pagepress

Anabolic hormones and heart failure with preserved ejection fraction: looking for Ariadne's thread

Mariarosaria De Luca[1], Giulia Crisci[1], Federica Giardino[1], Valeria Valente[1], Ilaria Amaranto[1], Olimpia Iacono[1], Roberta D'Assante[1], Francesco Giallauria[1,2], Alberto M. Marra[1,3]

[1]Department of Translational medical Sciences, "Federico II" University, Naples, Italy; [2]Faculty of Sciences and Technology, University of New England, Armidale, NSW, Australia; [3]Center for Pulmonary Hypertension, Thoraxklinik at Heidelberg University Hospital, Heidelberg, Germany

Abstract

Heart failure with preserved ejection fraction (HFpEF) is a complex clinical syndrome that accounts for more than half of all heart failure patients. Identification, early diagnosis and management of patients are still complex, and no targeted treatment is available, since all tested drugs were not able to lower hard clinical outcomes. A multi-hormonal deficiency syndrome has been described in HFpEF patients suggesting that different hormones may represent new biomarkers of the disease, but their clinical utility is still debated. The natriuretic peptides are the cornerstone biomarker in heart failure, predicting cardiovascular death and heart failure hospitalization. Testosterone and DHEA-S deficiencies have been reported in HFpEF and associated with right ventricular impairment and diastolic dysfunction. IGFBP-1/IGF-1 axis correlates with echocardiographic parameters of HFpEF patients and with several prognostic biomarkers including NT-proBNP and C reactive protein. Low triiodothyronine syndrome is frequently found in HFpEF and thyroid hormones should represent a potential biomarker of risk stratification and prognosis.

Correspondence: Dr. Alberto M. Marra, MD, PhD, Department of Translational Medical Sciences, "Federico II" University Hospital and School of Medicine, Via Pansini 5, I-80131 Napoli, Italy.
Tel. +39.081.7463492.
E-mail: albertomaria.marra@unina.it

Key words: Anabolic hormones; biomarkers; diagnosis; heart failure preserved ejection fraction; prognosis; risk stratification; outcomes.
Contributions:

Received for publication: 21 December 2020.
Accepted for publication: 29 June 2021.

Monaldi Archives for Chest Disease 2022; 92:1743
doi: 10.4081/monaldi.2021.1743

Introduction

Heart failure (HF) is a complex clinical syndrome characterized by typical symptoms and signs (dyspnea, fatigue, pulmonary crackles, peripheral oedema) that result from structural and functional cardiac impairment at rest or during stress. It represents a major public health problem, with an incidence of ≈1.000.000 in 2014 in persons ≥55 years of age, progressively increasing in industrialized countries with ageing populations [1]. Current classification of HF is based on Left Ventricular Ejection Fraction (LVEF) and includes distinct clinical profiles with different etiologies, demographics, co-morbidities and responses to therapies: HF with reduced ejection fraction (HFrEF): symptomatic HF with LVEF ≤40%; HF with mildly reduced ejection fraction (HFmrEF): symptomatic HF with LVEF 41-49%; HF with preserved ejection fraction (HFpEF): symptomatic HF with LVEF ≥50%; and HF with improved ejection fraction (HFimpEF): symptomatic HF with a baseline LVEF ≤40%, a ≥10 point increase from baseline LVEF, and a second measurement of LVEF > 40% [2]. Diastolic dysfunction is the main mechanism involved in HFpEF: left atrial and right ventricular dysfunction, pulmonary hypertension and increased vascular stiffness are involved [3,4]. Although HFpEF accounts for more than half of all HF patients, identification, early diagnosis and management of patients are still complex, with severe implications for patient's health and treatment costs. Furthermore, differently to HFrEF no targeted treatment is available, since all tested drugs were not able to lower hard clinical outcomes in randomized controlled trials. For this reason, several authors speculated that different phenotypes are included under the HFpEF category. These difficulties impose to the scientific community the incessant research for biomarkers that might represent a possible treatment target in a cluster of HFpEF patients, given its complex pathophysiology. Biomarkers are defined as any measured characteristic representing an indicator of normal biological or pathogenic processes or responses to an exposure or intervention [5,6]. Some biomarkers have already been successfully identified and integrated into the clinical routine [7 8]; others are currently under discussion (Table 1) [9-11]. In particular, biomarkers associated with HFpEF are related with inflammation and angiogenesis, confirming their role in the pathophysiology of the disease [12]. Catabolic mechanisms correlate with mortality and morbidity in HF and a multi-hormonal deficiency syndrome has been described both in HFrEF and in HFpEF patients, although less pronounced in HFpEF [13-16]. These studies suggest that different hormones may represent biomarkers with a crucial role in disease management (Table 2) (Figure 1).

Aim of this review is to examine and summarize the current evidence on the role of hormonal biomarkers and to evaluate their clinical utility in each phase of HFpEF disease.

Natriuretic peptides (NPs)

The natriuretic peptides (NPs), B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP), are the cornerstone biomarker in HF disease. Their role is crucial in diagnosis and risk stratification. BNP is a peptide hormone released by cardiomyocytes in response to stretching derived by increased ventricular volume or pressure overload, NT-proBNP is the inactive protein cleaved from the prohormone of BNP. Guidelines establish the upper limit cut-off of normal in the non-acute setting in 35 pg/mL for BNP and 125 pg/mL for NT-proBNP, undistinguishing HFpEF from HFrEF even if NPs levels are lower in HFpEF in respect of HFrEF [2]. NPs plasmatic levels may represent an initial diagnostic test, especially when echocardiography is not immediately available, and have demonstrated a very high negative predictive

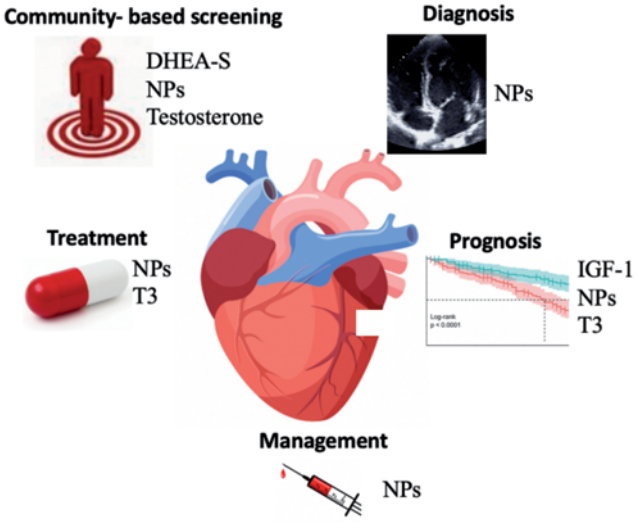

Figure 1. Clinical utility of hormonal biomarkers in heart failure with preserved ejection fraction.

Table 1. Predictive value of the main biomarkers in heart failure with preserved ejection fraction.

First Author, year	Hormonal biomarker	Setting	Follow upduration (median)	Results
Cleland *et al.*, 2006 [58]	NT-proBNP	375 HFpEF patients	1 year	If ↑: ↑all-cause death ↑HF hospitalization
Anand *et al.*, 2011 [25]	NT-proBNP	2612 HFpEF patients	6 months	If ↑: ↑cardiovascular death ↑HF hospitalization
Zhao *et al.*, 2020 [28]	DHEA-S and testosterone	4107 men and 4839 women	19.2 years	If ↓: ↑risk of incident HFpEF
Shah *et al.*, 2011 [59]	sST2	200 patients with dyspnea and normal LV systolic function	1 year	If ↑: ↑all-cause mortality
De Boer *et al.*, 2011 [46]	Galectin-3	114 HFpEF patients	18 months	If ↑: ↑all-cause mortality ↑HF hospitalization
Carrasco-Sánchez *et al.*, 2011 [51]	Cystatin C	218 HFpEF patients	1 year	If ↑: ↑all-cause mortality

Table 2. Correlation between hormonal biomarkers and cardiac structure and function in heart failure with preserved ejection fraction.

First Author, year	Hormonal biomarker deficiency	Setting	Results
Favuzzi *et al.* 2020 [29]	Testosterone DHEA-S	40 patients with HFpEF	↑SPAP ↑TPV ↑LAVI
Barroso *et al.* 2016 [37]	IGF-1	77 patients with HFpEF	↑E/e' ratio ↑LAVI
Bruno *et al.* 2020 [30]	IGF-1	84 patients with HFpEF	↑LAV ↑LAVI
Favuzzi *et al.* 2020 [29]	IGF-1	40 patients with HFpEF	↑LAV ↑SPAP ↓TAPSE ↑TPV
Selvaraj *et al.* 2012 [42]	T3	89 patients with HFpEF without a prior diagnosis of thyroid dysfunction	↑E ↑E/e' ratio ↓E deceleration time

LAVI, left atrial volume index; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TPV, tricuspid peak velocity values.

values but a low positive predictive value: patients with normal NPs concentrations are unlikely to have HF, *vice versa*, the only presence of abnormal NPs values does not allow the diagnosis of HF. Recently the European Society of Cardiology suggested a new score for the diagnosis of HFpEF: the Heart Failure Association Pre-test assessment, Echocardiography and natriuretic peptide, Functional testing, Final etiology (HFA-PEFF) score [17], which is a stepwise approach that incorporates NPs evaluation to hypothesize HFpEF diagnosis. Several conditions impact on NPs levels: higher levels can be observed in the elderly, in women, in atrial fibrillation, and in renal dysfunction [18]. Differently, obese individuals show reduced NPs levels as compared to general population [19]. It would seem prudent to use NPs for diagnosis together with a combination of clinical, biochemical, electrocardiographic, and imaging data. The rationale for using NPs in HF-pEF diagnosis is that their levels are related to the presence of diastolic dysfunction, which in turn is associated with increased LV filling pressure and consequently pressure overload to left atria [20,21]. The relationship between NPs levels and diastolic dysfunction was observed also in the preclinical phase [22] so that, besides their diagnostic utility, NPs levels might be used in community-based screening programs for detecting HFpEF [23]. Moreover, NPs play a key prognostic role in patients with HFpEF. The i-PRESERVE and the PEP-CHF studies demonstrated that NT-proBNP values and their change from baseline correlate with mortality and heart failure rehospitalizations [24,25].

Dehydroepiandrosterone-sulfate (DHEA-S) and Testosterone

Testosterone deficiency represents a fundamental element in the pathophysiology of chronic heart failure, resulting in a reduction of muscle mass, impaired use of energy, dyspnea and fatigue [26,27]. Lower plasma levels of total testosterone and DHEA-S were associated with an increased risk of incident HF, both in HFpEF and HFrEF [28], suggesting a possible use in community-based screening programs. The relationship between DHEA-S, testosterone and HFpEF has been poorly investigated. Salzano *et al*. [13] reported testosterone and DHEA-S deficiencies in a population of mild-to-moderate chronic HFpEF. Subsequent studies have confirmed the association between DHEA-S and testosterone deficiency with right ventricular impairment and diastolic dysfunction in patients with HFpEF [29]: patients with testosterone deficiency showed lower E wave, higher systolic pulmonary artery pressure and tricuspid peak velocity values [29]. Moreover, testosterone may improve endothelial function and insulin resistance, by acting on muscle insulin sensitivity or visceral adipocytes metabolism, and testosterone supplementation may increase HDL-cholesterol [26]. MDHEA-S and testosterone showed to influence antioxidant levels measured as the appearance of the chromogen ABTS [30,31]. Actually, there is no evidence that low testosterone and DHEA-s levels are associated with a worse prognosis in HFpEF patients due to the lack of large longitudinal studies.

Insulin-like growth factor 1 (IGF-1)

The insulin-like growth factor-1 (IGF-1) is an essential mediator in the regulation of growth and cellular differentiation in many tissues. Its activity is neutralized by IGF-binding protein 1 (IGFBP-1). Alterations in IGF-1/IGFBP-1 system were associated with a worse clinical course contributing to diastolic disfunction via increased collagen deposition and myocardium fibrosis [30]. In addition, it has been demonstrated that human heart shifts from IGF-1 production to utilization in chronic heart failure [32]. In HFrEF patients, IGF-1 has demonstrated a prognostic role, predicting clinical outcomes [33-35], while its importance in HFpEF is still discussed [36]. Barroso *et al.* described a correlation between IGFBP-1/IGF-1 axis and echocardiographic left ventricular (LV) diastolic parameters in HFpEF patients [37]. Similarly, patients with IGF-1 deficiency showed higher left atrial volume [29-30], higher systolic pulmonary artery pressure and tricuspid peak velocity and lower tricuspid annular plane systolic excursion [29]. Moreover, IGF-1 and IGFBP-1/IGF-1 ratio seem to be positively correlated with prognostic biomarkers including NT-proBNP and C reactive protein (CRP) [30,37,38]. Only one study has not confirmed IGF-1 deficiency in HFpEF, demonstrating a positive correlation of the hormone levels with the prognosis in HFrEF but not in HFpEF patients [38]. No other studies have correlated IGF-1 deficiency with cardiovascular prognosis in HFpEF.

Thyroid hormones

Thyroid hormones impact on cardiovascular system and their alterations increase cardiovascular risk through genomic and non-genomic mechanisms [39,40]. A local cardiac hypothyroidism may be present even if plasmatic thyroid hormones are normal due to an upregulation of type 3 iodothyronine deiodinase [40]. Both clinical and subclinical hypothyroidism increase risk of HF [41], and data from epidemiological studies described low triiodothyronine (T3) syndrome in about 22% of HFpEF patients and subclinical hypothyroidism in 10 to 20% [29,42]. T3 levels seems to be inversely associated with BNP and D-Dimer, markers of HFpEF severity, and correlate with echocardiographic parameters of diastolic dysfunction [42]. HFpEF patients with T3 deficiency also showed higher right ventricular mid cavity diameter values [29]. Disthyroidism affects the cardiovascular system also modifying oxygen consumption: patients with hyperthyroidism show a lower increment of heart rate between rest and anaerobic threshold, and lower VO_2 and oxygen pulse at anaerobic threshold when performing cardiopulmonary exercise test [43]. These data suggest that thyroid hormones should represent a potential biomarker of risk stratification and prognosis in HFpEF patients even if we do not dispose of trials specifically focused. Furthermore, it may be assumed that thyroid hormone supplementation improves diastolic function of HFpEF patients, as suggested by clear evidence in HFrEF [44]. According this hypothesis, T3 should represent a promising therapeutic target in this setting of HF patients.

Other biomarkers

In addition to the above-mentioned hormones, several other molecules have shown a potential clinical utility in HFpEF patients. Patients with HFpEF have significantly higher levels of soluble suppression of tumorigenesis-2 (sST2) and high sensitivity troponin T (hsTnt) and their values predict overall survival and HF rehospitalizations [45]. De Boer *et al.* demonstrated that Galectin-3 increases HF hospitalization and all-cause mortality [46]. Similar

data were obtained with osteopontin and neuropilin [12]. It has been demonstrated that trimethylamine N-oxide (TMAO) adds to risk stratification, when combined with BNP [47]. Inflammation concurs to the pathophysiology of HFpEF and inflammatory cytokines IL1, IL6, IL8, and CRP are elevated in HFpEF patient [8,48]. TNF-α and its specific receptors TNF-R1 and TNF-R2 contribute directly to the development and progression of heart failure, by determining ventricular remodeling, interstitial fibrosis, and cardiomyocyte apoptosis. The role of TNFα antagonists on TNFα cardiotoxicity is still debated with conflicting findings between animal model investigations and early clinical trials [49,50]. Finally, Cystatin C, a strong predictor of cardiovascular disease, is associated with poor prognosis in patients with acute heart failure, regardless of renal function [51].

Conclusions

Despite recent progresses, HFpEF morbidity and mortality are still too high due to the complex pathophysiology, the heterogeneous presentation and the lack of effective treatments. A multihormonal deficiency syndrome has been described both in HFpEF and HFrEF. Only few biomarkers have already been successfully identified and introduced in the routine practice, but their clinical perspective are extremely interesting. Different hormones may represent an *Ariadne's thread* in understanding the complex pathophysiology of HFpEF and, at the same time, biomarkers useful not only for screening, diagnosis, and prognosis of the disease, but also for clinical management and assessment of response to treatment. Finally, anabolic deficiencies represent possible therapeutic targets, considering positive results from preliminary reports [52-57]. Further studies need to be carried out in order to identify main anabolic biomarkers and their exact clinical utility.

References

1. Virani SS, Alonso CA, Benjamin EJ, et al. Heart disease and stroke statistics - 2020 Update a report from the american heart association. Circulation 2020;141:139–596.
2. Bozkurt B, Coats AJS, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. Eur J Heart Fail 2021;23:352-80.
3. Marra AM, Egenlauf B, Ehlken N, et al. Change of right heart size and function by long-term therapy with riociguat in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. Int J Cardiol 2015;15:19-26.
4. Marra AM, Arcopinto M, Bossone E, et al. Pulmonary arterial hypertension-related myopathy: an overview of current data and future perspectives. Nutr Metab Cardiovasc Dis 2015;25:131-9.
5. Califf RM. Biomarker definitions and their applications. Exp Biol Med 2018;243:213-21.
6. Salzano A, Marra AM, D'Assante R, et al. Biomarkers and imaging: complementary or subtractive? Heart Fail Clin 2019;15: 321-33.
7. De Luca M, Bosso G, Valvano A, et al. Management of patients with chronic heart failure and type 2 diabetes mellitus: the SCO-DIAC-II study. Intern Emerg Med 2021;16:895-903.
8. Suzuki T, Lyon A, Saggar R, et al. Editor's Choice - Biomarkers of acute cardiovascular and pulmonary diseases. Eur Heart J Acute Card 2016;5:416-33.
9. Arcopinto M, Salzano A, Isgaard J, Cittadini A. Hormone replacement therapy in heart failure. Curr Opin Cardiol 2015;30:277-84.
10. Bossone E, Arcopinto M, Iacoviello M. Multiple hormonal and metabolic deficiency syndrome in chronic heart failure: rationale, design, and demographic characteristics of the T.O.S.CA. Intern Emerg Med 2018;13:661-71.
11. Senni M, D'Elia E, Emdin M, Vergaro G. Biomarkers of heart failure with preserved and reduced ejection fraction. Handb Exp Pharmaco. 2017;243:79-108.
12. Tromp J, Khan MA, Klip IT, et al. Biomarker profiles in heart failure patients with preserved and reduced ejection fraction. J Am Heart Assoc 2017;30:6.
13. Salzano A, Marra AM, Ferrara F, et al. Multiple hormone deficiency syndrome in heart failure with preserved ejection fraction. Int J Cardiol 2016; 225:1-3.
14. Arcopinto M, Salzano A, Bossone E, et al. Multiple hormone deficiencies in chronic heart failure. Int J Cardio. 2015;184:421-3.
15. Napoli R, D'Assante R, Miniero M, et al. Anabolic deficiencies in heart failure: ready for prime time? Heart Fail Clin 2020;16:11-21.
16. Salzano A, Cittadini A, Bossone E, et al. Multiple hormone deficiency syndrome: a novel topic in chronic heart failure. Future Sci OA 2018;16:4.
17. Barandiarán Aizpurua A, Sanders-van Wijk S, Brunner-La Rocca HP, et al. Validation of the HFA-PEFF score for the diagnosis of heart failure with preserved ejection fraction. Eur J Heart Fail 2020;22:413-21.
18. D'Elia E, Vaduganathan M, Gori M, et al. Role of biomarkers in cardiac structure phenotyping in heart failure with preserved ejection fraction: critical appraisal and practical use. Eur J Heart Fail 2015;17:1231-9.
19. Singh S, Pandey A, Neeland IJ. Diagnostic and prognostic considerations for use of natriuretic peptides in obese patients with heart failure. Prog Cardiovasc Dis 2020;63:649-55.
20. Tschöpe C, Kasner M, Westermann D, et al. The role of NT-proBNP in the diagnostics of isolated diastolic dysfunction: correlation with echocardiographic and invasive measurements. Eur Heart J 2005;26:2277-84.
21. Lubien E, DeMaria A, Krishnaswamy P, et al. Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with doppler velocity recordings. Circulation 2002;105: 595–601.
22. Mogelvang R, Goetze JP, Pedersen SA, et al. Preclinical systolic and diastolic dysfunction assessed by tissue doppler imaging is associated with elevated plasma pro-B-type natriuretic peptide concentrations. J Card Fail 2009; 5:489–95.
23. Brouwers FP, van Gilst WH, Damman K, et al. Clinical risk stratification optimizes value of biomarkers to predict new-onset heart failure in a community-based cohort. Circ Heart Fail 2014;7:723–31.
24. Cleland JG, Tendera M, Adamus J, et al. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 2006;27:2338-45.
25. Anand IS, Rector TS, Cleland JG, et al. Prognostic value of baseline plasma amino-terminal pro-brain natriuretic peptide and its interactions with irbesartan treatment effects in patients

with heart failure and preserved ejection fraction: findings from the I-PRESERVE trial. Circ Heart Fail 2011;4:569-77.
26. Volterrani M, Rosano G, Iellamo F. Testosterone and heart failure. Endocrine 2012;42:272–7.
27. D'Assante R, Piccioli L, Valente P, et al. Testosterone treatment in chronic heart failure. Review of literature and future perspectives. Monaldi Arch Chest Dis 2018;88:976.
28. Zhao D, Guallar E, Ballantyne CM, et al. Sex hormones and incident heart failure in men and postmenopausal women: the atherosclerosis risk in communities study. J Clin Endocrinol Metab 2020;105:e3798-807.
29. Favuzzi AMR, Venuti A, Bruno C, et al. Hormonal deficiencies in heart failure with preserved ejection fraction: prevalence and impact on diastolic dysfunction: a pilot study. Eur Rev Med Pharmac 2020;24:352-61.
30. Bruno C, Silvestrini A, Calarco R, et al. Anabolic hormones deficiencies in heart failure with preserved ejection fraction: prevalence and impact on antioxidants levels and myocardial dysfunction. Front Endocrinol (Lausanne) 2020;11:281.
31. Mancini A, Fuvuzzi AMR, Bruno C, et al. Anabolic hormone deficiencies in heart failure with reduced or preserved ejection fraction. Int J Endocrinol 2020;2020:5798146.
32. D'Assante R, Napoli R, Salzano A, et al. Human heart shifts from IGF-1 production to utilization with chronic heart failure. Endocrine 2019;65:714-716.
33. Arcopinto M, Salzano A, Giallauria F, et al. Growth hormone deficiency is associated with worse cardiac function, physical performance, and outcome in chronic heart failure: insights from the T.O.S.CA. GHD study. PLoS One 2017;12:e0170058.
34. Motiwala SR, Szymonifka J, Belcher A, et al. Measurement of novel biomarkers to predict chronic heart failure outcomes and left ventricular remodeling. Cardiovasc Transl Res 2014;7:250-61.
35. Arcopinto M, Bobbio E, Bossone E, et al. The GH/IGF-1 axis in chronic heart failure. Endocr Metab Immune Disord Drug Targets 2013;13:76-91.
36. D'Assante R, Arcopinto M, Rengo G, et al. Myocardial expression of somatotropic axis, adrenergic, and calcium handling genes in heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. ESC Heart Fail 2021;8:1681-6.
37. Barroso MC, Kramer F, Greene SJ, et al. Serum insulin-like growth factor-1 and its binding protein-7: potential novel biomarkers for heart failure with preserved ejection fraction. BMC Cardiovasc Disord 2016;16:199.
38. Faxén UL, Hage C, Benson L, et. al. HFpEF and HFrEF display different phenotypes as assessed by IGF-1 and IGFBP-1. J Card Fail 2017;23:293-303.
39. Cerbone M, Capalbo D, Wasniewska M, et al. Effects of L-thyroxine treatment on early markers of atherosclerotic disease in children with subclinical hypothyroidism. Eur J Endocrinol 2016;175:11-9.
40. Neves JS, Vale C, von Hafe M, et al. Thyroid hormones and modulation of diastolic function: a promising target for heart failure with preserved ejection fraction. Ther Adv Endocrinol Metab 2020;11:2042018820958331.
41. Vale, C, Neves, JS, von Hafe, M, et al. The role of thyroid hormones in heart failure. Cardiovasc Drugs Ther 2019;33:179-88.
42. Selvaraj S, Klein I, Danzi S, et al. Association of serum triiodothyronine with B-type natriuretic peptide and severe left ventricular diastolic dysfunction in heart failure with preserved ejection fraction. Am J Cardiol 2012;110:234-9.
43. Irace L, Pergola V, Di Salvo G et al. Work capacity and oxygen uptake abnormalities in hyperthyroidism. Minerva Cardioangiol 2006;54:355-62.
44. Virtanen, VK, Saha, HH, Groundstroem, KW, et al. Thyroid hormone substitution therapy rapidly enhances left-ventricular diastolic function in hypothyroid patients. Cardiology 2001;96:59–64.
45. Sanders-van Wijk S, van Empel V, Davarzani N, et al. Circulating biomarkers of distinct pathophysiological pathways in heart failure with preserved vs. reduced left ventricular ejection fraction. Eur J Heart Fai. 2015;17:1006-14.
46. de Boer RA, Lok DJ, Jaarsma T, et al. Predictive value of plasma galectin-3 levels in heart failure with reduced and preserved ejection fraction. Ann Med 2011;43:60-8.
47. Salzano A, Israr MZ, Yazaki Y, et al. Combined use of trimethylamine N-oxide with BNP for risk stratification in heart failure with preserved ejection fraction: findings from the DIAMONDHFpEF study. Eur J Prev Cardiol 2020;27:2159-62.
48. Marra AM, Arcopinto M, Salzano A, et al. Detectable interleukin-9 plasma levels are associated with impaired cardiopulmonary functional capacity and all-cause mortality in patients with chronic heart failure. Int J Cardiol 2016;15:114-7.
49. Pergola V, Di Salvo G, Martiniello AR, et al. [TNF alpha e scompenso cardiaco].[Article in Italian]. Minerva Cardioangiol 2000;48:475-84.
50. Chung ES, Packer M, Lo KH, et al. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation 2003;107:3133-4.
51. Carrasco-Sánchez FJ, Galisteo-Almeda L, Páez-Rubio I, et al. Prognostic value of cystatin C on admission in heart failure with preserved ejection fraction. J Card Fail 2011;17:31-8.
52. Caminiti G, Volterrani M, Iellamo F, et al. Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study. J Am Coll Cardiol 2009;54:919-27.
53. Iellamo F, Volterrani M, Caminiti G et al. Testosterone therapy in women with chronic heart failure: a pilot double-blind, randomized, placebo-controlled study. J Am Coll Cardiol 2010;56:1310-6.
54. Cittadini A, Marra AM, Arcopinto M, et al. Growth hormone replacement delays the progression of chronic heart failure combined with growth hormone deficiency: an extension of a randomized controlled single-blind study. JACC Heart Fail 2013;1:325-30.
55. Salzano A, D'Assante R, Lander M, et al. Hormonal replacement therapy in heart failure: focus on growth hormone and testosterone. Heart Fail Clin 2015;15:377-91.
56. Salzano A, Marra AM, D'Assante R, et al. Growth hormone therapy in heart failure. Heart Fail Clin 2018;14:501-15.
57. Salzano A, Marra AM, Arcopinto M, et al. Combined effects of growth hormone and testosterone replacement treatment in heart failure. ESC Heart Fail 2019;6:1216-1.
58. Cleland JG, Taylor J, Freemantle N, et al. Relationship between plasma concentrations of N-terminal pro brain natriuretic peptide and the characteristics and outcome of patients with a clinical diagnosis of diastolic heart failure: a report from the PEP-CHF study. Eur J Heart Fail 2012;14:487-94.
59. Shah KB, Kop WJ, Christenson RH, et al. Prognostic utility of ST2 in patients with acute dyspnea and preserved left ventricular ejection fraction. Clin Chem 2011;57:874-82.