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Insulin-like growth factor-binding protein 7 (IGFBP7): Novel, independent marker of cardiometabolic diseases?

Insulin-like growth factor-binding protein 7 (IGFBP7) – nowoczesny, niezależny marker chorób kardiometabolicznych?

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Summary

Insulin-like growth factor-binding protein 7 (IGFBP7) is a 30kDa modular secreted protein involved in many physiologic processes, including cell proliferation, adhesion, senescence and angiogenesis. It is expressed in many organs and specific cells. It can interact with insulin-like growth factor 1(IGF-1), as well as with insulin. By binding to IGF-1, it limits IGF-1 access to IGF- receptor (IGF-R) and consequently neutralizes IGF-1 activity. Moreover, due to its high affinity to insulin, it may interfere with biological response of insulin and, therefore, it may be involved in the development of diabetes and cardiovascular diseases. According to research, it could be a good biomarker of heart failure. Its elevated serum concentrations were found in patients with heart failure, both with reduced ejection fraction and preserved ejection fraction. Moreover, IGFBP7 could be useful in predicting the presence of atherosclerotic lesions in coronary vessels, although its concentration does not reflect a degree of coronary artery disease (CAD) advancement and it cannot be used as a marker of acute ischemia. Its concentration is also associated with insulin resistance and the risk of metabolic syndrome. What is more, together with tissue inhibitor of metalloproteinases-2, it is a novel marker of tubular damage and it can be used for an early detection of acute kidney injury (AKI) endangered patients, which could allow for subsequent adjustments in medical therapy and the prevention of AKI. IGFBP7 is also regarded as a potential tumor suppressor in various cancers. Its low expression is potentially correlated with increased cancer cell proliferation.

Keywords: **insulin-like growth factor-binding protein 7 (IGFBP7) • heart failure • coronary artery disease • atherosclerosis**

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Abbreviations: **ADHF** – acute decompensated heart failure; **AHF** – acute heart failure; **AKI** – acute kidney injury; **AML** – acute myeloid leukemia; **BMI** – Body Mass Index; **CAD** – coronary artery disease; **CM** – conditioned media; **CPB** – cardio-pulmonary bypass; **DN** – diabetic nephropathy; **E/e' ratio** – ratio between early mitral inflow velocity and mitral annular early diastolic velocity; **eGFR** – Estimated Glomerular Filtration Rate; **GH** – growth hormone; **HCC** – hepatocellular carcinoma; **HDL** – high density lipoprotein; **HF** – heart failure; **HFpEF** – HF with preserved ejection fraction; **HFrEF** – HF with reduced ejection fraction; **IGF** – insulin-like growth factor; **IGFBP7** – insulin-like growth factor-binding protein 7; **IGFBP-rP** – IGFBP related proteins; **IGFBPs** – insulin-like growth factor-binding proteins; **IGF-R** – IGF- receptor; **Ins-R** – insulin receptor; **IR** – insulin resistance; **LAVI** – left atrium volume index; **LDL** – low density lipoprotein; **LVDD** – left ventricular diastolic dysfunction; **LVEF** – left ventricular ejection fraction; **MetS** – metabolic syndrome; **MI** – myocardial infarction; **MSC**– mesenchymal stem cells; **mTOR** – the mammalian target of rapamycin; **NAG** – N-acetyl-beta-D-glucosaminidase; **NGAL** – neutrophil gelatinase-associated lipocalin; **NSCLC** – non-small cell lung carcinoma; **NSTEMI** – non-ST-elevation MI; **NT-proBNP** – N-terminal pro-B-type natriuretic peptide; **PAI-1** – plasminogen activator inhibitor-1; **PIIINP** – procollagen type 3 amino-terminal peptide; **PSF** – prostacyclin-stimulating factor; **RVSP** – right ventricular systolic pressure; **sST2** – soluble suppression of tumorigenicity-2; **STEMI** – ST-elevation MI; **T2D** – type 2 diabetes; **TAF** – tumor adhesion factor; **TGF-**β – transforming growth factor β; **TIMP-2** – tissue inhibitor of metalloproteinases-2; **VEGF** – vascular endothelial growth factor; **WC** – waist circumference; **WHR** – waist- to-hip ratio.

INTRODUCTION

The insulin-like growth factor system plays an essential role in the growth, differentiation and proliferation of human cells. It consists of insulin, two growth factors (IGF-1 and IGF-2), three cell surface receptors (InsR, IGF--IR, IGF-IIR), a group of insulin-like growth factor binding proteins (IGFBP1 to IGFBP7) and IGFBP protease [4, 17]. Each part of the axis has a specific role in this system and a few of them are promising cardiometabolic markers.

The primary mediator - IGF-1, together with IGF-2, by binding to the specific receptors, stimulates cells to absorb glucose. Its homology with insulin reaches 50%. IGF-1 improves cardiac metabolism, cell growth and cardiac function [17]. Its activity is regulated by insulin-like growth factor binding proteins (IGFBPs). IGFBPs are a group of homogenous proteins that can bind with insulin and IGFs [21]. Their binding with IGF-1 causes a limited IGF-1 access to IGF-R, and therefore IGF-1 lower activity. What is more, IGFs bind to IGFBPs with higher affinity than to IGF-R. IGFBPs also prevent IGFs from degradation. They can play a role of a reservoir and can enhance the role of IGF in the microenvironment by slowly releasing IGF ligands. IGFBPs are classified into two groups based on their affinity to IGFs: IGF high-affinity binding proteins (IGFBP1-6) and IGF-low affinity IGFBP-related proteins (IGFBP-rP1-10) [17]. Moreover, IGFBP1-6 has less affinity to insulin, whereas IGFBP-rP1 has a relatively high affinity to insulin [21]. In recent studies, IGFBP-related proteins are also called IGFBPs [17], and IGFBP-rP1 is known as IGFBP7.

IGFBP7 is a 30kDa modular secreted protein involved in many physiologic processes, including cell proliferation, adhesion, senescence and angiogenesis [4, 19, 21]. It is also called mac25, tumor adhesion factor (TAF), prostacyclin-stimulating factor (PSF), and angiomodulin [4, 19]. It is expressed in many organs and specific cells and also in peripheral nerves; smooth muscles (including those from blood vessels walls, gastrointestinal tract, urinary bladder and prostate); cilia from the respiratory system, epididymis and fallopian tube; breast tissue; certain cell types in kidney, adrenal gland and skeletal muscle; Weibel-Palade bodies [6, 19, 30]. It had not been found in fat cells, plasma cells and lymphocytes [6].

As mentioned earlier, IGFBP7 can interact with IGF-1, as well as with insulin [3, 4, 19]. It binds to IGF-1 with 100 times lower affinity than other IGFBPs, and by limiting its access to IGF-R, it neutralizes IGF-1 activity. Moreover, due to its high affinity to insulin, it may interfere with the biological response of insulin. Therefore, it may be involved in the development of diabetes and cardiovascular diseases [21]. IGFBP7 also has many IGF-independent actions. For instance, it is involved in transforming growth factor-β (TGF-β) signal pathway [21] and, due to its presence in Weibel-Palade bodies (unique storage organelles in vascular endothelial cells), it is suggested that it regulates angiogenesis [30]. What is more, IGFBP7 is regarded as a potential tumor suppressor in various cancers [1, 4, 20]. Its overexpression results in G1 arrest and it inhibits vascular endothelial growth factor (VEGF) – induced angiogenesis [4, 29]. Also, by binding to IGF-IR, it suppresses downstream signaling and it inhibits protein synthesis, cell growth and survival [7].

HEART FAILURE

IGFBP7 is proven to be a good biomarker of heart failure in mice and humans [5]. Its elevated serum concentra-

tions were found in patients with heart failure (HF), both with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF) [9].

Heart Failure with Preserved Ejection Fraction

M. Barroso et al. found that patients with HFpEF have higher IGFBP7 and IGFBP7/IGF-1 ratio values and lower IGF-1 concentration, comparing to patients with asymptomatic left ventricular diastolic dysfunction (LVDD) and control healthy individuals. There was a significant graded increase of IGFBP7 levels and IGFBP7/IGF-1 ratio from the control group to LVDD to HFpEF, while IGF-1 concentrations showed a graded decline. Moreover, IGFBP7/IGF-1 ratio was found to be positively correlated with markers of diastolic dysfunction (left atrium volume index (LAVI), ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e' ratio)), N-terminal pro-B-type natriuretic peptide (NT-proBNP) and soluble suppression of tumorigenicity-2 (sST2) [3]. According to research, IGFBP7 could be an even better marker for diastolic dysfunction than NT-proBNP [10]. The mechanism behind these findings remains unclear. It could be due to the fact that NT-proBNP concentrations are influenced by numerous factors, including diastolic abnormalities, whether IGFBP7 is rather selectively influenced by diastolic dysfunction [10]. What is more, Dinh et al. in their study showed that IGFBP7 could be a better early predictor of heart failure than NT-proBNP [5].

In research conducted by P. Gandhi et al., it was proven that the baseline concentration of IGFBP7 in patients with HFpEF was associated with the primary outcome, all-cause mortality and HF events. Its higher values correlated with greater risk. There were no significant differences in IGFBP7 levels over 6 months of observation. It is unclear why IGFBP7 may have a prognostic value in patients with HFpEF. It is possible that this is due to myocardial fibrosis, which is supposed to be an important factor in developing HFpEF [9]. The correlation between IGFBP7 and collagen deposition and between IGFBP7 and diastolic abnormalities has been found [9, 10]. IGFBP7 stimulates fibroblasts, possibly through a transforming growth factor β-mediated pathway [9, 16]. Transforming growth factor β (TGFβ) was proven to be involved in the pathogenesis of HFpEF; it causes fibroblasts stimulation and interstitial collagen deposition [25]. Moreover, there is also a strong correlation between IGFBP7 and other known markers of fibrosis – procollagen type 3 amino-terminal peptide (PIIINP), galectin-3 and sST2 [9].

In conclusion, an increase in the IGFBP-7 or IGFBP7/IGF-1 ratio may cause worsening diastolic function and adverse cardiac remodeling [3].

Heart Failure with reduced Ejection Fraction

In a study conducted by P. Gandhi et al., IGFBP7 serum concentrations in patients with HFrEF were correlated with parameters describing diastolic function – LAVI, transmitral E/A ratio, E/E' ratio, and right ventricular systolic pressure (RVSP). Patients with increased IGFBP7 values were more likely to have diastolic dysfunction. Moreover, there was a trend of an increased severity of diastolic abnormalities with higher IGFBP7 levels. Elevated concentration of IGFBP7 for a longer period of time was associated with worsening diastolic function, increasing LAVI or RVSP. IGFBP7 concentrations were not clearly correlated with left ventricular mass, volume and systolic function, including left ventricular ejection fraction (LVEF) [10]. Also, in a study by Lisowska et al., there were no statistically significant differences between the group of patients with EF>50% and EF<50% [19].

In conclusion, concentrations of IGFBP7 are correlated with diastolic dysfunction of the heart in patients with HFrEF and HFpEF. Most patients with HFrEF have a component of diastolic dysfunction. Whereas patients with HFpEF develop diastolic abnormalities due to hypertrophy and interstitial fibrosis, in patients with HFrEF fibrosis is a replacement process to substitute dead cardiomyocytes [10].

Moreover, IGFBP7 concentration can be predictive of an increased risk for cardiovascular events. Serial measurements of this marker can provide prognostic information – lower concentrations across observations of patients with chronic heart failure independently predicted fewer events [23].

CORONARY ARTERY DISEASE

Little is known about the role of IGFBP7 in atherosclerosis. According to research by Lisowska et al., IGFBP7 can be a good biomarker of coronary artery disease occurrence. Its concentration was considerably higher in the group of patients with myocardial infarction (MI) and coronary artery disease (CAD) than in the control group of healthy volunteers [18, 19]. There were no statistically significant differences in IGFBP7 level between patients with stable CAD and MI, and its values were similar in ST-elevation MI (STEMI) and non-ST-elevation MI (NSTEMI) patients. There was no correlation between IGFBP7 value and number of narrowed coronary arteries [18, 19]. Moreover, no correlation between IGFBP7 level and high-sensitivity cardiac troponin concentration was found, which may suggest that its elevation in acute ischemia is not a result of myocardial cells necrosis, but has a different source. It seems that, although we can use IGFBP7 to predict the presence of atherosclerotic lesions in coronary vessels, its concentration does not reflect a degree of CAD advancement (a number of narrowed coronary arteries) and it cannot be used as a marker of acute ischemia [18, 19]. What is more, there were no differences in IGFBP concentration in the group of MI patients who died during the follow-up, so it is not a good predictor of mortality in patients with MI [19]. In the study, the medical history of hypertension, dyslipidemia, and presence of type 2 diabetes did not affect IGFBP7 concentration [19].

In a study conducted by Goncharova et al., it was found that susceptibility to CAD and prognosis of disease progression is associated with polymorphism of certain genes, involved in the metabolism of the extracellular matrix and processes of fibrogenesis, including IGFBP7. Carriers with genotype GG of IGFBP7 gene were at a 2.4 times higher risk of developing atherosclerosis [12].

The role of IGFBP7 in atherosclerosis still remains unclear and it requires further studies.

DIABETES

IGFBP-7 concentration is also associated with insulin resistance (IR) and the risk of metabolic syndrome (MetS) [3, 19, 21]. As mentioned earlier, IGFBP7 has high affinity to insulin – 500 times higher compared to other IGFBPs [3]. It could compete with InsR for binding with insulin, substantially reducing the serum level of free insulin, blocking the binding of insulin to the InsR, diminishing the physiological response to insulin and therefore contributes to insulin resistance, development of diabetes and cardiovascular disease [3, 21]. IGFBP7 may be a new potential target for the treatment of IR and MetS.

In the study by Barroso et al., patients with MetS or with diabetes demonstrated a significant increase in the IGFBP-7/IGF-1 ratio, compared to the people without these illnesses [3]. Also, in research conducted by Liu et al. on the Chinese population, patients with MetS and IR had significantly higher serum concentrations of IGFBP7 than control healthy subjects [21]. High serum concentrations of IGFBP7 were also associated with an increased risk of IR and MetS. Moreover, correlation between serum IGFBP7 levels and some metabolic parameters (such as Body Mass Index (BMI), waist circumference (WC), waist- to-hip ratio (WHR), high density lipoprotein (HDL) and low density lipoprotein (LDL) was found [21]. On the other hand, in a study conducted by Gu et al. on Swedish subjects with and without type 2 diabetes, serum IGFBP7 protein levels were similar among nondiabetic subjects, newly diagnosed, and treated patients with type 2 diabetes (T2D). However, IGFBP7 DNA methylation levels were increased in Swedish men with newly diagnosed T2D. Moreover, a correlation between serum IGFBP7 levels and serum IGFBP-1 (marker of insulin production) levels were found in men but not women with newly diagnosed T2D, which may suggest that low IGFBP7 could be associated with IR in T2D [13].

What is more, IGFBP7 plays a role in diabetic nephropathy (DN). It might be involved in the TGF-β1-induced tubular injury in DN. According to a study conducted by Watanabe et al., its urinary levels were significantly higher in patients with albuminuria > 300 mg/24 h. They were also correlated with age, estimated glomerular filtration rate (eGFR), urinary β2-microglobulin and urinary N-acetyl-beta-D-glucosaminidase (NAG) [34].

ACUTE KIDNEY INJURY

Acute Kidney Injury (AKI) is a common complication in daily medical practice, also in Cardiology Departments, e.g. in patients with acute heart failure (AHF), after cardiac and non-cardiac surgeries. Its incidence in patients after cardiac surgery reaches 20-50% [24]. Cardiorenal syndrome occurrence is associated with a high risk of death. Early detection of endangered patients is crucial for nephroprotective therapy. Early application of appropriate treatment is associated with lower mortality after AKI [24, 27].

Tissue inhibitor of metalloproteinases-2 (TIMP-2) and IGFBP7 are markers of tubular damage [27]. They are inducers of G1 cell cycle arrest – a protective mechanism, which appears to be initiated during the earliest stages of tubule cell stress in response to a wide variety of factors, like oxidative stress, inflammation, toxins, drugs [15, 22, 27]. Through cell-cycle arrest, injured renal epithelium can shut down its function and stop the process of cell-division until repair takes place. It prevents more permanent damage, cell death, and senescence. TIMP-2*IGFBP7 system can be used for early detection of tubular damage and thus of AKI endangered patients, which could allow for subsequent adjustments in medical therapy and prevention of AKI [24]. The concentration of these two markers is found to be superior to other known biomarkers in critically ill patients [26, 33]. Compared to other prognostic candidates, including neutrophil gelatinase-associated lipocalin (NGAL), urinary TIMP2*IGFBP and IGFBP7 was demonstrated to be the most accurate biomarker of prediction and renal outcome in patients with AKI [2, 15]. Its significant upregulation predicted mortality, recovery and severity of AKI and it was associated with the duration of AKI.

In their study, Schanzet al. observed that urinary TIMP2*IGFBP7 concentration is useful in predicting moderate to severe AKI in patients with acute decompensated heart failure (ADHF) and it is associated with higher mortality. What is more, changes in TIMP-2*IGFBP7 were correlated with weight gain, suggesting an association between its levels and fluid overload, which is a known factor of increased mortality [27].

TIMP-2*IGFBP7 test can also sufficiently detect patients with a risk of AKI after major non-cardiac surgery [2] and after elective cardiac surgery [24, 35]. It is proven that patients with AKI, even those with stage 1, experience higher risk of mortality and readmission rates and a higher risk for developing heart failure as compared to patients without AKI [24]. Single urinary test TIMP2*IGFBP7 can accurately identify patients who are at risk for developing AKI within 12 hours after surgery [14]. In their study, Oezkur et al. discovered that measurements of TIMP2*IGFBP7 at Intensive Care Units admission directly after elective cardiac surgery was a strong and accurate predictor of AKI within next 48 hours. It was an independent and more spe-

cific marker than known clinical factors, such as preoperative kidney function, EuroSCORE II and time on cardio-pulmonary bypass (CPB) [24]. In another study, the diagnostic accuracy of TIMP2*IGFBP7 on day one after CABG for the prediction of AKI stage 2/3 (moderate to severe) was significantly better than the serum creatinine and eGFR [26]. According to research, measurement of TIMP2*IGFBP7 before surgery was not useful to predict AKI [24, 35]. The decline in urinary TIMP2*IGFBP7 values were proven to be the strongest predictor for renal recovery [22].

SENESCENCE AND AGING

Cell senescence is irreversible cell cycle arrest and it is closely connected with aging of the body. Numerous studies have proven that IGF-axis plays a significant role in regulating signal pathways linked to the aging process and aging-related diseases, like cardiovascular disease, osteoporosis, vertebral aging. Increased IGF signal promotes cell division, survival and development of cancer cells, and its inhibition is thought to be able to delay aging. IGF-1 and IGFBPs can interact with many aging related molecules, such as p53, growth hormone (GH), plasminogen activator inhibitor-1 (PAI-1), which participate in different signal transduction pathways (like insulin/IGF-1 signal, the mammalian target of rapamycin (mTOR) signaling pathway), leading to the aging of the body [17]. According to research, IGFBP7 along with IGFBP4, are secreted by senescent mesenchymal stem cells (MSC) and they are key components needed for triggering senescence in young MSC. This effect can be reversed by single or simultaneous immunodepletion of either proteins from senescent-conditioned media (CM). The IGFBP4/7 blocking also reduced apoptosis and promoted cell-growth. Moreover, stimulating young MSCs with rIGFBP4/7 accelerated senescence and induced apoptosis. These findings suggest that IGFBP4/IGFBP7 can play a big role in regenerative medicine and cancer therapy [28].

CANCERS

IGFBP7 is regarded as an apotential tumor suppressor in various cancers [1, 4, 20]. According to many research studies, no or very weak IGFBP7 expression is detected in many cancers, especially in their advanced stages, while healthy tissues express abundant IGFBP7 [4]. The correlation between IGFBP7 expression and tumor progression was found for instance in patients with hepatocellular carcinoma (HCC) [4], gastric cancer [20], cholangiocarcinoma [36], pancreatic cancer [1], non-small cell lung carcinoma (NSCLC) [32], breast cancer [7], high grade serous carcinoma [8], acute myeloid leukemia (AML) [31]. Low expression of IGFBP7 was often correlated with poor prognosis and it was potentially correlated with increased cancer cell proliferation [1, 7, 20], while high expression of IGFBP7 was correlated to better overall survival in patients [8, 36]. Moreover, IGFBP7 can play a big positive role in treatment AML. According to research, it has the ability to sensitize AML cells to chemiotherapy-induced cell death and, together with chemiotherapy, it may overcome conventional AML drug resistance and improve AML patients survival [31].

CONCLUSIONS

IGFBP7 seems to play a role in developing and progressing many cardiometabolic diseases. Its concentration is correlated with diastolic dysfunction of the left ventricular in patients with HFrEF and HFpEF. Its serial measurements can provide prognostic information in patients with chronic heart failure. It can be also used as a biomarker of coronary artery disease occurrence and it is also associated with insulin resistance and the risk of metabolic syndrome. It is a novel marker of tubular damage and it is used for the early detection of AKI endangered patients and it is regarded as a potential tumor suppressor in various cancers. Yet, its role in developing cardiometabolic diseases still remains unclear and it requires further studies.

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