Proteomic Profiling of IGFBP2: Modulation and Biomarker Potential in Atherosclerotic Cardiovascular Disease Prevention

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Population aging and growth have led to a dramatic rise in atherosclerotic cardiovascular disease (ASCVD) prevalence, particularly in Canada over the past two decades. As the national ASCVD burden grows, accurately identifying high-risk individuals is essential. Drawing on existing proteomic research, we have highlighted Insulin-like Growth Factor Binding Protein 2 (IGFBP2) as a potential novel biomarker for ASCVD development. Past literature examined four protein groups related to ASCVD progression: (1) extracellular matrix proteins, (2) lipid-binding and metabolic proteins, (3) inflammatory proteins, and (4) phagocytic ligands and apoptotic cell receptors. IGFBP2 affects arterial vascular smooth muscle cells (VSMC) by modulating the bioavailability of insulin-like growth factor 1 (IGF1), causing VSMC hypertrophy. Individuals with pre-existing cardiomyopathies display elevated levels of IGFBP2 and subsequent higher rates of mortality. Counterintuitively, higher IGFBP2 levels in healthy individuals correlate with reduced arterial stiffness and lower low-density lipoprotein (LDL) cholesterol levels—indicators of ASCVD severity. Although the relationship between IGFBP2 and ASCVD remains unclear, IGFBP2 presents as a promising biomarker due to its association with ASCVD-related effects and bioavailability. We propose further exploration of IGFBP2 across stages of ASCVD and its evaluation as a potential therapeutic target.

Introduction

Atherosclerotic cardiovascular disease (ASCVD) remains a significant health concern in Canada, with cardiovascular disease being the second leading cause of death from 2019-2022.[1] The 5-year prevalence of ASCVD in Canada alarmingly increased from 43.7 to 69.1 per 1000 individuals between 2004-2008 and 2013-2017, reinforcing the severity of this growing epidemic.[2] This rise disproportionately affects specific demographics. In Ontario, Black individuals have the highest risk of cardiovascular disease, likely due to a higher prevalence of major cardiovascular risk factors (11.1%). Whereas South Asians have the highest rates of heart disease or stroke (6.6%), likely due to greater glucose intolerance, elevated LDL, and reduced high-density lipoprotein (HDL) levels[3,4] Sex-based differences were also observed, with Canadian females aged 40-44 having a 2.3-times higher ASCVD prevalence than males, suggesting a need for targeted therapeutic approaches.[5]

ASCVD diagnosis and disease management remain a substantial financial burden for the Canadian healthcare system. Adjusted for inflation, first-year healthcare costs for a newly diagnosed ASCVD patient are ~$41,000 CAD, up from ~$37,000 CAD in 2022.[5,6] Rogoza et al. identified $66.6 billion CAD in costs for incident adult ASCVD between April 2005 and March 2016, adjusted to ~$85.1 billion CAD today[7] Key drivers of these annual costs are three events that are consequences of ASCVD: myocardial infarction (MI), stroke, and peripheral artery disease (PAD).[7] Therefore, increasing public funding and awareness are critical factors in preventing and mitigating the burden of ASCVD.

Early ASCVD detection is imperative to prevent disease progression. As the second most bioavailable Insulin-like Growth Factor Binding Protein (IGFBP), IGFBP2 enables easier detection and more reliable measurements, supporting its potential as an ASCVD biomarker. IGFBP2 has also been associated with other

https://doi.org/10.29173/hsi501
Received 28 March 2025
Accepted 8 July 2025

cardiovascular risk factors. For instance, Arai et al. reported a correlation between IGFBP2 and thrombolysis in MI risk scores, highlighting its potential as a biomarker for patients with acute coronary syndrome, a disease closely related to ASCVD, as it often results from the rupture of atherosclerotic plaques.[8] ASCVD's chronic and progressive nature burdens patients and the healthcare system, rendering the discovery of novel biomarkers for early disease identification a valuable advancement.

Pathophysiology of ASCVD

ASCVD is a chronic, inflammatory condition triggered by endothelial damage from factors like smoking, hypertension, or hyperlipidemia.[9] Endothelial injury promotes specific adhesion molecule expression, which leads to monocyte recruitment to the area of injury where they differentiate into macrophages that engulf oxidized LDL, and form foam cells.[9] Foam cells accumulate into fatty streaks—the earliest visible signs of ASCVD.[9] Vascular smooth muscle cells (VSMCs) then proliferate and migrate from the tunica media to the tunica intima to form a fibrous cap over the plaque.[9] Over time, plaques can enlarge from cholesterol, calcium, and cellular debris buildup.[10] Plaque instability may cause the fibrous cap to rupture and expose thrombogenic contents, leading to obstructed blood flow and complications such as MI or stroke.[9]

Identification of ASCVD and Clinical Perspectives

ASCVD diagnosis is often delayed due to the disease's asymptomatic onset and progression, increasing the risk of serious cardiovascular events like plaque rupture and MI.[11] This underscores the need for a biomarker that can detect early plaque development. Existing ASCVD biomarkers yield notable limitations. LDL cholesterol accumulates on the walls of arteries, oxidizes, and promotes arterial stiffness and plaque formation, making it a useful biomarker.[12] However, LDL is typically measured by mass, a time-consuming process that delays diagnosis.[13] Alternatively, nuclear magnetic resonance (NMR) spectroscopy provides quicker results,[14] but the cost of traditional high-field NMR systems used for lipoprofiles preclude their routine clinical use, costing millions per instrument and up to $450 per patient.[15,16] Consequently, current LDL cholesterol measurement methods are time-intensive, not widely accessible, and may offer limited utility in comprehensive cardiovascular risk assessment.

Bødtker Mortensen et al. assessed the association between LDL cholesterol and ASCVD events over 5 years in individuals with and without coronary artery calcification (CAC).[17] LDL cholesterol was strongly associated with ASCVD events in middle-aged participants with pre-existing coronary atherosclerotic buildup. However, LDL cholesterol showed limited predictive value for ASCVD in individuals without previous CAC, further demonstrating its limitations for early ASCVD detection.[17]

Given the drawbacks of current assessments and the lack of early detection methods, serum IGFBP2 shows promise as an emerging biomarker. Its' high binding affinity to insulin growth factor 1 (IGF1) enables regulation of cardiac hypertrophy and protection.[18] Berry et al. previously identified IGFBP2 as a candidate diagnostic biomarker for heart failure (HF) through mass spectrometry-based proteomics analysis of urine and plasma, noting elevated levels in HF patients.[19] Elucidating the cellular pathways involving IGFBP2 in ASCVD pathogenesis is key to understanding its potential utility as a biomarker.

Pathway and Insights into IGFBP2's Role in ASCVD

The IGF1/Phosphoinositide 3-Kinase (PI3K)/Protein Kinase B (Akt) signaling pathway is a critical regulator of physiological cardiac hypertrophy and protection.[19] This pathway is initiated by binding IGF1 to the insulin-like growth factor 1 receptor (IGF1R). Binding leads to the activation of PI3K, which subsequently activates Akt, a serine/threonine kinase involved in cell growth, survival, and metabolism. In adaptive settings, such as exercise, the activation of this pathway leads to physiological hypertrophy, characterized by an increase in heart mass with normal or enhanced cardiac function, in contrast to the pathological hypertrophy seen in heart disease.[19] Furthermore, enhanced IGF1/PI3K/Akt signaling has demonstrated cardioprotective benefits in preclinical rodent models of various cardiac diseases, including pressure overload and MI.[19,20] The pathway also inhibits signaling cascades involved in pathological cardiac hypertrophy and HF.[19]

IGFBP2 is a secreted protein that primarily binds to IGF1 and IGF2, modulating their bioavailability and receptor interactions as the second most abundant IGFBP in circulation.[20,21] Depending on surrounding cell types,

IGFBP2 can inhibit or enhance IGF actions, prolonging the half-life of IGF1 and increasing its cardioprotective effects.[20] IGFBP2 also exerts IGF-independent effects by binding to cell surface receptors like α5β1 integrin, which is linked to cardioprotective effects in its active form.[25] This interaction can activate downstream signaling pathways, including focal adhesion kinase and integrin-linked kinase, which maintain myocardial structure and function.[20,22] Altered levels of IGFBP2 have been associated with various metabolic conditions, including metabolic syndrome and insulin resistance, known risk factors for cardiovascular diseases.[20]

The interplay between the IGF/PI3K/Akt pathway, IGFBP2, and atherosclerosis is multifaceted. IGF1 has antiatherogenic effects through its modulation of anti-inflammatory and pro-repair pathways, potentially reducing atherosclerotic plaque burden and increasing plaque stability.[22] These effects are often coupled with changes in vascular oxidative stress, with IGF1 enhancing antioxidant activity.[22] IGFBP2's role in atherosclerosis is increasingly recognized in current research. It has been shown to play a crucial part in regulating the mitogen-activated protein kinase (MAPK) pathway and the PI3K/Akt signaling pathway, both of which are implicated in the pathological processes of atherosclerosis. Furthermore, IGFBP2 can enhance the migration and proliferation of VSMCs, promoting atherosclerotic plaque formation.[23]

Studies have linked circulating IGFBP2 levels with atherogenic metabolic risk profiles.[23-25] For instance, higher IGFBP2 levels have been associated with a more favourable metabolic risk profile, characterized by lower fasting insulin and glucose.[24] Paradoxically, elevated IGFBP2 levels are also linked to higher mortality in elderly men, reflecting its potential role in age-related conditions such as bone loss and cancer progression.[23] Adiposity, a major risk factor for atherosclerosis, is inversely associated with IGFBP2 levels.[24] Lower IGFBP2 levels in the context of obesity and insulin resistance may impair cardioprotective signaling, potentially contributing to left ventricular remodeling and dysfunction seen in aortic stenosis (AS).[20,25]

Several hypotheses and confounders may help explain this paradox. The disease state and its severity are crucial determinants of IGFBP2's impact.[26,27] Reduced IGFBP2 in conditions like obesity or mild-to-moderate AS may impair cardioprotective signaling via integrin binding or disruption of the IGF1/PI3K/Akt pathway, contributing to adverse remodeling and dysfunction.[18,20,28] Conversely, high IGFBP2 in severe disease (e.g., advanced AS, PAD, or HF) may reflect disease severity or a maladaptive compensatory response, rather than a direct cause.[26-29] IGFBP2's impact may also depend on whether it acts through IGF-dependent mechanisms (modulating IGF1/IGF2) or IGF-independent pathways, such as integrin-mediated signaling involved in growth and angiogenesis.[30] In advanced disease, high IGFBP2 may inhibit IGF1's cardioprotective effects.[18,28] Additionally, IGFBP2 levels increase with age, and associations with mortality in older adults may reflect aging-related processes rather than metabolic dysfunction.[27,31] Interpretation is further complicated by its integration in the broader IGF system, which includes multiple IGFBPs and regulators such as growth hormone and estradiol.[30] Collectively, these findings suggest that IGFBP2 may be contextually pleiotropic, exerting protective metabolic effects in some settings while signaling disease severity or poor prognosis in others.

Modulation of IGFBP2 Through Exercise

Exercise is known to protect against atherosclerosis and can modulate the IGF1 system, although its specific effects on IGFBP2 require further investigation.[32,33] While studies have shown conflicting results on the optimal exercise mode, chronic exercise consistently demonstrates superior protective effects compared to acute exercise.[33-35] Chronic exercise improves insulin sensitivity and reduces adiposity, both correlated with increased IGFBP2 levels, suggesting a potential link.[36] We hypothesize that IGFBP2 mediates exercise's anti-atherosclerotic effects by modulating IGF-dependent and independent signaling pathways that support vascular homeostasis. Elucidating how exercise modulates IGFBP2 and downstream IGF/PI3K/Akt signaling may reveal mechanisms supporting chronic exercise as a targeted intervention for preventing ASCVD and related vascular diseases. Adopting a systems-level proteomic approach to investigating protein dynamics during exercise may uncover novel biological mechanisms.

Role of Proteomics in ASCVD Biomarker Identification

A greater understanding of these novel mechanisms can be achieved through omics. Omics refers broadly to the many scientific fields that aim at measuring large numbers

of molecules in a biological system to understand underlying functions and processes.[37] Proteomics is a widely applicable field that studies protein expression, modification, and interaction,[38] and can be applied to study disease mechanisms to help identify potential biomarkers for diagnosing and treating diseases.[36]

Proteomics has been used to study various cardiovascular conditions, leading to the discovery of several diagnostic biomarkers.[39] For example, research using proteomic techniques has led to cardiac troponin I being included in the diagnosis of MI.[40,41] Proteomics is used in the study of ASCVD by revealing proteins involved in the formation, progression, and rupture of atherosclerotic plaques.[39] It is especially applicable in the early diagnosis of ASCVD before the appearance of clinical symptoms. Analyzing blood proteins with proteomic technologies offers a promising approach to identifying biomarkers for ASCVD development.[39]

To detect IGFBP2 as a biomarker for conditions such as cardiovascular disease, researchers employ highly precise analytical techniques known as Selected Reaction Monitoring or Multiple Reaction Monitoring.[42] These methods are targeted molecular probes, identifying specific proteins within complex blood samples. The process begins with the automated preparation of plasma samples, followed by micro-scale liquid chromatography to separate proteins. Subsequently, mass spectrometry fragments IGFBP2 and measures its unique molecular signatures with exceptional sensitivity and specificity. This methodology enables the detection of even minute quantities of IGFBP2, facilitating comparative analyses between healthy individuals and patients with atherosclerosis.[42] Such comparisons can elucidate patterns that contribute to understanding disease risk and progression, thereby offering valuable insights into the precise relationship between ASCVD and IGFBP2 levels in the body.

Conclusion

ASCVD is a major global health concern. Measuring serum IGFBP2 levels may offer healthcare practitioners greater insight into atherosclerotic progression and support earlier diagnosis of ASCVD.[21,43] However, previous studies show that IGFBP2's relationship with ASCVD varies depending on the developmental stage, highlighting the need for further research. Proteomics targeting IGFBP2 expression may clarify this relationship, while examining protein function through biochemical and functional analyses could reveal molecular mechanisms that can be modulated as possible interventions for ASCVD and other cardiovascular diseases.

Plaque buildup contributes significantly to age-related cardiovascular mortality. Identifying early biomarkers like IGFBP2 brings us closer to preventing ASCVD, a major contributor to the world's leading cause of death, cardiovascular disease.

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