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COMMENTARY

Commentary on the Article "Multiple Hormonal and Metabolic Deficiency Syndrome Predicts Outcome in Heart Failure: The T.O.S.CA. Registry", Antonio Cittadini *et al*. Eur. J. Prev. Cardiol. 2021

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Abstract: Chronic heart failure represents a relevant concern for public health. The endocrine system is heavily involved in the induction and progression of chronic heart failure. Among endocrine disorders, the most relevant alterations are related to the growth hormone-insulin like growth factor 1 axis, serum testosterone, dehydroepiandrosterone sulfate, triiodothyronine levels, insulin resistance, and type 2 diabetes mellitus. It is currently debated whether these changes might be simple adaptive mechanisms or, instead, they may deteriorate myocardial pump function over time. In this commentary on a recently published paper by Antonio Cittadini *et al*. (Eur J Prev Cardiol. 2021), we briefly presented and discussed data form the "Trattamento Ormonale nello Scompenso CArdiaco; Hormone Treatment in Heart Failure (TOSCA) Registry". One or more hormonal deficiencies or metabolic disorders, including insulin resistance and diabetes mellitus, were more commonly diagnosed in patients with heart failure (358 patients, 75% of study group). The presence of multiple hormone deficiency identified a subset of patients at increased risk of hospitalization and death, with a graded relation between the number of deficiencies and total events. This finding suggests a possible causal role of hormone deficiencies in CHF progression. Screening of hormonal and metabolic imbalances in CHF patients would be an interesting opportunity for improving the prognosis of patients with heart failure as it would identify high-risk patients requiring an additional medical management of the underlying endocrine and metabolic disorders.

Keywords: Multiple hormonal and metabolic deficiency syndrome, chronic heart failure, testosterone, growth hormone, insulin-like growth factor, triiodothyronine, dehydroepiandrosterone sulfate, insulin resistance, diabetes mellitus.

The paper by Cittadini *et al*. reports data from the "Trattamento Ormonale nello Scompenso CArdiaco; Hormone Treatment in Heart Failure (TOSCA) Registry", a prospective multicenter observational study involving nineteen Italian centers. The study was conceived for verifying if Multiple Hormonal and Metabolic Deficiency Syndrome (MHDS) may foster a worse progression in patients with Chronic Heart Failure (CHF) [1].

The study protocol has been reported in a previously published paper [2]. Four-hundred-eighty CHF patients, mostly men (80%) with ejection fraction ≤45%, were enrolled. Serum levels of thyroid hormones, growth hormone (GH) and insulin-like growth factor-1 (IGF-1), total testosterone (TT), dehydroepiandrosterone sulfate (DHEAs), and parameters of glucose control were assessed. The primary endpoint was a composite of all-cause mortality and hospital admission rate due to cardiovascular events. MHDS was defined when two or more established hormonal alterations were diagnosed.

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MHDS (including type 2 diabetes and insulin resistance) was diagnosed in 358 patients (75%). More specifically, only 6% of participants displayed no hormonal and metabolic deficiency (HD). Almost 20% of them had one HD; 32.9% had two HD; 27.9% had three HD, and 13.8% had four or more HD.

More than half (56%) of patients experienced the primary endpoint (97 deaths, 20%; 174 hospital admissions due to cardiovascular events, 36%) through a patient-average follow-up of 36 months. Two-hundred twenty-one events were recorded among 62% of CHF patients with MHDS (82 deaths, 23%; 139 hospital admissions due to cardiovascular events, 39%). These rates were higher than those observed among CHF patients without MHDS (41% of patients; 50 events: 15 deaths, 12%; 35 cardiovascular hospitalizations, 29%) and reached statistical significance (p<0.001). Moreover, the primary endpoint was reached in 70% of patients with type 2 diabetes mellitus (T2D) and 52% in the patients without T2D (p-0.001).

Testosterone deficiency [HR: 1.59 (1.25-2.01), p<0.001], DHEAs deficiency [HR: 1.40 (1.07-1.81), p-0.011], GH deficiency (GHD) [HR: 1.43 (1.13-1.82), p-0.003], and T2D [HR: 1.55 (1.20-2.01), $p < 0.001$] were associated with the primary endpoint. The number of HD influenced the prognosis of CHF patients significantly, and

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MHDS was identified as a critical factor because it fosters higher mortality [HR 2.2 (1.28-3.83), *p*-0.01] and hospital admission due to cardiovascular events [HR: 1.81 (1.29-2.54), *p*-0.001]. After adjustments for confounding factors, MHDS remained significantly associated with the primary endpoint [HR: 1.93 (1.37-2.73), $p<0.001$].

CHF represents a relevant concern for public health as the prognosis still remains poor doespite improvements in pharmaceutical and electrical management. Up to one-third of patients do not survive beyond one year following diagnosis, and the mortality rate over the past decade remained elevated [3]. This matter may be attributable to the burden of several comorbidities frequently diagnosed in these patients. Endocrine, metabolic, immunological, and nutritional disorders could be implicated in worsening the CHF prognosis [4]. As some examples, hypothyroidism and hyperthyroidism (both subclinical or overt), male hypogonadism, T2D, and obesity are frequently observed in CHF patients and accelerate CHF progression [5-16]. Undernourishment is another risk factor, as described in patients with cachexia [17]. Medical management of these comorbidities and their related complications can be a challenge in this clinical setting [5, 18-20].

The endocrine system is heavily involved in the induction and progression of CHF. Neuroimmune activation has a pivotal role in CHF and represents a target of pharmacological interventions [21-23]. It has been observed that anabolic hormonal deficiency may coexist with CHF. In this sense, the most relevant alterations are related to the GH-IGF1 axis, serum TT, DHEAs, and triiodothyronine levels, insulin resistance (IR) and T2D [24-27]. Lower circulating IGF-1 levels have been associated with worst New York Heart Association classes, impaired exercise capacity, sarcopenia, systemic inflammation [28-31], left and right ventricular remodeling, ventricular dysfunction, and increased mortality [26]. Male hypogonadims has been associated with significant impairment of skeletal muscle strength, reduced exercise capacity [32], and increased risk of metabolic syndrome and T2D [33]. Patients with non-thyroidal illness syndrome usually exhibit worse cardiovascular performance and increased mortality, especially when CHF coexists as comorbidity [34]. Severe non-thyroidal illness syndrome is usually observed in patients with severe and acutely decompensated heart failure. In this cluster of patients, the mortality rate is high and some short-term studies demonstrate that cardiac output may improve after triiodothyronine supplementation [35]. IR is involved in deteriorating myocardial kinetic and remodeling and has been associated with a more severe CHF progression [36].

CONCLUSION

It is currently debated whether these changes might not be simple adaptive mechanisms or, instead, they may contribute to deteriorate myocardial pump function over time. Medical management of patients exhibiting one or more hormonal deficiencies or metabolic imbalances may have a therapeutic role [37]. The results of the TOSCA Registry showed a very high prevalence of HD in CHF patients, and the presence of MHDS could be specifically diagnosed in a cluster of patients at high risk of mortality/recurrent cardiovascular hospitalizations. Moreover, there is a graded relation between the number of HDs and the above-mentioned cardiovascular endpoints, and the number of HDs could probably predict survival chances among CHF patients. Given this assumption, well-designed clinical trials aimed to demonstrate the potential benefits of hormonal deficiency screening strategies and hormonal replacement therapy when necessary in CHF patients could help to clarify the issue.

LIST OF ABBREVIATIONS

CHF	=	Chronic Heart Failure
DHEAs	=	Dehydroepiandrosterone sulfate
GH	=	Growth hormone
IGF-1	=	GInsulin-like growth factor-1
IR	=	Insulin resistance
HD	=	Metabolic deficiency
MHDS	=	Multiple Hormonal and Metabolic Deficiency Syndrome
TT	=	Total testosterone
T2D	=	Type 2 diabetes mellitus

AUTHORS' CONTRIBUTIONS

V.T. conceived the commentary; V.T. and G.L. analyzed and selected the references. V.T. and G.L. drafted the manuscript. V.T. and G.L. read and improved the manuscript and accepted the final content for publication.

CONFLICT OF INTEREST

Vincenzo Triggiani is the Associate Editor of the journal Endocrine, Metabolic & Immune Disorders - Drug Targets.

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