of FOXO1 in the hepatic cells. FOXO1 may regulate AGT expression in various cell types, including adipocytes (18).

The adipose tissue is a well-established source of ANG II, which has been demonstrated to have local effects, ranging from the regulation of local blood flow to complex influences on adipocyte growth and differentiation (19). Increased levels of ANG II seem to promote obesity through the conversion of preadipocytes to adipocytes (19).

Also, studies have shown the expression and localization of ACE, as well as other components of the RAS pathway, in human adipocytes (20). A study regarding the ACE polymorphism in heart failure patients, published in *Acta Endocrinologica (Buc)*, reported that in heart failure patients, there is an inverse correlation between BNP value and BMI, obese patients having lower BNP fragment (8-29) values, irrespective of ACE polymorphisms (DD, II or ID allele) (21). Furthermore, there is strong evidence linking the DD genotype to obesity (22). Moreover, Wacker *et al.* also found a significant association between the ACE I/D polymorphism and obesity, but only in men (22). Hormonal differences between sexes may influence the effects of ACE I/D polymorphism on the weight gain (22).

The presence of AT1 receptors of ANG type II at the adipose cell level has also a major clinical impact in heart failure patients. For example, there is evidence that the administration of angiotensin receptor blockers increases the adiponectin level (23). However, additional studies are required to establish the effects of the RAS blockade on different adipokines, especially

in the presence of various genetic polymorphisms.

The adipose tissue represents an important endocrine organ, secreting besides adipokines, multiple inflammatory cells - CRP, IL-6, angiotensinogen, PAI-1, TNF- α (24). Inflammatory cells have synergic effects with leptin and resistin on the atheroma, by inhibiting the nitric oxide production and stimulating the LL-cholesterol, endothelin secretion and AT1 receptors (24). ANG II AT1 receptors are highly expressed in the adipose tissue. Three genetic types of AT1 receptors: CC, AA and AC have been identified, depending on the type of nucleotide found in the AT1 mRNA 1116 position. Of all these genotypes, the CC homozygous type is mostly associated with cardiovascular diseases (arterial hypertension, heart failure) (25). AGT synthesis, an important SRA precursor, is encoded by a gene located on the chromosome 1q42-q43, found in the proximal tubule of the kidneys (26). Human AGT has 485 amino acids, including a 33 amino acids long signal peptide. It has two sites for glycosylation of several aminoacids (ASN-X / THR-X in the 295 and 319 position). The glycosylation takes place in the liver. The AGT gene has two variants: T235M and T174M, threonine being replaced with methionine in the 235, respectively 174 position (26). The M235T gene variant, induced by a single nucleotide change of the exon 2 of the AGT gene was associated with high AGT plasma levels. 10-20% higher levels of plasma AGT levels were described in 235TT homozygotes in comparison with 235MM homozygotes. These genetic variants have shown a significant association with the risk of arterial hypertension and metabolic syndrome development (26). Moreover, the association of two AGT mutations (M235T and T174M) was found as being an independent predictive factor for mortality in heart failure, by doubling the mortality risk (26). The M235T AGT gene variant has been explored in humans also in relation with obesity. For example, Procopciuc *et al.* demonstrated the role of the AGT mutations in the pathogenesis of the metabolic syndrome (MetS), showing that in hypertensive subjects with MetS, the presence of TT235, MM174, DD and CC1166 genotypes represent risk factors for central obesity and dyslipidemia (27). Thus, it can be assumed that high AGT secretion from the adipose tissue, consequently leading to high plasma ANG levels, especially in the presence of genetic mutations, has important implications in the heart failure's pathogenesis. Also, leptin has synergic effects on the AT1 receptors with its possible genetic variants (25), being a trigger in the pathogenesis of heart failure by stimulating the aldosterone production

and sympathetic nervous system, with consequent vasoconstriction and oxidative stress.

AT1 receptors are located in the vascular smooth muscle cells and myocardium, mediating vasoconstriction and salt-conserving actions of the RAS, and therefore represent an interesting candidate gene for heart failure, especially in obese patients with hyperleptinemia. A single nucleotide polymorphism (SNP), A1166C, located in the 3' untranslated region (UTR) of AT1 gene, has been characterized and investigated in relation to arterial hypertension and metabolic syndrome (27). AT1 receptor gene polymorphisms are associated with a worse prognosis of heart failure as studies show that a single-nucleotide polymorphism A1166C has important consequences on ventricular remodeling (28).

There is a clear relationship between AT1 receptor A1166C single-nucleotide polymorphism and the development of heart failure in patients with coronary heart disease and hypertension. This genetic variant leads to increased expression of AT1 receptors with important consequences for ventricular remodeling, increased aldosterone secretion and fluid retention (28).

The following figure tries to illustrate the above mentioned links between the adipose tissue, RAS and leptin secretion in obese heart failure patients.

At the same time, the high expression of the AT1 receptors in the adipose tissue observed in obese patients may increase the sensitivity to serum ANG II with subsequent activation of the heterotrimeric G proteins, thus influencing the production of adipokines. So far, there is no data in the literature regarding the association between patients with heart failure, A1166C genetic mutation of the AT1 receptor and the adipocyte secretion of the key adipokines, in particular leptin. Further research in this area is needed in order to evaluate if genetic mutations of AT1 receptor influence leptin concentrations in obese patients.

Future research will determine if the reduction of circulating leptin and/or blockade of its peripheral actions can improve diastolic function or confer favorable myocardial remodeling in hyperleptinemic patients (29, 30). Furthermore, the response to drugs strongly depends on the genetic background, that is why pharmacogenetics continues to develop new possibilities in order to find the best therapy for each patient with heart failure and different comorbidities. Therefore, research in the field of genetic factors implicated in heart failure has not only scientific, but also an important practical value.

By studying the relationship between the AT1 polymorphism and the secretion of leptin and also by describing their potential direct effects in obese heart failure patients, we can add some valuable data in this field of research, yet far from being fully understood.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; 37: 2129-2200.
2. Ebong IA, Goff DC Jr, Rodriguez CJ, Chen H, Bertoni AG. Mechanisms of heart failure in obesity. *Obes Res Clin Pract* 2014; 8(6):e540-548.
3. Von Haehling S, Ebner N, Dos Santos MR, Springer J, Anker SD. Muscle wasting and cachexia in heart failure: mechanisms and therapies. *Nat Rev Cardiol*. 2017; 323-341.
4. Lima-Leopoldo AP, Leopoldo AS, Silva DC, Nascimento AF, Campos DH, Luvizotto RA, Oliveira Júnior SA, Padovani CR, Nogueira CR, Cicogna AC. Influence of long-term obesity on myocardial gene expression. *Arq Bras Cardiol* 2013; 100(3):229-237.
5. Yamawaki H. Vascular effects of novel adipocytokines: focus on vascular contractility and inflammatory responses. *Biol Pharm Bull* 2011; 34(3):307-310.
6. Hass A, Oz H, Mashavi M, Shargorodsky M. Role of RAAS and adipokines in cardiovascular protection: effect of different doses of angiotensin II receptor blocker on adipokines level in hypertensive patients. *J Am Soc Hypertens* 2014; 8(10):709-714.
7. Smith CCT, Dixon RA, Wynne AM, Theodorou L, Ong SG, Subrayan S, Davidson SM, Hausenloy DJ, Yellon DM. Leptin-induced cardioprotection involves JAK/STAT signaling that may be linked to the mitochondrial permeability transition pore. *Am J Physiol Heart Circ Physiol* 2010; 299(4):H1265-H1270.
8. Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Sattar N. Obesity and risk of incident heart failure in older men with and without pre-existing coronary heart disease: does leptin have a role?. *J Am Coll Cardiol*. 2011; 58(18):1870-1877.
9. Martin SS, Qasim A, Reilly MP. Leptin resistance: a possible interface of inflammation and metabolism in obesity-related cardiovascular disease. *J Am Coll Cardiol*. 2008; 52(15):1201-1210.
10. Koh KK, Park SM, Quon MJ. Leptin and cardiovascular disease: response to therapeutic interventions. *Circulation*. 2008;117(25):3238-3249.
11. Kalupahana NS, Moustaid-Moussa N. The adipose tissue renin-angiotensin system and metabolic disorders: a review of molecular mechanisms. *Crit Rev Biochem Mol Biol*. 2012;47(4):379-90.
12. Van Berendoncks AM, Garnier A, Ventura-Clapier R, Conraads VM. Adiponectin: key role and potential target to reverse energy wasting in chronic heart failure. *Heart Fail Rev*. 2013;18(5):557-566.

13. Szabó T, Scherbakov N, Sandek A, Kung T, von Haehling S, Lainscak M, Jankowska EA, Rudovich N, Anker SD, Frystyk J, Flyvbjerg A, Pfeiffer AF, Doehner W. Plasma adiponectin in heart failure with and without cachexia: catabolic signal linking catabolism, symptomatic status, and prognosis. *Nutr Metab Cardiovasc Dis.* 2014;24(1):50-56.
14. Bastien M, Poirier P, Lemieux I, Despres JP. Overview of epidemiology and contribution of obesity to cardiovascular disease. *Prog Cardiovasc Dis.* 2014;56(4):369-381.
15. Faulkner JL1, Belin de Sex Differences in Mechanisms of Hypertension Associated With Obesity. *Hypertension.* 2018;71(1):15-21.
16. Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Soubrier F. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. *J Clin Invest.* 1990;86:1343-1346.
17. Say YH. The association of insertions/deletions (INDELs) and variable number tandem repeats (VNTRs) with obesity and its related traits and complications. *J Physiol Anthropol.* 2017;36(1):25.
18. Sapouckey SA, Deng G, Sigmund CD, Grobe JL. Potential mechanisms of hypothalamic renin-angiotensin system activation by leptin and DOCA-salt for the control of resting metabolism. *Physiol Genomics.* 2017;49(12):722-732.
19. Schütten MT, Houben AJ, de Leeuw PW, Stehouwer CD. The Link Between Adipose Tissue Renin-Angiotensin-Aldosterone System Signaling and Obesity-Associated Hypertension. *Physiology (Bethesda).* 2017;32(3):197-209.
20. Schling P, Löffler G. Effects of angiotensin II on adipose conversion and expression of genes of the renin-angiotensin system in human preadipocytes. *Horm Metab Res.* 2001; 33(4):189-195.
21. Pop D, Procopciuc L, Sitar-Tăut A, Bodisz G, Poantă L, Zdrenghea D. BNP fragment (8-29) level and angiotensin converting polymorphism in heart failure patients in relationship with body mass index. *Acta Endo (Buc).* 2011; 7(1):39-48.
22. Wacker MJ, Godard MP, McCabe EH, Donnelly JE, Kelly JK. Sex difference in the association of the Angiotensin Converting Enzyme I/D polymorphism and Body Mass Index. *Med Sci Monit.* 2008; 14(7): CR353-357.
23. Han SH, Quon MJ, Kim JA, Koh KK. Adiponectin and cardiovascular disease: response to therapeutic interventions. *J Am Coll Cardiol.* 2007; 49(5):531-538.
24. Calabro P, Yeh ET. Obesity, inflammation, and vascular disease: the role of the adipose tissue as an endocrine organ. *Subcell Biochem.* 2007; 42:63-91.
25. Mishra A, Srivastava A, Kumar S, Mittal T, Garg N, Agarwal SK, Pande S, Mittal B. Role of angiotensin II type I (AT1 A1166C) receptor polymorphism in susceptibility of left ventricular dysfunction. *Indian Heart J.* 2015; 67(3): 214-221.
26. Procopciuc L, Popescu T, Jebeleanu Gh, Pop D, Zdrenghea D. Essential hypertension and polymorphism of angiotensinogen M235T gene. *J.Cell. Mol.Med.*2002;245-250.
27. Procopciuc LM, Sitar-Tăut A, Pop D, Sitar-Tăut DA, Olteanu I, Zdrenghea D. Renin angiotensin system polymorphisms in patients with metabolic syndrome (MetS). *Eur J Intern Med.* 2010; 21(5):414-418.
28. Mishra A, Srivastava A, Mittal T, Garg N, Mittal B. Genetic predisposition to left ventricular dysfunction: a multigenic and multi-analytical approach. *Gene.* 2014; 546(2):309-317.
29. Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Papacosta O, Sattar N. The obesity paradox in men with coronary heart disease and heart failure: the role of muscle mass and leptin. *Int J Cardiol* 2014; 171(1):49-55.
30. Pop D, Dădărlat A, Bodizs G, Stanca L, Zdrenghea D. The response of circulating leptin levels to exercise stress testing in subjects diagnosed with metabolic syndrome. *ISRN Endocrinol.* 2014; 2014:689260.