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THE ROLE OF NEUROTROPHINS IN ACUTE CORONARY SYNDROME - PROGNOSTIC AND DIAGNOSTIC VALUE OF NEW BIOMARKERS

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ULOGA NEUROTROFINA U AKUTNOM KORONARNOM SINDROMU – PROGNOSTIČKA I DIJAGNOSTIČKA VREDNOST NOVIH BIOMARKERA

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ABSTRACT

Acute coronary syndrome (ACS) remains the leading cause of morbidity and mortality worldwide. While existing diagnostic and prognostic biomarkers have improved patient care, there is still a need for newer, more specific markers to enable more precise risk stratification and individualized treatment. Neurotrophins are a family of proteins essential for neuronal survival and function. In recent years, their role in cardiovascular diseases has become increasingly recognized. The aim of this review is to present current knowledge on the role of neurotrophins, primarily brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), in the pathophysiology of ACS, and to evaluate their potential as novel diagnostic and prognostic biomarkers. The studies analyzed indicate significant changes in neurotrophin levels during ACS, linking them to ischemia, reperfusion injury, inflammation, and myocardial remodeling. There is evidence that elevated or decreased levels of certain neurotrophins can predict short-term and long-term outcomes in patients with ACS. Further research, especially large multicenter studies, is necessary to confirm the value of neurotrophin measurement in ACS as a significant biomarker in clinical practice.

Key words: *acute coronary syndrome; brain-derived neurotrophic factor; nerve growth factor; biomarkers; prognosis; diagnosis.*

SAŽETAK

Akutni koronarni sindrom (AKS) predstavlja vodeći uzrok morbiditeta i mortaliteta širom sveta. Iako su postojeći dijagnostički i prognostički biomarkeri unapredili lečenje pacijenata, i dalje postoji potreba za novim, specifičnijim markerima koji bi omogućili precizniju stratifikaciju rizika i individualni pristup lečenju. Neurotrofini predstavljaju porodicu proteina esencijalnih za preživljavanje i funkciju neurona. Poslednjih godina sve više se prepoznaje njihova uloga u bolestima kardiovaskularnog sistema. Cilj ovog revijalnog rada bio je da predstavi aktuelna saznanja o ulozi neurotrofina, prvenstveno brain-derived neurotrophic factora (BDNF) i nerve growth factora (NGF) u patofiziologiji AKS-a, kao i da proceni njihov potencijal kao novih dijagnostičkih i prognostičkih biomarkera. Analizirane studije ukazuju na značajne promene u nivoima neurotrofina tokom AKS-a, povezujući ih sa ishemijom, reperfuzionom povredom, inflamacijom i remodelovanjem miokarda. Postoje dokazi da povišeni ili sniženi nivoi određenih neurotrofina mogu predvideti kratkoročne i dugoročne ishode kod pacijenata sa AKS-om. Dalja istraživanja, posebno velike multicentrične studije, neophodna su da bi se potvrdila vrednost određivanja neurotrofina u AKS kao značajnog biomarkera u praksi.

Ključne reči: *akutni koronarni sindrom; neurotrofički faktor izveden iz mozga; faktor rasta nerava; biološki markeri; prognoza; dijagnoza.*

INTRODUCTION

Acute coronary syndrome (ACS) encompasses unstable angina pectoris (UA), non-ST elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI), representing a global health challenge (1). The diagnosis of myocardial infarction (MI) is associated with cardiac troponin release and is made based on the fourth universal definition of MI. UA is defined as myocardial ischaemia at rest or on minimal exertion in the absence of acute cardiomyocyte injury/necrosis (2). ACS often represents the initial clinical presentation of cardiovascular disease (CVD). In 2019, the 57 member countries of the European Society of Cardiology (ESC) recorded an estimated 5.8 million new occurrences of ischaemic heart disease. Cardiovascular disease continues to be the primary cause of mortality across ESC member nations. In the most recent year for which data is available, CVD was responsible for nearly 2.2 million female deaths and slightly over 1.9 million male deaths. Among all CVD-related fatalities, ischaemic heart disease stands out as the leading cause, accounting for 38% of deaths in women and 44% in men (3). Rapid and precise diagnosis, as well as adequate risk assessment, are crucial for timely treatment and improved outcomes. Currently, the diagnosis of myocardial infarction is based

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on clinical presentation, electrocardiographic changes, and levels of cardiac enzymes, predominantly highly sensitive troponins, while prognosis is assessed based on clinical characteristics and other biomarkers such as natriuretic peptides (2, 3). However, these markers have certain limitations in early detection, predicting complications, and identifying high-risk patients for adverse outcomes. There is a need to investigate new biomarkers that would complement the existing diagnostic and prognostic arsenal. Neurotrophins are a family of signaling proteins primarily known for their crucial role in the development, survival, and function of neurons. However, a growing body of research indicates their significant role in peripheral tissues as well, including the cardiovascular system (4). They are known to be present in the heart muscle and participate in various physiological and pathophysiological processes, including cardiac remodeling, angiogenesis, and inflammation. Given the complex interaction between the nervous system and the heart, as well as the presence of neuroinflammation and neuronal damage during ACS, neurotrophins emerge as potential candidates for new biomarkers with diagnostic and prognostic value. Depression is a common comorbidity in patients with ACS, significantly impacting their outcomes and quality of life (5). Neurotrophins, particularly BDNF, are crucial for neurogenesis and synaptic plasticity, and their reduced levels are frequently linked to the pathophysiology of depression. Given the presence of neuroinflammation and neuronal damage during ACS, neurotrophins emerge as promising biomarkers. Therefore, neurotrophin status may be associated with the occurrence of depression in ACS patients, offering potential diagnostic and prognostic value (5-7).

The aim of this review paper is to present the current understanding of the role of neurotrophins, with a special focus on BDNF and NGF, in the pathophysiology of ACS. Additionally, the paper will analyze existing research that has evaluated the prognostic and diagnostic value of neurotrophins as new biomarkers in patients with ACS, and identify future research directions.

NEUROTROPHINS

Neurotrophins comprise a family of proteins consisting of four main members: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5). All neurotrophins exert their effects by binding to two classes of receptors: specific tyrosine kinase receptors (TrkA for NGF, TrkB for BDNF and NT-4/5, TrkC for NT-3) and the non-specific p75NTR (p75 neurotrophin receptor) (4). Activation of Trk receptors typically leads to the activation of survival and growth signals, whereas binding to p75NTR can induce apoptosis, depending on the cellular context and the presence of Trk receptors (4). While traditionally studied within the nervous system, the role of neurotrophins is also being investigated in other systems, including the cardiovascular system. NGF and BDNF have been shown to be present in cardiomyocytes, endothelial cells, and vascular smooth muscle cells (4, 8, 9). In the early embryonic developmental stage, neurotrophins (NTs), especially BDNF, NT-3, and TrkB, as well as NT receptors, are highly important for the formation of a normal heart and vascular system. In the postnatal period, NTs participate in controlling the survival of vascular smooth muscle cells (VSMCs) and endothelial cells (ECs) and are involved in regulating angiogenesis (8, 9). Beyond their function in controlling heart and blood vessel development, NTs regulate the innervation of sympathetic, parasympathetic, and sensory neurons during development. This complex interrelationship is termed the "brain-heart axis." Neurotrophins influence cardiovascular system development via the nervous system, as cardiac-specific overexpression of NGF induces cardiac hypertrophy through hyperinnervation (8-11). Conversely, mice with a deletion, or "knockout," of NGF and TrkA show few morphological abnormalities in cardiovascular development. Therefore, the NGF/TrkA signaling pathway is crucial for the growth, survival, differentiation, shaping, and synaptic strength of sympathetic nerves, rather than for direct regulation of cardiovascular system morphogenesis (4, 10, 11).

In the heart, neurotrophins are involved in regulating cardiomyocyte growth, cell survival, angiogenesis, and the modulation of the autonomic nervous system, indicating their potential relevance in cardiac conditions, including ischemia and myocardial infarction (8, 9). Specifically, experimental studies have shown that BDNF-deficient mice exhibited impaired endothelial cell development, reduced cardiac function, and early postnatal death. Furthermore, mice with a blocked cardiac-specific high-affinity receptor for BDNF (tropomyosin-related kinase receptor B, TrkB) showed impaired cardiac contraction and relaxation, demonstrating that BDNF/TrkB signaling acts constitutively to maintain *in vivo* myocardial performance (9-11).

NEUROTROPHINS IN MYOCARDIAL ISCHEMIA AND REPERFUSION INJURY

Myocardial ischemia and subsequent reperfusion initiate a complex cascade of events involving cellular death, inflammation, and tissue remodeling. Neurotrophin levels undergo significant changes during these processes. Research has indicated that plasma NGF levels can fluctuate in patients experiencing ACS. Some studies propose that NGF might play a protective role by reducing

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cardiomyocyte apoptosis and fostering angiogenesis within ischemic myocardium (9). However, elevated NGF levels have also been associated with increased sympathetic activity, which could contribute to arrhythmias and adverse cardiac remodeling post-infarction (11). Heightened NGF expression has been observed in ischemic myocardium, suggesting its involvement in the injury response (11, 12). BDNF is the most extensively studied neurotrophin in the context of ACS. Plasma BDNF levels frequently exhibit a bimodal response: an acute decrease during the early phase of ACS, followed by a later recovery or elevation (13). It is believed that the reduction in BDNF during the acute phase may be linked to impaired endothelial function and heightened inflammation. BDNF can exert cardioprotective effects through the activation of anti-apoptotic pathways, reduction of oxidative stress, and modulation of the inflammatory response (14). Studies in animal models of myocardial infarction have demonstrated that BDNF administration can improve left ventricular function and reduce infarct size (15-17). In this research, the authors highlighted that BDNF/TrkB signaling is essential for normal cardiac function: The study showed that constitutive (constantly present and active) signaling via BDNF and its receptor TrkB is crucial for maintaining normal cardiac muscle contraction and relaxation in mice. BDNF deficiency leads to cardiac defects: Mice genetically lacking BDNF exhibited impaired endothelial cell development, reduced cardiac function, and early postnatal death. Cardiac-specific TrkB receptor deficiency negatively impacts the myocardium of the studied mice. Experiments in mice where the cardiac TrkB receptor was selectively "knocked out" (cardiac-specific knockout) resulted in impaired cardiac contraction and relaxation. This directly proves the vital role of the BDNF/TrkB pathway in maintaining myocardial performance (18-20). Researchers emphasized that the role of BDNF/TrkB signaling is not merely developmental, as previously thought. Although neurotrophins are known for their role in embryonic development, this research underscores that BDNF/TrkB signaling has a continuous role in maintaining heart health and function into adulthood (15, 16). BDNF, but not NT-3, showed rapid induction after transient myocardial ischemia. Levels of BDNF, but not NT-3, in the unstable angina group exhibited significantly larger differences between the coronary sinus and aorta compared to groups with stable exertional angina or without coronary artery disease. Consistent with serum levels, BDNF expression in atherosclerotic coronary arteries was enhanced. More recent studies have shown that BDNF and pro-BDNF proteins are induced in mouse hearts after left coronary artery occlusion, and that plasma BDNF is increased in patients after AMI (21-23). The significance of this research is that it indicated that BDNF expression is enhanced directly in atherosclerotic coronary arteries. This supports the idea that BDNF is not just a systemic marker but also plays a local role in processes related to atherosclerosis. Furthermore, the induction of BDNF and pro-BDNF after myocardial infarction in animal models shows that both BDNF and its precursor form, pro-BDNF, are induced in the heart after coronary artery occlusion (i.e. in a myocardial infarction model) (22, 23). These research findings indicate that BDNF is not merely a marker but an active participant in the heart's response to ischemia and infarction, with local production in coronary arteries and clear changes in plasma levels during acute coronary events. Montone et al. investigated the role of BDNF in ACS patients using optical coherence tomography (OCT) for direct visualization of coronary artery plaques. The authors highlighted that BDNF is a factor highly expressed in coronary plaques, particularly in macrophages and activated platelets. A possible role in the pathogenesis of acute coronary syndrome (ACS) was therefore suggested. They assessed systemic BDNF levels according to different clinical presentations of ACS. Additionally, they evaluated the association between BDNF levels and the presence of macrophage infiltrates (MØI) defined by OCT and healed plaques along the culprit vessel. The study included consecutive patients presenting with ST-elevation myocardial infarction (STEMI) or non-ST-elevation ACS (NSTE-ACS). Serum BDNF levels were determined by enzyme-linked immunosorbent assay. Plaque characteristics in the culprit vessel (responsible for ACS) were assessed using OCT. BDNF levels were higher in STEMI patients compared to NSTE-ACS (24). OCT assessment was performed in 53 (42.1%) patients. The patients with macrophage infiltrates (MØI) (n = 27) had higher BDNF levels compared to the patients without MØI. Moreover, the patients with healed plaques (n = 13) had lower BDNF levels than the patients without healed plaques. The authors found that BDNF levels were independently associated with MØI and with the absence of healed plaques along the culprit vessel, suggesting a possible role for BDNF in promoting plaque inflammation, destabilization, and occlusive thrombosis (19). Current research indicates that neurotrophin levels in ACS exhibit a complex pattern. Generally, many studies suggest a reduction in circulating plasma levels of BDNF and NGF in ACS patients compared to healthy controls, which can be attributed to increased consumption in damaged tissue or decreased synthesis due to ischemia (25, 26). However, there are significant differences in dynamics and specific roles among ACS subtypes. BDNF has proven to be an important marker in acute ischemic events. On the other hand, the role of NGF, while also showing reduced systemic levels in ACS, is more focused on modulating sympathetic innervation and recovery processes. Its essential role in the growth and survival of sympathetic nerves influences cardiac function, where

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excessive innervation can contribute to cardiac hypertrophy. Following acute myocardial injury, an early but transient increase in NGF levels is observed. It is believed to contribute to angiogenesis, cardiomyocyte survival, and nerve regeneration in the damaged area (27). However, NGF levels among different ACS subtypes (unstable angina, NSTEMI, STEMI) are more heterogeneous across studies, with some research finding no significant differences between subgroups, despite an overall reduction compared to healthy controls (28). Understanding the pathophysiological mechanism of NGF action in the context of myocardial ischemia and reperfusion is crucial for comprehending its role in ACS. Research suggests that, like BDNF, NGF is not merely a passive marker but actively participates in cellular responses to stress and damage. NGF exerts its effects by binding to specific receptors on the cell surface:

1. TrkA receptor (tropomyosin receptor kinase A): This is a high-affinity receptor with tyrosine kinase activity. NGF binding to TrkA initiates a cascade of intracellular signaling pathways.

2. p75NTR (p75 neurotrophin receptor): This is a low-affinity receptor that binds all neurotrophins. Its role is more complex; it can act as a co-receptor with TrkA, but also independently, promoting both survival and apoptosis, depending on the cellular context and the presence of other ligands.

When NGF binds to its receptors, particularly TrkA, key signaling pathways within myocardial cells and associated structures are activated:

- PI3K/Akt pathway: This pathway is known for its pro-survival and anti-apoptotic effects. Activation of PI3K/Akt signaling by NGF helps protect cardiomyocytes from death induced by ischemia and reperfusion injury, which is critical for reducing infarct size and preserving myocardial function (20).
- Ras/MAPK (ERK) pathway: This pathway is involved in cellular proliferation, differentiation, and remodeling. Activation of Ras/MAPK by NGF contributes to processes such as angiogenesis (formation of new blood vessels) and sympathetic sprouting after ischemic injury (20, 23).
- PLC-γ (phospholipase C-gamma) pathway: Also involved in various cellular responses, including the modulation of intracellular calcium.

Specific mechanisms of NGF action in ischemia and reperfusion include:

1. Cellular protection and survival: NGF protects cardiomyocytes from apoptosis (programmed cell death) and necrosis, which is crucial for limiting myocardial damage. This occurs through the activation of survival pathways such as PI3K/Akt (20, 21).

2. Modulation of sympathetic innervation: The myocardium is richly innervated by sympathetic nerves. Ischemia and reperfusion can lead to damage to these nerves ("neural stunning") or abnormal regeneration (hyperinnervation). NGF is crucial for maintaining nerve integrity and can protect against post-ischemic neural dysfunction (24). After infarction, NGF stimulates sympathetic nerve sprouting, which can have a dual effect: contributing to healing, but also potentially increasing the risk of arrhythmias due to inhomogeneous innervation.

3. Angiogenesis: NGF promotes the growth of new blood vessels, which improves blood flow and oxygen supply to the ischemic area, fostering myocardial recovery (23, 24).

4. Regulation of inflammation and fibrosis: NGF can play a complex role in inflammatory processes; it can be pro-inflammatory in some contexts, while acting anti-inflammatory in others (6). It can also influence the degree of fibrosis (scar tissue formation) in the heart after infarction, which is crucial for remodeling (24).

The results to date indicate that the pathophysiological mechanism of NGF action in myocardial ischemia and reperfusion involves the activation of key signaling pathways that contribute to cell survival, modulation of the heart's nervous system, formation of new blood vessels, and modulation of the inflammatory response, all aimed at adaptation and recovery of the heart after injury.

Chinese researchers investigated the impact of neurotrophins on immune system modulation in ACS conditions. This research group previously indicated a link between aortic dissection and neurotrophin status. Their study showed that the upregulation of brain-derived neurotrophic factor precursor (proBDNF) in M2-like monocytes can contribute to a pro-inflammatory response in acute Stanford type A aortic dissection. Instead of mature BDNF (mBDNF), the focus here is on its precursor, proBDNF. The authors concluded that proBDNF has its own signaling pathways and biological effects that can differ from, or even be opposite to, those of mBDNF (e.g., proBDNF often binds to the p75NTR receptor and sortilin, promoting apoptosis and synaptic inhibition, while mBDNF binding to the TrkB receptor promotes survival) (25). It is particularly interesting that proBDNF upregulation occurs in M2-like monocytes/macrophages. Traditionally, M2 macrophages are considered anti-inflammatory and reparative, while M1 are pro-inflammatory. However, this research suggests that even within the "M2-like" population, proBDNF can reverse or modulate their function towards a pro-inflammatory response (25). Aortic dissection is a condition where the layers of the aortic wall tear, and inflammation plays a crucial role in weakening the blood vessel wall. Stanford type A dissections are the most dangerous, as they involve the ascending aorta near the heart. This suggests that proBDNF may mediate or

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enhance inflammatory processes leading to the destabilization and rupture of the aortic wall (26).

This finding further emphasizes the complexity of macrophage polarization and their functions. It is not always simple to classify them as exclusively "good" (M2) or "bad" (M1), but their profiles and activity can be modulated by the local microenvironment and specific molecules like proBDNF. This research highlighted proBDNF as a potential therapeutic target. Modulating the levels of proBDNF or its receptors could be a strategy to alleviate inflammation and prevent disease progression. This specific finding opens new questions about the role of proBDNF not only in aortic dissection but also in other inflammatory cardiovascular diseases, including acute coronary syndrome, where macrophage inflammation within the plaque plays a central role. The immune system is activated upon exposure to myocardial damage. Monocytes/macrophages have been shown to be involved in the pathogenesis of AMI, and these patients tend to have monocyte imbalance (27-29). After AMI, macrophages are recruited to infarct zones, producing pro-inflammatory and anti-inflammatory mediators, including cytokines, chemokines, matrix metalloproteinases (MMPs), and phagocytosing dead cells, as well as promoting angiogenesis and scar formation (26, 28).

These diverse activities are attributed to different macrophage subtypes and polarization states. Macrophages exhibit a pro-inflammatory phenotype in the early phase and polarize towards an anti-inflammatory phenotype in the later phase after AMI. Early inflammatory responses after AMI are crucial for heart repair and scar formation in later stages. Pro-inflammatory macrophages (M1) are the first to be recruited to the infarct zone. Their role is to initiate the inflammatory response, remove dead cells and cellular debris. They are crucial for "clearing the field" and initiating the repair process. The second wave consists of anti-inflammatory macrophages (M2). After the initial pro-inflammatory wave, a second wave of macrophages polarizes towards an anti-inflammatory phenotype. These M2 macrophages are responsible for resolving inflammation, promoting scar formation, angiogenesis (growth of new blood vessels), and tissue remodeling. The process of macrophage recruitment and polarization (from M1 to M2) is similar to what has been previously described for monocytes, given that macrophages are differentiated forms of monocytes. This temporally coordinated macrophage polarization is crucial for successful myocardial recovery.

An early pro-inflammatory response is necessary for removing damaged tissue, while a later anti-inflammatory and reparative response is vital for forming a stable scar and functional remodeling (29-31). Accordingly, therapeutic targeting of these monocyte/macrophage disorders may mitigate AMI-induced injury. This research revealed an unexpected, protective role of proBDNF in monocytes/macrophages after AMI. Instead of contributing to harmful inflammation, as might have been expected, blocking proBDNF (with McAb-proB treatment) was shown to worsen outcomes, including impaired cardiac function, increased infarct size, increased mortality rate, and exacerbated inflammation. The key mechanism for these detrimental effects, as the study showed, is the mediation of MMP-9 (matrix metalloproteinase-9). This means that proBDNF, by acting on monocytes/macrophages, indirectly helps regulate MMP-9 activity, thereby preventing excessive inflammation and detrimental remodeling. ProBDNF in monocytes/macrophages plays a protective role in cardiac remodeling after AMI. This finding is extremely important as it challenges conventional thinking about the role of inflammation and its components in the post-infarction period. The authors conclude that their results have direct implications for therapeutic strategies. It is suggested that targeting proBDNF in AMI therapy might be counterproductive and that further research is needed to precisely elucidate these complex mechanisms (26, 27, 29, 30).

NEUROTROPHINS AS PROGNOSTIC BIOMARKERS

Changes in neurotrophin levels, particularly BDNF, hold promise as novel diagnostic and prognostic biomarkers in ACS. BDNF's ability to reflect the degree of plaque inflammation and the risk of destabilization makes it potentially useful for more precise risk stratification and personalized treatment. Much attention has been devoted to the prognostic value of neurotrophins in ACS, given their role in pathophysiological processes. BDNF has emerged as a promising prognostic marker. Low plasma BDNF concentrations are often associated with poorer outcomes, including an increased risk of major adverse cardiovascular events (MACE) and mortality. For instance, a study by Xiong et al. (2018) found that low BDNF levels upon admission predicted an increased risk of heart failure and death in STEMI patients (31, 32). It is hypothesized that lower BDNF levels reflect greater myocardial damage, reduced reparative capacity, or persistent inflammatory activity. The authors investigated the association between neurotrophin levels and cardiovascular rehabilitation. Exercise-based cardiac rehabilitation (CR) increases aerobic capacity and exercise tolerance, and improves prognosis in patients with cardiovascular diseases. Cochrane reviews have reported beneficial effects of CR on quality of life, morbidity, and mortality. However, several other studies have reported that a significant number of patients, approximately 21–23%, do not respond favorably to the applied

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Table 1. Comparison of neurotrophins and standard clinical biomarkers in ACS.

Biomarker	Clinical role	Detection onset	Peak	Return to baseline	Notes
Troponin I / T	Gold standard for MI	3–4 h	12–24 h	7–14 days	Highest accuracy
BNP / NT-proBNP	HF & wall stress	Hours	24–48 h	Days–weeks	Prognostic
CK-MB	Reinfarction marker	3–6 h	12–24 h	2–3 days	Less specific
Myoglobin	Very early marker	1–2 h	6–9 h	24 h	Low specificity
LDH	Late injury marker	12 h	48–72 h	8–14 days	Old marker
hs-CRP	Inflammation	6 h	48 h	7–10 days	Non-specific
BDNF	Endothelial dysfunction	Hours	Variable	Variable	Prognostic value
NGF	Remodeling/ANS	Hours	Variable	Variable	Emerging data

rehabilitation (so-called "non-responders"). Since exercise produces BDNF in skeletal muscles, BDNF is considered to be associated with myokine function. In heart failure, reduced exercise capacity is due to abnormalities in peripheral skeletal muscles. Previous studies have also shown that low BDNF levels are associated with impaired exercise capacity and poor prognosis in patients with chronic heart failure. Therefore, the authors aimed to establish the influence of baseline serum BDNF levels on the response to CR before and after 3 weeks of such training in CVD patients. Low baseline BDNF levels were associated with malnutrition in CVD patients. A positive association was also shown between baseline BDNF levels and CR-induced increase in maximal VO2, implying that patients with lower basal neurotrophin values have a weaker response to CR during the subacute phase. BDNF may be a useful biomarker for creating a tailored, optimized exercise program in CVD patients. As a limitation, the authors cite the small number of subjects, and therefore at this stage, it can only serve for hypothesis generation (33, 34).

The prognostic value of NGF is more complex. While some papers suggest that elevated NGF levels may be associated with unfavorable outcomes, such as arrhythmias and recurrent ischemic events, due to the role of NGF in sympathetic hyperactivity, other papers indicate a potential protective role in long-term remodeling. Consistent findings are needed for a clearer assessment of its prognostic value (35, 36).

METHODOLOGICAL CHALLENGES AND FUTURE PERSPECTIVES

Although current research is promising, there are significant methodological challenges hindering the translation of neurotrophins into clinical practice. Diverse patient populations included in research, sample collection protocols, neurotrophin measurement methods, and monitored outcomes contribute to result variability. Neurotrophin levels can fluctuate throughout the day and under the influence of various factors, complicating measurement standardization. Numerous chronic diseases (diabetes, chronic kidney disease) and medications can affect neurotrophin levels, which complicates the interpretation of results in the complex clinical picture of ACS. Large multicenter prospective studies are necessary to confirm the diagnostic and prognostic value of neurotrophins in larger and more diverse patient populations.

CONCLUSION

Neurotrophins, particularly BDNF and NGF, represent a promising group of molecules with a potential role in the diagnosis and prognosis of acute coronary syndrome. Changes in their levels during ACS reflect complex pathophysiological processes, including cellular injury, inflammation, and remodeling. Although initial studies have shown that BDNF and NGF levels may be associated with disease severity and outcomes, further multicenter, prospective research is necessary to confirm their clinical utility and define clear reference values. Understanding their precise role could lead to the development of new diagnostic tools and more personalized therapeutic strategies for patients with ACS.

ABBREVIATIONS

ACS - Acute Coronary Syndrome
AIM - Acute Myocardial Infarction
BDNF - Brain-Derived Neurotrophic Factor
CR - Cardiac Rehabilitation
CVD - Cardiovascular Disease
EC - Endothelial Cell
ELISA - Enzyme-Linked Immunosorbent Assay
ERK - Extracellular Signal-Regulated Kinase
MACE - Major Adverse Cardiovascular Events
MAPK - Mitogen-Activated Protein Kinase (part of Ras/MAPK (ERK) pathway)
mBDNF - Mature Brain-Derived Neurotrophic Factor
MMP-9 - Matrix Metalloproteinase-9
MØI - Macrophage Infiltrates
NGF - Nerve Growth Factor

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NSTE-ACS - Non-ST-Elevation Acute Coronary Syndrome

NT - Neurotrophin

NT-3 - Neurotrophin-3

NT-4/5 - Neurotrophin-4/5

OCT - Optical Coherence Tomography

p75NTR - p75 Neurotrophin Receptor

PI3K/Akt - Phosphatidylinositol 3-Kinase/Akt pathway

PLC-γ - Phospholipase C-gamma

proBDNF - Precursor Brain-Derived Neurotrophic Factor

Ras - Rat Sarcoma

STEMI - ST-Elevation Myocardial Infarction

TrkA - Tropomyosin Receptor Kinase A

TrkB - Tropomyosin Receptor Kinase B

TrkC - Tropomyosin Receptor Kinase C

VSMC - Vascular Smooth Muscle Cell (used within VSMCs)

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