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## CLINICAL SIGNIFICANCE OF NATRIURETIC PEPTIDES (review)

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<https://doi.org/10.35339/ic.9.1.5-13>

### Abstract

Natriuretic peptides are widely known for their protective effects against the development of metabolic syndrome and cardiovascular disease. The important role of determining the levels of natriuretic peptides in the diagnosis, assessment of severity, prognosis and effectiveness of treatment of heart failure has been proven in many studies and noted in clinical guidelines worldwide. Visceral obesity reduces the production and action of natriuretic peptides, increasing the risk of heart failure and 2 type diabetes mellitus. Metabolic syndrome is present in 60% of patients with chronic heart failure, most of its components contribute to the development and progression of chronic heart failure and include obesity, hypertension, dyslipidemia, insulin resistance, impaired glucose tolerance. The prevalence of metabolic syndrome in the general population is 34% and is constantly increasing due to unhealthy diet, sedentary lifestyle and chronic stress. The prevalence of chronic heart failure is increasing rapidly in all industrialized countries, affecting 2% of adults and 10% of the elderly. Therefore, the problem of early diagnosis and treatment of metabolic syndrome and chronic heart failure is relevant nowadays. The review focuses on the pathophysiological relationships between natriuretic peptides, heart failure and metabolic syndrome, and the approaches to the correction of natriuretic peptides' metabolism.

**Keywords:** *2 type diabetes mellitus, heart failure, metabolic syndrome, natriuretic peptides.*

### INTRODUCTION

Natriuretic peptides (NUPs) are widely known for their protective effects against the development of metabolic syndrome (MS) and cardiovascular remodeling. Physiological levels of NUPs in serum are effective for prevention of arterial hypertension, sodium and fluid overload, obesity, vascular inflammation, dyslipidemia, insulin resistance (IR), hyperglycemia, myocardial hypertrophy and fibrosis [1]. Excessive visceral adiposity decreases synthesis of NUPs and impairs tissue sensitivity to them by inhibiting NUPs receptors, increasing renal clearance of NUPs, thus contributing to higher risk of heart failure (HF) and 2 type diabetes mellitus (DM-2) [2]. The importance of determining serum natriuretic peptides (NUPs) levels for the diagnosis, assessment of severity, prognosis of HF, and also for the assessment of treatment efficacy, has been extensi-

vely investigated in cardiovascular studies worldwide. Over the recent 20 years, the prevalence of chronic HF has substantially increased in all industrialized countries, and in recent years has been 3 to 20 cases per 1,000 adults and 100 cases per 1,000 elderly people [1]. The presence of chronic HF impairs quality of life and significantly increases overall morbidity and mortality. The main risk factors for HF are closely related to MS and include visceral obesity, arterial hypertension, dyslipidemia, IR, hyperglycemia, and DM-2. The prevalence of MS in the general population is 34% and is constantly increasing due to poor nutrition, sedentary lifestyle and chronic stress. MS is observed in 60% of patients with chronic HF, most of its components contribute to the development and progression of chronic HF. Therefore, the concern about early diagnosis and treatment of MS and chronic HF is very serious nowadays, and NUPs play a significant role in managing these healthcare problems [2, 3]. The review focuses on the pathophysiological relationships between natriuretic peptides, heart failure and metabolic syndrome, and approaches to the correction of natriuretic peptide metabolism.

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**GENERAL INFORMATION**

NUPs are produced in the atria and ventricles of the heart as well as in the endothelium. These hormones act as vasodilators, diuretics and natriuretics, activate lipolysis of adipose tissue and insulin secretion, increase oxidation of free fatty acids (FFA) in skeletal muscles and liver. The main stimulus for their secretion is elevation of myocardial tension with increasing pressure or volume overload. In cardiovascular diseases NUPs reflect contractile capacity of a myocardium [4]. Brain natriuretic peptide (BNP) and N-terminal pro-b-type natriuretic peptide (NT-proBNP) are widely used for the diagnosis of HF in clinical practice, since their elevation is observed in the majority of HF types, they can exclude the presence of heart failure with a high sensitivity, in case when the diagnosis is uncertain [5, 6]. The use of these biomarkers has the highest class of recommendations for confirming the diagnosis or exclusion of HF in the latest clinical guidelines [4, 6].

The NUPs family includes a group of hormones that have a similar molecular structure and are natural antagonists of the renin-angiotensin and sympatho-adrenal systems, aldosterone and vasopressin. There are four members of this family: Atrial Natriuretic Peptide (ANP), Brain Natriuretic Peptide (BNP), Natriuretic Peptide-C (CNP) and Dendroaspis Natriuretic Peptide-D (DNP) [4].

**NUPs: physiological and pathophysiological mechanisms of action**

The main stimulus for increased secretion of ANP and BNP is stretching of the atria, caused by pressure or volume overload. BNP synthesis and secretion can also be triggered by hypoxia and ischemia of cardiomyocytes, angiotensin II, endothelin-1, glucocorticosteroids and tachycardia, even in the absence of dilation of the heart chambers [2]. Significant increase of BNP levels in serum within 1 hour and ANP levels within 3 hours is observed in response to hemodynamic stress [9]. ANP and BNP are known to reduce the sympathetic tone and suppress both renin and aldosterone secretion [3]. Increased levels of proinflammatory cytokines, especially tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 and 6 (IL-1, IL-6) or thyroid hormones impair release of ANP and BNP in response to mechanical stretching and ischemia of the heart [1]. Physiologically, ANP and BNP secretion is stimulated by estrogen, thus ANP and BNP levels are higher in women. On the other hand, CNP synthesis and release is activated by testosterone and growth hormone [3]. CNP release and production in endothelium and vascular smooth

muscle cells is stimulated by transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1), TNF- $\alpha$ , and IL-1, which are released in response to hypoxia, hyperglycemia, pressure and volume overload [8]. CNP plays an important role in vasorelaxation, acting together with another potent vasodilators – nitric oxide (NO) and prostacyclin [11].

ANP and BNP provide cardiovascular and kidney protection and metabolic effects by multiple physiological mechanisms:

1. Reduction of systemic blood pressure and venous return (preload) to the heart, balancing electrolyte homeostasis by:

- increase in glomerular filtration;
- inhibition of sodium reabsorption and enhancement of natriuresis and diuresis; inhibition of vasopressin / antidiuretic hormone reactions;
- relaxation of vascular smooth muscles.

2. Reducing the impact of the sympathetic nervous system on the heart and blood vessels by inhibiting the effects of RAAS by inactivating renin and aldosterone, angiotensin II.

3. Prevention of remodeling of the myocardium and vascular walls as a result of:

- inhibition of inflammatory, hypertrophic and proliferative processes in the endothelium, smooth muscle cells, myocardium;
- reduction of the activity of RAAS and cytokine systems, growth factors, matrix metalloproteinases, catecholamines, etc.;
- decrease of hypercoagulation and atherothrombosis.

4. Prevention of obesity, IR and DM-2 by stimulation of lipolysis in adipose tissue, increasing oxydation of FFAs in skeletal muscles, liver and adipose tissue, increasing sensitivity to insulin, decreasing production of proinflammatory cytokines [10–15, 18, 35–39].

**Clinical significance of NUPs in the diagnosis of heart diseases**

BNP is important in the diagnosis of heart failure, for risk stratification and control of the effectiveness of heart failure therapy [1, 2]. BNP increases in serum before clinical and instrumental signs of LV dysfunction and congestive HF become apparent, thus BNP is indispensable for early diagnosis of this pathology, being more sensitive than echocardiography. The results of The Breathing Not Properly Multinational Study showed that elevated serum BNP indicates the presence of HF. In addition, the BNP levels have clear correlation with the functional class of HF according to the classification of the New York Heart Association [16]. Similar data were obtained

in a study involving 250 older patients (94% were men), 97 of who had congenital and acquired heart defects. In this study, BNP levels in patients with heart disease were significantly higher than in the group of patients with respiratory pathology [17].

#### Diagnostic levels of NUPs

The latest ESC and ACC/AHA guidelines for the diagnosis and treatment of heart failure identified diagnostic threshold values of NUPs in different clinical situations. Thus, for exclusion of acute HF, the diagnostic threshold for NT-proBNP less than 300 pg/ml and for BNP less than 100 pg/ml; for exclusion of chronic HF, the cut-off NT-proBNP level was less than 125 pg/ml and BNP less than 35 pg/ml were determined. Normal serum levels of NUPs in the absence of previous treatment exclude significant cardiac damage [2, 3, 18].

#### Evidence based data about diagnostic significance of NUPs

Multiple clinical conditions, besides HF, such as chronic kidney disease (CKD), atrial fibrillation (AF), pericardial disease, pulmonary embolism, and even age >75 y.o., can be the cause of increased levels of NUPs. On the other hand, MS is associated with decreased levels of NUPs, emphasizing the importance of establishing comorbidities [19].

NT-proBNP is excreted only through the kidneys. Therefore, kidney dysfunction can significantly increase NT-proBNP serum levels. In addition, neprilysin increases production of BNP, thus BNP levels can increase during ARNI (sacubitril/valsartan) therapy. However, NT-proBNP is not a substrate for neprilysin, a successful decrease in NT-proBNP is observed with effective ARNI treatment [18].

BNP level >17.9 pg/ml is reported to be a significant independent predictor of mortality from all causes in patients with chronic HF with reduced ejection fraction (HFrEF) ( $p=0.006$ ). The mean BNP is 7.8 (3.4–13) pg/ml in 4-year survivors with HFrEF ( $p<0.0001$ ) [25]. Reduction of NT-proBNP to <1000 pg/ml is associated with significant reverse myocardial remodeling in response to treatment and more favorable prognosis [12].

The PRIDE study showed that NT-proBNP levels >300 pg/ml in 600 patients with dyspnea were 90% sensitive and 85% specific for the diagnosis of acute HF [1]. Also, BNP>100 pg/ml has 83.4% probability of acute HF, while BNP<50 pg/ml excludes acute HF with 96% sensitivity [3]. Body mass index affects the threshold level of BNP for the diagnosis of acute HF: for 90% sensi-

tivity for the diagnosis of acute HF, BNP>170 pg/ml cut-off point should be used for patients with BMI 18.5 to <25 kg/m<sup>2</sup>, 110 pg/ml for BMI 25 to <40 kg/m<sup>2</sup> and 54 pg/ml in morbid obesity with BMI>40 kg/m<sup>2</sup>. BNP is also useful for the differential diagnosis of acute HF. BNP ≤200 pg/ml provides 91% specificity for acute respiratory distress syndrome, while BNP≥1200 pg/mL has 92% specificity for cardiogenic pulmonary edema [27].

The 2021 ESC guidelines state that the sensitivity and specificity of BNP and NT-proBNP for the diagnosis of chronic HF are higher during exacerbations and lower in the compensation phase. The threshold BNP level for the diagnosis of chronic HF was set at 35 pg/ml [30]. BNP threshold for the diagnosis of congestive heart failure is 80 pg/ml (95% accuracy). NT-proBNP cut-off point 125 pg/ml rules out chronic HF with a 97% probability [2]. BNP levels increase significantly according to each of the following NYHA functional class of HF: class I – 21.6±2.8 pg/ml, class II – 108.6±16.3 pg/ml, class III – 197.1±27.2 pg/ml and class IV – 363.0±67.8 pg/ml,  $p<0.0001$ ) [28].

Determining serum levels of NUPs allows to clarify treatment strategy and to avoid unnecessary or inappropriate therapy. The latest ESC clinical guidelines for the management of patients with chronic HF emphasize the importance of assessing BNP and NT-proBNP in patients with acute dyspnea in order to exclude other causes of dyspnea not related to HF [20]. Also, in the same clinical guidelines, serum BNP and/or NT-proBNP levels greater than 35 and 125 ppg/ml, respectively, are considered to be necessary criteria for the diagnosis of HF with preserved ejection fraction (HFpEF), in addition to clinical manifestations and certain echocardiographic parameters [2].

In the latest version of the American (ACC/AHA) guidelines for the management of patients with HF, published in 2017, determining BNP levels in serum in order to exclude or confirm the diagnosis of HF in patients with dyspnea, has class I recommendation with the evidence level A [4].

Low level of NUPs, if adjusted to BMI, can rule out HF with high level of confidence [21]. But sensitivity of elevated NUPs levels to confirm the presence of HF is not so high, because increase of NUPs levels can be caused by comorbid non-cardiovascular conditions [9]. Causes of increased BNP and NT-proBNP levels in serum include cardiomyopathies, myocarditis, acute coronary syndrome, chronic coronary syndromes, valvular heart disease, atrial fibrillation and flutter, cardiotoxicity, kidney failure, anemia, sepsis, severe burns,

adult respiratory distress syndrome and other severe forms of pulmonary diseases [27].

Determining BNP or NT-proBNP levels for the assessment of HF severity and prognosis has class I recommendations with evidence level A in latest ACC/AHA and ESC guidelines [2, 4]. Patients with HFpEF usually show 2 times lower level of NT-proBNP (median level 2723 ng/l) compared to patients with HF with reduced ejection fraction (HFrEF), whose median NT-proBNP is 5644 ng/l ( $p < 0.001$ ) [22]. The latest ACC/AHA clinical guidelines emphasize the purpose of determining BNP, NT-proBNP and cardiospecific troponins at the time of hospital admission and several weeks after initiation of treatment for the assessment of prognosis in patients with acute heart failure (class of recommendations I, level of evidence A) [10, 12].

High concentrations of BNP and NT-proBNP at the time of hospitalization are often accompanied by pathological elevation of cardiospecific troponins in patients with acute HF decompensation, even in the absence of obvious signs of myocardial ischemia or concomitant coronary heart disease [10, 12]. Such clinical situations are usually associated with a high risk of adverse clinical outcomes, including death from all causes and death from cardiovascular complications in patients with decompensated HF [2, 4, 12, 23, 24].

For certain level of NT-proBNP, prognosis is similar regardless the ejection fraction: survival rates are similar for patients with HFpEF and HFrEF in terms of death from any cause (88.4% vs. 86.9%;  $p = 0.471$ ) or cardiovascular death or HF decompensation at 1 year (73.8% vs. 70.6%;  $p = 0.225$ ) [23]. NT-proBNP is a strong and independent prognostic factor for all-cause death and major adverse cardiovascular events (MACEs) in elderly patients and MACEs in younger individuals. A 4.8-year study has shown 0.8% all-cause mortality in low NT-proBNP group ( $< 19.8$  pg/ml) and 7.8% high NT-proBNP group ( $\geq 81.9$  pg/ml;  $p < 0.001$ ). The rate of MACEs was reported to be 3.1% in low NT-proBNP group and 18.9% in the high NT-proBNP group ( $p < 0.001$ ) [25]. In get-ABI-study with 7-year follow-up the rates of all-cause and cardiovascular mortality were: 35.4% and 6% for NT-proBNP  $> 300$  pg/ml; 16.2% and 40% for NT-proBNP 125–300 pg/ml and 11.4%/4% for NT-proBNP  $\leq 125$  pg/ml [26]. High serum BNP levels are reported to be a reliable predictor of poor outcome not only in HFrEF but also in HFpEF. BNP level shows good correlation with LV end-diastolic pressure. BNP levels are asso-

ciated with HF severity across the spectrum of HF stages [27].

The PEACE study, which involved low-risk patients with stable coronary artery disease and preserved ventricular function, elevated BNP and NT-proBNP has shown association with increased risk of HF development; higher NT-proBNP was also associated with increased risk of cardiovascular death, HF and stroke [28].

Recent studies indicated that NT-proBNP levels were significantly associated with cardiovascular outcomes and mortality in patients with DM-2 [2, 4, 12-15]. In a cohort study elevated NT-proBNP levels are reported to be independent predictors of major adverse cardiovascular events (MACEs) in patients with chronic coronary syndromes (CCS), preserved systolic function and prediabetes or DM-2 [29]. NT-proBNP was suggested to be superior to traditional risk factors for predicting cardiovascular events in prediabetic or diabetic patients with CCS. A group of patients with CCS and normoglycemia did not show significant associations between NT-proBNP levels and the risk of MACEs, which may need further investigations with a larger size of cohort [29].

Additionally, the evidence is provided that the NT-proBNP level has prognostic value in patients with ACS [14, 30]. Moreover, NT-proBNP has shown to be a strong predictor of MACEs and mortality in ACS patients, who underwent PCI with stent placement. NT-proBNP  $> 1568$  pg/ml is related to the high risk of all-cause death in nonST-elevation ACS patients [31]. Newly published study reported that high NT-proBNP level before primary PCI was independently associated with poor myocardial reperfusion in patients with ST-elevation MI [32].

#### **The purpose of determining BNP and NT-proBNP levels in the assessment of treatment effects in HF patients**

PARADIGM-HF study has detected statistically significant direct association between the reduction in NT-proBNP to  $\leq 1,000$  pg/ml and the 59% reduction in overall mortality [33]. In this trial 2/3 of investigated patients had baseline NT-proBNP values  $> 1,000$  pg/ml, which reflects high risk of complications. All the patients were reassessed at 1 and 8 months after the initiation of the treatment. Patients, who received sacubitril/valsartan treatment, had significantly lower NT-proBNP levels after 1 month of therapy, compared to patients, who received enalapril, also sacubitril/valsartan group showed significantly higher rate of NT-proBNP decrease below  $\leq 1,000$  pg/ml



compared to enalapril group: in 31% versus 17% of patients [33].

In addition, the results of a recent meta-analysis have shown that the decrease in BNP and NT-proBNP levels in HFrEF patients is associated with lower risk of HF decompensation, which requires hospitalization [34].

#### **NUPs in regulation of lipid and glucose metabolism**

NUPs increase lipolysis in adipose tissue, oxidation of FFA in skeletal muscles, liver and adipose tissue, sensitivity to insulin, insulin production and secretion, adiponectin secretion, decrease the secretion of proinflammatory cytokines and excessive leptin production. Visceral obesity has inverse association with levels of ANP and BNP and sensitivity of their receptors. Decreased levels of ANP and BNP are directly associated with the development of arterial hypertension, proatherogenic dyslipidemia, obesity and DM-2 [35]. But loss of visceral fat as a result of healthy diet and moderate physical activity is capable to restore physiological levels of NUPs and appropriate function of the receptors [34–36].

Glucagon-like peptide-1 (GLP-1) and physical activity increase ANP release from cardiac atrium, thus healthy dieting habits and avoiding sedentary lifestyle are cornerstones in maintenance of proper ANP level. The less known stimulators of ANP secretion are vitamin D, retinoids and glucocorticoids. Physical activity increases BNP expression and secretion [36]. C-type natriuretic peptide (CNP) increases in serum in case of endothelial damage, sepsis, hypoxia and chronic renal failure, due to influence of various cytokines and growth factors such as tumor necrosis factor (TNF- $\alpha$ ), lipopolysaccharide (LPS), basic fibroblast growth factor (bFGF), interleukin-1 (IL-1), transforming growth factor beta (TGF- $\beta$ ) and thrombin [37]. ANP, BNP and CNP regulate metabolic processes by interaction with their receptors: natriuretic peptide receptor A (NPR-A), natriuretic peptide receptor B (NPR-B) and natriuretic peptide receptor C (NPR-C) [36]. Angiotensin II, endothelin, and endothelial NOS regulate NPR-A expression [36].

The expression of NPR-C significantly increases in patients with MS, which stimulates FFA oxidation and energy expenditure, in order to prevent the progression of obesity, excessive visceral adiposity, hyperproduction of proinflammatory cytokines. All the mentioned protective effects of NPR-C decrease insulin resistance, improve glucose tolerance and thus decrease the risk

of new-onset DM-2 and diabetic complications [37]. Sedentary behavior, high-fat and high-sugar diet increase the expression of NPR-C in adipose tissue, whereas regular physical activity and healthy diet restore their physiological levels [38].

#### **NUPs effects in adipose tissue**

ANP is the most potent activator of lipolysis, followed by BNP and CNP [36].

Hyperinsulinemia caused by MS or intensive insulin therapy can attenuate NUPs-mediated lipolysis by reducing the level of circulating NUPs [35]. Increase of ANP levels and NPR-A activation in response to hypocaloric diet and moderate aerobic exercise decreases accumulation and inflammation of visceral adipose tissue, decreases release of proinflammatory cytokines from human adipocytes and adipose tissue macrophages, improves sensitivity to insulin according to HOMA-IR index, improves the results of oral glucose tolerance test (OGTT), thus decreasing the risk of DM-2 and cardiovascular diseases [36, 39].

#### **NUPs effects on lipid oxidation and mitochondrial function**

NUPs-induced lipolysis dramatically increases the availability of FFA for metabolically active tissues such as skeletal muscles and liver. Moreover, studies in humans and mice show that NUPs enhance oxidation of lipids in adipose tissue, skeletal muscles and liver, allowing these tissues to oxidate FFA more effectively, and use them as the predominant energy substrate [40].

It was found that short-term intravenous administration of ANP significantly increases lipid oxidation and energy expenditure after meals in healthy volunteers [41]. In addition to enhancing acute lipid oxidation, ANP and BNP induce mitochondrial biogenesis in skeletal muscles, increase lipid oxidation in human and rodent cells in vitro and in vivo. Chronic overexpression of BNP leads to increase in amount of mitochondria in skeletal muscles. Increased oxidative metabolism is known to be protective against obesity and IR caused by a high-fat diet [42].

#### **NUPs interaction with adipokines**

ANP significantly increases serum levels of adiponectin [36]. ANP reduces the release of leptin from human adipocytes [37]. Significant inverse correlation between serum BNP and leptin levels was reported in patients with chronic HF [39]. In case of NUPs deficiency, these mechanisms may contribute to the development of metabolic syndrome [36].

#### **NUPs, insulin secretion and glucose homeostasis**

A number of studies suggest that NUPs directly

and indirectly affect glucose metabolism. Clinical studies revealed an increase in serum insulin level during the infusion of ANP [43]. The effect can be explained by a direct stimulating effect on the  $\beta$ -cells. ANP directly enhances glucose-stimulated insulin secretion in cultured islets. In addition, ANP induced  $\beta$ -cell growth in isolated islets of the rat pancreas, whereas significantly smaller islets with reduced  $\beta$ -cell mass were found in ANP deficiency [44]. Finally, ANP increases glucose uptake by human adipocytes, preventing postprandial hyperglycemia [43].

It is interesting to note that infusion of NUPs in ten healthy young people on an empty stomach slightly increased blood glucose [45]. This effect can be explained by potent lipolytic effect of ANP on adipose tissue, which can dramatically increase the influx of FFAs to insulin-sensitive metabolic organs, and thus induce insulin resistance. In contrast, short-term infusion of BNP, without increasing FFA levels, slightly reduces circulating glucose concentrations during the initial phase of glucose and glucose tolerance test. This effect may be mediated by increased peripheral vasodilation and improved glucose transport through the capillary wall into the interstitial space [36]. Together, these studies suggest that NUPs can increase insulin secretion and insulin-stimulated glucose uptake, thus preventing DM-2 and diabetic complications.

NUPs can reduce lipid-induced IR by activating lipid oxidation in liver and muscle tissue. NUPs also preserve mitochondrial function and insulin sensitivity while using high fat diet in mice [39].

#### **NUPs in obesity**

In recent years, numerous studies have shown an inverse relationship between the levels of circulating NUPs and body weight [46]. This correlation may also be observed in patients with chronic HF, despite elevated levels of NUPs, due to oxidative stress in the myocardium [47].

Genetic polymorphism of CNP receptors is associated with lower prevalence of obesity and visceral adiposity compared to individuals with intact CNP receptors [48]. Another genetic polymorphism in the ANP promoter is associated with higher ANP levels and a favorable cardiometabolic phenotype, including lower prevalence of MS [49].

Visceral adiposity is reported to reduce NUPs release, increase their clearance, negatively affects receptor responses to NUPs in subcutaneous adipose tissue, liver and skeletal muscles. In contrast to patients with normal body weight, in obese

patients serum NUPs levels are reduced and rapid NUPs responses to stimuli are blunted [50], but they can be restored by regular physical activity [51]. A survey of 7,770 patients and volunteers from the Framingham Heart Study and the Malmö Diabetes and Cancer Study found that obesity and IR were associated with markedly reduced plasma NUP levels [52]. ARIC study (Atherosclerosis Risk in Communities) has shown that NT-proBNP levels were inversely related to the risk of new-onset DM-2 during 12 years of follow-up [53].

Aerobic exercise and hypocaloric balanced diet can significantly increase NT-proBNP levels and tissue responses to ANP [53]. In patients with moderate obesity and HFpEF regular aerobic exercises, especially swimming, significantly increase ANP and BNP levels [27]. This effect may be explained by increase in venous return and cardiac filling pressure as a result of physical activity. Exercise-induced ANP secretion can be increased by taking  $\beta$ -adrenoblockers [29].

#### **NUPs in insulin resistance and diabetes**

In the latest studies, decreased levels of NUPs were associated with chronic hyperglycemia and hyperinsulinemia, regardless of body composition and distribution of adipose tissue [54]. Framingham Heart Study and Malmö Diet and Cancer Study have shown that low levels of BNP and NT-proBNP are strongly associated with the development of IR and new-onset DM-2 in both lean and obese patients [56, 59]. Moreover, in patients with NT-proBNP levels at the upper reference level, the risk of new-onset diabetes is significantly lower [57]. In healthy individuals' acute elevation of serum glucose causes rapid increase in ANP levels in response to hyperglycaemia-induced sodium and fluid retention, but this response is blunted in MS [55]. Heinisch et al. reported that BNP infusion during glucose tolerance test temporarily decreases serum glucose levels in healthy men [58].

These data suggest that NUPs may protect against the development of DM-2 due to antihyperglycemic effect and increasing lipid oxidation and mitochondrial function, as described above. On the contrary, NUPs deficiency probably contributes to IR and DM-2.

#### **NUPs and Lipid Profile**

The results of meta-analysis of studies, which investigated the relationship between NUPs and the components of serum lipid profile, demonstrated inverse association between NUPs levels and serum levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides, and direct

association with high-density lipoprotein cholesterol levels. These data underline the association between decreased NUPs levels and a proatherogenic lipid profile [40].

#### **NUPs in arterial hypertension**

The prevalence of AH in obese patients is 2–3 times higher than in people with normal body weight [48]. In lean healthy patients, sodium load or vasopressors induce release NUPs in order to enhance natriuresis, but in obese patients this response is blunted [26]. Partially, obesity contributes to the development of AH by reduction of vasodilation and natriuretic responses to NUPs and attenuation of NUP-mediated inhibition of RAAS and sympatho-adrenal system [18]. Brunner-La Rocca et al. demonstrated inhibitory effects of BNP on systemic and cardiac sympathetic nervous system activity. Thus, insufficient response to NUPs may increase the activity of the sympathetic nervous system in obesity [8].

In addition to regulation of blood pressure, NUPs also have a beneficial effect on heart remodeling in AH, reducing left ventricular hypertrophy and fibrosis. Rubattu et al. demonstrated that hypertensive patients with MS have lower levels of ANP and NT-proBNP, higher myocardial mass and a higher prevalence of left ventricular hypertrophy compared to hypertensive patients without MS [60].

In general, these results suggest that decreased levels of NUPs are associated with obesity and an increased risk of MS and cardiovascular diseases, while physiological levels of NUPs are associated with more favorable cardiometabolic phenotype.

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#### **CONCLUSIONS**

NUPs show multifaceted protective cardiovascular and metabolic effects, which prevent myocardial remodeling, obesity, insulin resistance, hyperglycemia, dyslipidemia and hypertension. MS and cardiovascular diseases have close pathophysiological association and cause serious public healthcare system burden worldwide. Recent studies reported decreased NUPs levels and impaired action of NUPs receptors in patients with MS, which can increase cardiovascular risk. Healthy diet and rational physical activity together with pharmacological interventions, recommended by the latest cardiologic guidelines, show beneficial effects on NUPs production and effects. More wide use of NUPs for early diagnosis, risk stratification, and guided pharmacological intervention in patients with MS and HF has a significant potential for improving the cardiovascular care worldwide.

#### **DECLARATIONS:**

##### **Statement of Ethics**

The authors have no ethical conflicts to disclosure.

##### **Consent for publication**

All authors give their consent to publication.

##### **Disclosure Statement**

The authors declare that the review was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

##### **Funding Sources**

There are no external sources of funding

##### **Data Transparency**

The data can be requested from the authors.

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Received: 14 Dec 2021

Accepted: 23 Feb 2022