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Research Status of Growth Differentation Factor-15 in Acute Coronary Syndrome

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Abstract: *Acute coronary syndrome (ACS) is a group of clinical syndromes caused by acute myocardial ischemia, including ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA). Currently, the clinical diagnosis of ACS relies on three key factors: clinical data (such as medical history, age, symptoms, etc.), electrocardiogram (ECG), and cardiac biomarkers (cTn, MyO, CK-MB, NT-proBNP, etc.). However, diagnosing UA patients and some NSTEMI patients can be challenging due to the absence of characteristic electrocardiogram dynamic evolution seen in STEMI patients. This is particularly true in cases with mild symptoms or no obvious chest pain and negative detection of myocardial injury markers. Recent studies have highlighted the potential clinical value and availability of growth differentiation factor 15 (GDF-15) as a new cardiac biomarker closely associated with the occurrence and prognosis of ACS [1]. However, further investigation is needed to fully understand its role in ACS. This article aims to review the clinical application value of GDF-15 in acute coronary syndrome.*

Keywords: *Acute Coronary Syndrome (ACS), Growth Differentiation Factor-15 (GDF-15), Early Diagnosis, Prognostic Evaluation, Clinical Treatment*

1. Background

Acute coronary syndrome (ACS) is a malignant cardiovascular disease characterized by a sudden onset and rapid development, posing a potential life-threatening risk at any time. The main pathological mechanism of ACS involves the rupture or erosion of coronary atherosclerotic plaque, leading to platelet activation and coagulation system initiation, resulting in acute thrombosis in the coronary artery. Platelet activation plays a crucial role in this process. ACS encompasses three main types: ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA). The incidence of ACS is on the rise, as reported in the 'China Cardiovascular Health and Disease Report 2022'. This increase can be attributed to factors such as an aging population and unhealthy lifestyle habits. Consequently, it is imperative for medical professionals to identify more specific and sensitive laboratory diagnostic markers to enable early diagnosis and treatment. Such advancements can significantly improve patient prognosis and enhance the success rate of clinical interventions. The definition and reference standard for acute coronary syndrome (ACS) are still unclear. ACS is a clinical syndrome diagnosed based on clinical observations, which poses significant challenges for clinicians, particularly in diagnosing NSTE-ACS patients. According to foreign studies, GDF-15 is a novel cardiac biomarker that shows potential clinical value and availability. It is considered a risk factor for cardiovascular disease (CVD) and can indicate the severity of coronary artery disease; changes in cardiac function load, cardiac stress, and predict cardiovascular adverse events (MACE) in ACS patients. Therefore, this paper discusses the clinical application value of GDF-15 in ACS, taking into account the latest research progress. The aim is to provide insights for early diagnosis, prognosis evaluation, and clinical treatment of ACS.

2. GDF-15

GDF-15, also known as MIC-1, NAG-1, PLAB, pTGFB, and PDF, is a member of the TGF-β superfamily [2]. It exists as a biologically active homodimer formed by disulfide bonds, with a relative

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molecular mass of 25kDa. GDF-15 is soluble and can be detected in the blood. Bootcov MR et al. [3] have demonstrated that it may function as an autocrine regulator involved in monocyte/macrophage differentiation and induction in inflammation and immune response. It also has the ability to limit the activation of macrophages in the later stages. In animal and cell experiments, Tibor Kempf et al. [4] provided the first evidence that GDF-15 plays a significant functional role in cardiovascular diseases. Through the PI3K-Akt signaling pathway, GDF-15 can protect myocardial cells by inhibiting necrosis during acute ischemia and apoptosis during subsequent reperfusion. Thus, GDF-15 acts as a myocardial cell protective factor. Clinical experimental research and related literature on the role of GDF-15 in cardiovascular disease have been reported.GDF-15 plays a crucial role in cell growth, tissue development, and the occurrence and progression of inflammation. However, its exact biological function is still not fully understood. The effects of GDF-15 are closely linked to the body's environment. Normally, GDF-15 is expressed at low levels in tissues like the heart, kidney, and lung, but during pregnancy, it is highly expressed in placental villus cells. However, in pathological conditions such as hypoxia, oxidative stress, and inflammation, GDF-15 continues to be highly expressed and secreted, leading to a significant increase in its concentration in plasma [5, 6]. Additionally, GDF-15 has been identified as a downstream marker of P53 during cellular stress [7]. Despite these findings, the receptor for GDF-15, its downstream signaling pathways, and its biological effects are still not well understood. In individuals at low risk for acute coronary syndrome (ACS), an increase in plasma GDF-15 concentration has been independently associated with coronary atherosclerosis [8]. This suggests that GDF-15 could serve as a valuable clinical reference for cardiovascular disease diagnosis, disease progression, prognosis, and treatment. However, further clinical experimental studies are needed to confirm its potential value as a new cardiac biomarker.

3. The Early Diagnostic Value of GDF-15 in ACS Patients

Efficient and rapid diagnosis of ACS requires reliable and accurate biomarkers to confirm myocardial ischemic necrosis. Currently, cardiac troponin (cTn) remains the gold standard biomarker for myocardial injury[9], typically used in conjunction with creatine kinase isoenzyme (CK-MB) and myoglobin (MyO). A multicenter clinical trial conducted in the U.S. Emergency Department [10] revealed that when hs-cTnT is less than 6 ng/L, approximately 33% (610/1849) of patients with non-ischemic ECG were classified as low risk. This finding could be utilized to identify a significant number of patients with acute myocardial injury and a very low risk of infarction. However, based on relevant reports and clinical practice, it has been observed that some patients with unstable angina (UA) and some patients with non-ST elevation myocardial infarction (NSTEMI) who exhibit normal ECG results, negative detection of myocardial injury markers (such as cTn), and mild or absent clinical symptoms are still prone to being overlooked. To improve the accuracy of diagnosing Acute Coronary Syndrome (ACS), it is crucial to identify laboratory diagnostic indicators with high sensitivity and specificity. This would facilitate early diagnosis and treatment, which is essential for reducing patient mortality, complications, and improving prognosis. Traditionally, it was believed that myocardial cells in the adult heart are permanent and non-dividing, leading to permanent loss upon ischemic necrosis. However, recent in vitro studies have discovered the presence of atrial appendage stem cells (CASC) [11] in human heart tissue, which retain some ability to divide. Additionally, mesenchymal stem cells (MSC) are adult stem cells that possess self-renewal and multi-differentiation capabilities. Animal models of myocardial infarction have shown that MSCs promote cardiac repair through the secretion of soluble factors, mediating paracrine effects. During cardiac injury, GDF-15 is induced by various cell types, such as cardiomyocytes, adipocytes, macrophages, endothelial cells, and smooth muscle cells [12]. Elevated levels of GDF-15 can lead to vascular endothelial dysfunction and contribute to cardiac fibrosis [13, 14], thereby causing microvascular disease, ventricular diastolic and systolic dysfunction, and further deterioration of cardiac function. However, the exact mechanism of action requires further research for clarification. Studies have confirmed that GDF-15 has been detected in infarcted myocardium and atherosclerotic plaques in both mice and humans [4, 15, 16]. Additionally, relevant literature has reported that GDF-15 serves as an independent biomarker for all-cause mortality and MACE in patients with coronary artery disease [17]. The concentration of GDF-15 can reflect the extent of coronary atherosclerosis, which may aid in the early diagnosis of patients with non-ST-segment elevation acute coronary syndrome for prompt revascularization and guide drug treatment. In a recent prospective clinical trial, 6332 patients with cardiovascular disease were included, and their GDF-15 levels were measured upon admission. Among these patients, 5215 (82.5%) were diagnosed with ACS. The findings revealed that these patients had higher levels of GDF-15 upon admission [18]. However, the underlying cause for the increase in GDF-15 and the optimal cut-off value for the clinical diagnosis of ACS remain unclear. Numerous studies have consistently shown that

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GDF-15 serves as a biomarker for various clinical diseases [19]. While there has been a notable increase in serum GDF-15 concentration among patients with myocardial ischemia and reperfusion injury [4, 12], its tissue specificity is somewhat limited. Therefore, it is important to consider excluding the influence of malignant tumors, severe liver and kidney failure, and other diseases when investigating GDF-15 as a biomarker for cardiovascular disease. Nevertheless, the differential expression of GDF-15 in patients with acute coronary syndrome (ACS) and healthy individuals suggests its potential value in the early diagnosis of ACS patients. Further clinical experimental studies are warranted to validate this potential.

4. The Prognostic Value of GDF-15 in ACS Patients

B-type natriuretic peptide (BNP) and its prohormone N-terminal pro-brain natriuretic peptide (NT-proBNP) are powerful predictors of mortality and heart failure (HF) in patients with acute coronary syndrome (ACS). They primarily indicate left ventricular dysfunction and are important prognostic factors for adverse outcomes. However, there is ongoing research to identify other laboratory cardiac biomarkers that can predict cardiovascular complications and prognosis in ACS patients. Recent studies have highlighted GDF-15 as a highly valuable biomarker for predicting ACS prognosis [20, 21], surpassing BNP and NT-proBNP in terms of predicting all-cause mortality [22, 23]. GDF-15 not only reflects changes in cardiac function load and stress levels, but also indicates the stability of atherosclerotic inflammatory plaques [24]. Combining GDF-15 with NT-proBNP has been shown to be more valuable than using any single biomarker in predicting all-cause mortality [25]. A recent prospective study [18] has demonstrated that the concentration of GDF-15 at admission can serve as a predictor for various outcomes in ACS patients. These outcomes include the incidence of heart failure, non-coronary artery bypass grafting-related major bleeding, and severe cardiovascular death within 1 year. Furthermore, GDF-15 has been incorporated into the ABC-ACS ischemia score by Gorav Batra et al. to predict the occurrence of recurrent myocardial infarction and cardiovascular death in ACS patients undergoing PCI [21]. For patients with stable clinical symptoms after ACS, findings from a BIOMArCS cohort study [26] have indicated that GDF-15 is an independent prognostic factor for cardiovascular death and recurrent AMI. Continuous measurement of GDF-15 can reflect the ongoing inflammatory response during cardiac remodeling. A follow-up study [27] involving 358 ACS patients over a period of more than 6 years revealed a significant increase in all-cause mortality, MACE, and the risk of hospitalization for heart failure when the GDF-15 concentration exceeded 1800 ng/L. Moreover, higher levels of GDF-15 were consistently associated with an increased prevalence of cardiovascular risk factors, a history of cardiovascular disease, and adverse outcomes during admission. Relevant experimental studies have provided the clinical definition of GDF-15 in patients with acute coronary syndrome (ACS) [23]. The normal upper limit of serum GDF-15 concentration in healthy elderly individuals is 1200ng/L, defined in risk stratification as low risk: <1200ng/L, medium risk: 1200-1800ng/L, and high risk: >1800ng/L. GDF-15 has been found to be associated with recurrent events following ACS [28]. Further studies conducted by Nermina Buljubasic et al. [29] demonstrated that the concentration of GDF-15 in patients with recurrent myocardial infarction after ACS was 26% higher than that in patients with non-recurrent ACS. Additionally, the concentration of GDF-15 in patients with recurrent events remained significantly higher than that in patients with non-recurrent ACS within 1 year. This indicates that GDF-15 not only reflects the degree of myocardial injury or infarct size, but also indicates the severity of the burden of atherosclerotic disease at any given time point. In summary, most current studies have confirmed that GDF-15 is a prognostic marker for cardiovascular disease, providing unique prognostic information and serving as a valuable reference for accurate prognostic evaluation in clinical practice.

5. The Guiding Clinical Value of GDF-15 in ACS Patients

The timing of invasive operation for the treatment of ACS patients is currently a topic of controversy. In clinical practice, early intervention methods are often considered based on factors such as the patient's onset time, symptom persistence, electrocardiogram evolution, and cardiac biomarkers. GDF-15, a non-necrotic biomarker, has shown potential in providing guidance for the early intervention of ACS patients. A recent PLATO trial [30] reported that early percutaneous coronary intervention (PCI) can reduce the concentration of GDF-15 in patients with STEMI-ACS, which may be attributed to the timely restoration of myocardial blood flow, reduction of myocardial injury after reperfusion, and prevention of myocardial dysfunction. However, the study also observed that the concentration of GDF-15 in patients with NSTE-ACS did not decrease as expected. Similarly, other

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studies have indicated that patients with elevated GDF-15 concentration may benefit the most from early invasive procedures [31]. Nevertheless, further research is needed to determine the optimal timing and cut-off value for early invasive operation based on GDF-15 in ACS patients.

Dual antiplatelet therapy (DAPT) is the standard treatment for patients with acute coronary syndrome (ACS) [32], as it helps reduce the risk of myocardial ischemia. However, the amount of treatment during the acute phase of coronary intervention (PCI) and the secondary prevention after PCI can increase the risk of severe bleeding complications in different areas [33, 34]. In a large PLATO experimental study conducted by Daniel Lindholm et al. [35], it was confirmed that the level of GDF-15 at 1 month after acute myocardial infarction is associated with the risk of bleeding during antiplatelet therapy. The study included 4049 patients who were randomly divided into groups. The results indicated that when GDF-15 levels were > 1800 ng/L after 1 month, there was a significant increase in the risk of bleeding in patients receiving antiplatelet therapy. Furthermore, patients with elevated GDF-15 levels also had a higher probability of experiencing serious cardiovascular complications leading to death. GDF-15 has been found to be independently associated with major bleeding in patients receiving antiplatelet therapy, and it has been included in the new bleeding risk score. This finding may serve as a reference for determining the appropriate type, intensity, and duration of antiplatelet therapy [33]. However, the exact mechanism behind the association between GDF-15 and major bleeding events after DAPT remains unclear. Some studies suggest that GDF-15 may inhibit platelet activation, similar to the mechanism of glycoprotein IIb / IIIa inhibition, leading to a reduced ability to form blood clots [33]. Another PLATO trial [36] found that in patients with NSTE-ACS, higher levels of GDF-15 (>1200 ng/L) were associated with an increased risk of cardiovascular death and recurrent myocardial infarction. Furthermore, patients who received intensive antiplatelet therapy showed greater benefits.

HF, a common serious complication in patients with ACS, has been associated with GDF-15, a promising new predictive biomarker for HF. Studies have indicated that measuring GDF-15 levels can help optimize the safety, tolerance, and effectiveness of heart failure drug treatment [37]. In clinical practice, patients with ACS complicated by heart failure often receive β-blockers, ACEI, or ARB drugs to counter ventricular remodeling after discharge. Experimental studies have observed the involvement of GDF-15 in the process of left ventricular remodeling (LVR) [38], with higher serum GDF-15 concentrations found in patients with LVR. This suggests that further clinical experimental studies are needed to determine whether adjusting the type, dose, and intensity of anti-ventricular remodeling drugs based on GDF-15 concentration would be beneficial.

6. GDF-15 and Traditional Cardiac Markers

Cardiac markers play a crucial role in guiding cardiovascular disease diagnosis. Traditional cardiac markers such as aspartate aminotransferase (AST), CK-MB, MyO, cTn, BNP, and NT-proBNP are widely used in the diagnosis of ACS. GDF-15, a non-necrotic cardiac marker, is independent of traditional cardiac biomarkers and its serum concentration reflects the degree of coronary atherosclerosis as well as changes in cardiac load and stress. The potential value of GDF-15 in cardiovascular disease is currently a topic of research interest. Different cardiac biomarkers provide distinct information about cardiovascular disease, and while they are interrelated, they also have their unique characteristics.

Rapid bedside testing (POCT) combined with a variety of cardiac biomarkers can aid clinicians in promptly and accurately diagnosing and evaluating patients with high-risk chest pain in the emergency department. This approach can improve the accuracy of ACS diagnosis and facilitate early revascularization and reperfusion for ACS patients. Additionally, it can help identify low-risk patients who can safely be discharged from the hospital without excessive medical treatment. Studies have shown that elevated concentrations of GDF-15 and cTn serve as strong indicators for early invasive procedures in patients with NSTE-ACS. In a study [31] involving 2457 patients with suspected NSTE-ACS and a follow-up period of up to 15 years, it was found that early invasive procedures in NSTE-ACS patients with elevated GDF-15 and cTn concentrations resulted in an average delay of 18 months in the recurrence of myocardial infarction or cardiovascular death, and a delay of 37 months in the next hospitalization due to myocardial ischemia symptoms. This significantly improves the prognosis of patients. Furthermore, relevant studies have confirmed that the combination of GDF-15 and brain natriuretic peptide (BNP, NT-proBNP) has a higher clinical value in evaluating the prognosis of heart failure in patients with ACS [39, 40].

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7. The Risk Stratification Value of GDF-15 in ACS Patients

The use of GDF-15 in risk stratification of ACS patients has gained importance due to its unique prognostic evaluation ability. In clinical practice, the TIMI score and GRACE score are commonly used tools to identify high-risk ACS patients who may benefit from early revascularization. These scores are mainly based on clinical data and cardiac marker results at admission. Eggers et al. [41] conducted a study with 453 patients with chest pain and found that GDF-15 significantly improved the predictive value of the GRACE score for mortality in these patients. Other studies [42] have also shown that adding GDF-15 to the GRACE score can enhance the accuracy of risk assessment for NSTE-ACS patients and improve the prediction of long-term all-cause mortality or myocardial infarction risk. Additionally, another study [43] reported that in STEMI patients with a TIMI score > 3, a GDF-15 level > 1800 ng/L increased the risk of death by 4.9 times within 1 year. These findings suggest that GDF-15 can refine the original risk stratification and further research is needed to determine its role and critical points in ACS patients.

8. Summary and Prospect

The determination of GDF-15 concentration is crucial in identifying and evaluating high-risk ACS patients in clinical practice, providing decision support. Further clinical experimental studies should be conducted to confirm the early diagnostic and prognostic value, as well as the clinical utility of GDF-15 in ACS patients.

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