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Research Article

Indicators of endothelial function and systemic immune inflammatory response in patients with chronic heart failure and coexisting primary hypothyroidism

Yuliia Ihorivna Mykula[1], Iryna Hryhorivna Kupnovytska[1], Oksana Ihorivna Danulyk[1]

1 *Department of Clinical Pharmacology and Pharmacotherapy, Ivano-Frankivsk National Medical University of Ministry of Health of Ukraine, Ivano-Frankivsk, Ukraine*

Corresponding author: Yuliia Ihorivna Mykula (yuliamykula@gmail.com)

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Abstract

Chronic heart failure is one of the leading causes of death globally, affecting 1.5 to 2% of the total world population and 2.9 to 3.9% of the total Western European population. Chronic heart failure often progresses rapidly in coexistence with endocrine pathology, namely hypothyroidism, that results in a more rapid development and further progression of endothelial dysfunction and the development of a systemic inflammatory response. The aim of our research was to study the levels of endothelin-1, C-reactive protein, tumor necrosis factor α and their correlation with the levels of thyroid-stimulating hormone, thyroxine in patients with chronic heart failure and coexisting hypothyroidism. There were examined 38 patients with chronic heart failure and coexisting hypothyroidism and 42 patients with chronic heart failure without hypothyroidism. The serum levels of endothelin-1, C-reactive protein, tumor necrosis factor α were determined by the enzyme-linked immunosorbent assay, while the levels of thyroid-stimulating hormone and thyroxine were determined by the electrochemiluminescence immunoassay. In patients with chronic heart failure and coexisting hypothyroidism, the levels of endothelin-1, C-reactive protein, and tumor necrosis factor α were 2.9, 1.5 and 2.27 times higher than those in patients without hypothyroidism. In Group I, there was a moderate positive correlation between the serum levels of endothelin-1 and thyroid-stimulating hormone and a weak negative correlation between the levels of thyroxine and endothelin-1. In Group II, there was a weak correlation between the levels of endothelin-1 and thyroid-stimulating hormone and no correlation between the levels of thyroxine and endothelin-1. In Group I, there was a strong positive correlation between C-reactive protein and thyroid-stimulating hormone levels as well; in Group II, no similar correlation was found. In Group I, there was found a moderate negative correlation between tumor necrosis factor α and thyroxine levels. According to our results, there was a close correlation between the markers of endothelial dysfunction, immune inflammatory response, and single markers of hypothyroidism.

Keywords

Chronic heart failure, C-reactive protein, Endothelin-1, Hypothyroidism, Thyroid-stimulating hormone, Tumor necrosis factor α

Introduction

Chronic heart failure (CHF) is currently one of the most common public health issues that ranks first in mortality worldwide (Francois J et al. 2020). Considering the age structure of the population, the global average life expectancy has increased, the absolute numbers of older patients with HF have increased dramatically as well due to a remarkable increase in the proportion of older and elderly people, increased life expectancy, better quality of medical care, medical advances, global population growth (Roth et al. 2015).

CHF is often accompanied by endocrine disorders, namely hypothyroidism. Structural and functional cardiac changes are present in patients at all the stages of hypothyroidism; however, the degree of these changes correlates with the severity and duration of the disease (Drapkina et al. 2016). On the other hand, congestive heart failure, blood stasis, hypoxia and hypercapnia affect thyroid function. Thus, subclinical thyroid dysfunction with the serum thyroid-stimulating hormone (TSH) level > 10 mU/L is associated with a higher risk of HF progression. In addition, low levels of thyroid hormone triiodothyronine (T3) alongside with normal TSH and thyroxine (T4) levels, the so-called low T3 syndrome, are associated with a higher risk of death (Kannan et al. 2018).

In both CHF and hypothyroidism, elevated levels of endothelin-1 (ET-1), that acts as a potent vasoconstrictor and is a biomarker to predict HF severity, are observed (Alieva et al. 2014; Melnik 2018). An elevated plasma ET-1 level is associated with a high risk of cardiovascular mortality, serves as a predictor of long-term negative outcomes in CHF (Vizir et al. 2003) and a marker of endothelial dysfunction and atherosclerosis (Melnik AA 2018). Hypothyroidism leads to metabolic changes, negatively affects lipoprotein metabolism that results in vascular atherosclerosis and endothelial dysfunction.

Among the mechanisms contributing to CHF development, there is the systemic inflammatory response that negatively affects myocardial function. This immune inflammatory response is characterized by increasing serum levels of biomarkers such as C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α) (Abernethy et al. 2018). At the same time, the immune inflammatory response is typical for primary hypothyroidism as well, which is regarded as an inflammatory condition characterized by elevated levels of cytokines, CRP, interleukin-6 (IL-6) and TNF-α. These markers may be involved in the pathogenesis of many hypothyroidism-related complications, causing endothelial dysfunction, proliferation of smooth muscle cells, as well as recruiting and activating other factors of immune inflammation (Tayde et al. 2017). In addition, they induce the production of interferon gamma (IFN-γ) and mediate apoptosis.

In the literature, there is information related to the concentrations of ET-1, CRP, TNF- α in patients with CHF and their role in assessing the risk of CHF progression; however, there are very few studies that considered the increase in these markers in the context of several comorbidities, namely the coexistence of HF and hypothyroidism.

Our aim was to study the serum levels of ET-1, CRP, TNF-α, TSH, T4 in patients with CHF and coexisting hypothyroidism.

Materials and methods

There were examined 80 (56 females and 34 males) patients with CHF NYHA Functional Class I-II, who were hospitalized to the Department of Arterial Hypertension of the Ivano-Frankivsk Regional Clinical Cardiology Centre of Ivano-Frankivsk Regional Council. The patients were divided into two groups: Group I included 38 patients with CHF and coexisting hypothyroidism; Group II comprised 42 patients with CHF without hypothyroidism. The control group included 10 (6 women and 4 men) apparently healthy individuals. The average age of patients was 56.31±2.34 years in Group I, 54.6±2.41 years in Group II and 48±6.21 years in the control group. The duration of CHF was on average 5.7±1.56 years. The exclusion criteria were diabetes mellitus, acute myocardial infarction, CHF NYHA FC III-IV, secondary and tertiary hypothyroidism. All the patients underwent general medical examination, determination of ET-1 levels. The stage of hypothyroidism was determined by the clinical picture, TSH and T4 levels.

The serum concentration of TSH and T4 was determined by the electrochemiluminescence immunoassay (ECLIA) on the Cobas 8000 modular analyzer (Switzerland), using Roche Diagnostics reagents (Switzerland).

The serum level of ET-1 was determined by the enzyme-linked immunosorbent assay on the Stat Fax analyzer, by means of the Human ET-1 (Endotelin-1) ELISA kit (Czech Republic).

The level of TNF-α was determined by the enzyme-linked immunosorbent assay on the Stat Fax analyzer, using the Vector-Best reagent kit (Belarus).

The serum level of CRP was determined by the enzyme-linked immunosorbent assay on the Stat Fax analyzer, by means of the AccuBind ELISA Microwells reagent kit (USA).

The Research Ethics Committee of the Ivano-Frankivsk National Medical University approved the research protocol, according to which the study was carried out (protocol No. 97/17 dated October 19, 2017). All the patients signed informed consent to participate in this research study. The study was carried out in accordance with the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects dated October 01, 2008, No. 900_005.

The results obtained were statistically processed using an advanced analytics software package Statistica 6.0, the Student's t-test. The correlation was assessed using the Spearman rank correlation coefficient. A p-value less than 0.05 was considered statistically significant.

Results

ET-1 levels in patients of Group I and Group II exceeded those in healthy individuals by 7.2 and 6.4 times, respectively ($p < 0.001$). Since ET-1 is a marker of endothelial dysfunction and atherosclerosis, after comparing ET-1 levels in both groups, it was found to be 2.9 times higher in patients with CHF and coexisting hypothyroidism as compared to those without hypothyroidism (Table 1). Therefore, there was a positive correlation between ET-1 and TSH levels.

Table 1. Serum concentration of ET-1, TNF-α, CRP, TSH, T4 in patients with CHF and coexisting hypothyroidism and those without hypothyroidism.

Indicators	Healthy individuals, n = 10	Group I, n = 38	Group II, n = 42
ET-1, pg/ml	0.46±0.18	3.32±0.21*°	1.14±0.22*
TNF-α, pg/ml	0.69±0.15	5.41±0.56*°	2.38±0.29*
CRP, μg/ml	1.22±0.16	11.86±1.14*°	7.73±1.19*
TSH mU/ml	0.91±0.21	11.95±0.51*°	1.26±0.51
T4 pg/ml	14.21±1.84	6.4±0.82*°	13.64±1.31

*- statistically significant as compared to healthy individuals, $p < 0.05$
° - statistically significant as compared to patients of Group I and Group II, $p < 0.05$

In patients of Group I, there was a moderate positive correlation between ET-1 and TSH levels ($r = 0.43$, $p < 0.05$) and a weak negative correlation between ET-1 and T4 levels ($r = - 0.26$, $p < 0.05$) that indicated a more intensive development of endothelial dysfunction as compared to patients without hypothyroidism.

Similar correlations were found for the indicators of the immune inflammatory response. The level of CRP was found to be 9.7 times higher in patients with hypothyroidism as compared to healthy individuals, while in patients without hypothyroidism, it was 6.3 times higher, respectively ($p < 0.001$). In patients of Group I, CRP level was 1.5 times higher than that in patients without hypothyroidism. Therefore, we found a strong positive correlation between CRP and TSH levels ($r = 0.76$, $p < 0.05$) and a moderate negative correlation between CRP and T4 levels ($r = 0.51$, $p < 0.05$). In patients of Group II, no similar correlations were found.

The serum levels of TNF-α in patients of Group I and Group II were 7.8 and 3.4 times higher ($p < 0.001$) than those in healthy individuals. In patients of Group I, there was a moderate positive correlation between TNF-α and TSH levels ($r = 0.56$, $p < 0.05$) and a moderate negative correlation between TNF-α and T4 levels ($r = 0.47$, $p < 0.05$). In patients of Group II, no similar correlations were found. The coexistence of both pathologies resulted in a 2.27-fold increase in serum concentration of TNF-α as compared to patients without hypothyroidism as evidenced by intensive development of systemic inflammation in comorbid patients.

Discussion

The issue of cardiovascular involvement in hypothyroidism is today of great relevance as the prevalence of this syndrome is steadily increasing. It affects 1.4 to 2% of adult women and 0.2% of adult men (Francois et al. 2020). In addition, the incidence of hypothyroidism increases with age. Hypothyroidism is most prevalent in elderly patients over 60 years of age; among the patients examined (without past thyroid conditions), hypothyroidism was diagnosed in 6% of females and 2.5% of males (Pankiv 2013). Similar trend was observed among patients with CHF as the prevalence of this syndrome is estimated at 1 to 2% of the adult population and increases with age as well (Mosterd et al. 2007). Therefore, a coexistence of these two pathologies was often observed that significantly worsened their clinical course.

Endothelial dysfunction plays an important role in the progression of both conditions and is involved in the development of complications (Drapkina et al. 2016; Malyarska et al. 2017). Endothelial dysfunction is presented as an imbalance between the production of vasodilating, angioprotective, antiproliferative factors and vasoconstricting, prothrombotic and proliferative factors (Hang et al. 2017). The diagnosis of endothelial dysfunction is a challenge in the healthcare system; therefore, a lot of methods, both instrumental and laboratory, have been developed and standardized to assess endothelial function and endothelial dysfunction severity. The determination of various factors secreted by the endothelium in biological fluids, namely the blood serum, is a very important method for determining the degree of endothelial dysfunction severity (Ivanov et al. 2014; Kazimli et al. 2014; Vasina et al. 2017). The determination of specific blood biochemical markers is an effective method to detect endothelial dysfunction which is used to characterize the state of the vascular endothelium (Stepanova et al. 2019). Among these markers, there is ET-1 that reflects the state of endothelial vasomotor function (Sokolov et al. 2013). It stimulates both vasospasm and mitogenic activity in endothelial cells and cardiomyocytes. Elevated ET-1 concentrations are observed in hypoxia, ischemia, high levels of cholesterol, low-density lipoproteins, and glucose (Sokolov et al. 2013; Davenport et al. 2016) and are common in both CHF and hypothyroidism. Thus, we could explain the findings obtained, namely a significantly higher ET-1 level in patients with CHF and coexisting hypothyroidism and a positive correlation between ET-1 and TSH in these patients.

Since the immune inflammatory activation, which stimulates myocardial fibrosis and remodeling, plays a significant role in the development and progression of CHF (Jones DP et al. 2018) and CRP is regarded as a marker for immune inflammation, we focused on the increase in its serum concentration and its correlation with the levels of thyroid hormones. The plasma level of CRP increases in patients with HF; therefore, it is regarded as an independent predictor of future adverse events in this group of patients (van Wezenbeek et al. 2018; Jones et al. 2018) as evidenced by the LURIC study which has found a strong positive correlation between plasma CRP levels and clinical and laboratory indicators of HF severity. Moreover, CRP turned out to be a strong and independent predictor of overall mortality and an especially strong predictor of cardiovascular mortality (Koller et al.

2014). In our study, CRP levels were significantly higher in patients with a comorbidity; hence, more aggressive clinical course of the systemic inflammatory process was observed in patients with CHF and coexisting hypothyroidism.

Elevated serum concentration of TNF-α, which is one of the most important markers of immune inflammation as well and corelates with NYHA FC, plays the same role in CHF (Hartupee et al. 2013). In our study, TNF-α levels were significantly higher in patients with CHF and coexisting hypothyroidism as compared to those without hypothyroidism. Thus, the coexistence of CHF and hypothyroidism is accompanied by a stronger immune inflammatory response and will potentially be accompanied by rapid progression and complication development.

Conclusion

In patients with CHF and coexisting hypothyroidism, endothelial dysfunction and systemic immune inflammatory response intensified as compared to healthy individuals; however, their signs were observed in isolated HF as well. These changes require new approaches to the treatment of these comorbidities, which will be the focus of our future research.

Conflict of interest

The authors declare that there is no conflict of interest.

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