Growth differentiation factor-15 and cardiovascular dysfunction and disease: malefactor or innocent bystander?

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Received 19 January 2010; revised 12 February 2010; accepted 24 February 2010; online publish-ahead-of-print 18 March 2010

Introduction

It is widely recognized that around 20% of cardiovascular events occurring in the general population cannot be inferred from conventional risk factors.1 This led to a growing interest in novel measurable humoral biomarkers, hopefully leading to an improvement of global cardiovascular risk stratification. Growth differentiation factor-15 (GDF-15) is the latest promising marker in this field. Growth differentiation factor-15 is a protein belonging to the transforming growth factor-β (TGF-β) superfamily, which includes more than 40 proteins with crucial functions in adult tissue homeostasis by modulating cell survival, proliferation, differentiation, and tissue repair in different organs. Initially cloned from an activated macrophage cell line, GDF-15 has been proposed as a cell death promoter in several tumour cell lines, highlighting its potential role as an inducer of apoptosis in some cancer cells.2 Expression of GDF-15 is rapidly induced by IL-1, TNF-α, and TGF-β in macrophages, thereby limiting macrophage activation and inflammation.3 Results of analysis from human tissues evidenced the presence of GDF-15 also in the kidney, prostate and placenta, breast and colon, as well as in the heart.4

Growth differentiation factor-15 and cardiovascular disease

Since GDF-15 is a product of activated macrophages, its serum or plasma concentration might be useful in the identification of atherosclerosis. Several studies documented that activated macrophages are greatly involved in the pathogenesis of atherosclerosis and vascular thrombosis, which is often the final endpoint of atherosclerotic disease.5 An increased expression of GDF-15 has been identified in atherosclerotic lesions4 and within the myocardium of mice with acute myocardial infarction.6 The first clinical trial which assessed any association between plasma concentration of GDF-15, also known as macrophage inhibitory cytokine-1 (MIC-1), and risk of cardiovascular events derives from a prospective, nested, case-control study, conducted in apparently healthy elderly women, with no previous evidence of cardiovascular disease, participating in the Women’s Health Study. The authors found that women with the highest concentration of MIC-1 at baseline had a risk of future myocardial infarction, thrombo-embolic stroke, or cardiovascular death around three times higher than that of women with lower MIC-1 concentrations.7

The impact of GDF-15 as a predictor of adverse events was also assessed in two therapeutic trials including patients with ST-segment elevation myocardial infarction (STEMI)8 and non-ST elevation acute coronary syndrome (NSTEMI).9 Both in STEMI and NSTEMI patients, GDF-15 emerged as a significant independent predictor of mortality. In particular, in patients with NSTEMI, both GDF-15 and N-terminal pro-brain natriuretic peptide (NT-proBNP) resulted in being independent predictors of death, whereas in STEMI patients, GDF-15, but not NT-proBNP, was an independent predictor of mortality during 1-year follow-up (Figure 1). The promising role of such protein as a marker of cardiovascular disease has been reinforced by a recent clinical report conducted in patients with acute myocardial infarction.10 In this prospective study, the authors investigated whether GDF-15 alone or in combination with NT-proBNP would be of benefit in determining the long-term prognosis post-acute myocardial infarction. The authors demonstrated that GDF-15 is a prognostic marker of long-term mortality and heart failure in these patients, independent of established conventional risk factors.10 Taken in conjunction, these interesting findings allow us to consider that circulating levels of GDF-15 may provide useful prognostic information after acute myocardial infarction. A combined approach with GDF-15 and NT-proBNP is even more informative than either marker alone and might inform high-risk patient management, e.g. by identifying patients with non-ST-segment elevation...
Growth differentiation factor-15 and cardiovascular events: pathophysiological mechanisms

Although convincingly highlighted GDF-15 as a new biomarker in cardiovascular disease, the above-mentioned studies failed to provide any pathophysiological basis for the association of GDF-15 with future cardiovascular events. To this purpose, in a recent interesting study, Lind et al. characterized the relations of GDF-15 to some indices of cardiovascular dysfunction and disease in a community-based cohort of subjects aged 70 years from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. All individuals were characterized in terms of carotid intima-media thickness, plaque burden, and left ventricular geometry and function by ultrasound. Peripheral endothelium-dependent vasodilation was assessed both in the forearm microcirculation and brachial artery by the plethysmographic and the flow-mediated dilation technique, respectively. An accurate individual cardiovascular diagnosis was also collected. Elevated GDF-15 values showed a relationship with major cardiovascular risk factors. The novel aspect of the present study is the demonstration, for the first time in a community-based cohort of elderly subjects, that after adjustment for cardiovascular risk factors, a significant positive relation exists between elevated plasma values of GDF-15 and a reduced endothelium-dependent vasodilation at the level of resistance vasculature, plaque burden, left ventricular mass and concentric hypertrophy, reduced ejection fraction, and clinical manifestations of coronary artery disease. These findings allowed the authors to conclude that GDF-15 may be identified as a marker of cardiac and vascular pathologies, independently of traditional cardiovascular risk factors, in elderly individuals from a general population, thus providing new insight into the pathophysiology of this emerging cardiovascular biomarker. This interesting and well-conducted report provides evidence of an independent relationship between elevated levels of GDF-15 and several indicators of early atherosclerosis, cardiac parameters, and clinical signs of cardiovascular disease. However, some aspects require further considerations.

One concerns the impact of GDF-15 on cardiovascular disease. May GDF-15 be considered a biomarker of atherosclerotic disease and of a reduced cardiac and vascular function or does it represent an active mediator of cardiovascular disease? Unfortunately, the cross-sectional design of the study by Lind et al. does not allow definitive conclusions. This is substantially because of the temporal sequence of sample collection and disease occurrence. Thus, GDF-15 circulating levels and extent of disease were assessed concurrently, and thus cannot exclude the possibility that elevated GDF-15 may be the consequence rather than a putative cause of cardiovascular disease. Prospective studies have the major advantage of collecting blood specimens before any relevant cardiovascular disease has occurred. Thus, the temporal relationship between elevated GDF-15 levels and cardiovascular alterations is more clearly defined in longitudinal studies, most of them having been performed by the same working group. Thus, in a recent prospective report, the same authors explored the prognostic utility of GDF-15 in patients with chronic heart failure. In this study, a cohort of 455 patients with a history of chronic heart failure for at least 6 months and stable on medication before blood sampling were enrolled. The GDF-15 levels were closely related to New York Heart Association functional class and to NT-proBNP values. The risk of death during follow-up was raised with increasing levels of GDF-15. After a multivariate analysis, which included established clinical and biochemical markers of adverse prognosis, GDF-15 resulted in being an independent predictor of mortality. Therefore, according to these findings, together with the above-mentioned demonstrated utility of GDF-15 in predictive death in STEMI and NSTEMI patients, the prognostic value of elevated GDF-15 for cardiovascular events among high-risk individuals seems to be convincingly demonstrated across the cardiovascular continuum, from stable coronary artery disease to acute coronary syndrome and heart failure. Nevertheless, its causal impact on earlier steps of atherosclerosis, such as the atherosclerotic vascular plaques or the even more early endothelial dysfunction, needs to be assessed by prospective controlled studies.

Another still unsolved question is whether elevated GDF-15 values may have a potential protective or detrimental effect on the cardiovascular system. This issue derives from an important experimental finding recently put in evidence. Thus, Kempf et al. examined the expression of myocardial GDF-15 after ischaemic injury. The authors found an increased expression of GDF-15 in cardiomyocytes subjected to ischaemia/reperfusion. Growth differentiation factor-15 was actively secreted into the culture supernatant, suggesting that it may exert autocrine/paracrine effects during ischaemia/reperfusion. These in vitro data were supported by in vivo experiments, in which animals underwent a coronary artery ligation. Myocardial GDF-15 expression rapidly increased in the area-at-risk after ischaemic injury. Gdf-15-deficient mice developed greater hypertrophy, which could also be attributable to exaggerated hyperplasia, with reduced left ventricular function.
in response to pressure overload,\textsuperscript{12} and infarct sizes and cardiomyocytes apoptosis in the infarct border zone and ischaemia/reperfusion compared with controls.\textsuperscript{6} The potential clinical relevance of these results is strengthened by the up-regulated GDF-15 levels in myocardial samples from patients with a fatal acute myocardial infarction. Cardiomyocytes in the ischaemic area contributed to the induction of GDF-15 in the infarcted human heart. These findings indicate that endogenous GDF-15 may limit myocardial tissue damage, thus identifying this protein as a novel heart protective molecule. If one takes a look at the known upstream stimuli of GDF-15, it appears evident that several inductors, including proinflammatory cytokines, transcription factors, or cardiovascular events triggering oxidative stress, such as heart failure, atherosclerosis, or pressure overload, may rapidly stimulate GDF-15 expression, which in turn exerts anti-inflammatory, anti-apoptotic, and anti-growth effects,\textsuperscript{2} as summarized in Figure 2. Several of the above-mentioned inductors, mainly low-grade vascular inflammation and oxidative stress, have acquired progressive recognition over the past few years as pathogenetic mechanisms for endothelial dysfunction and cardiovascular damage.\textsuperscript{13} For these reasons, the association between elevated GDF-15 levels and reduced endothelium-dependent vasodilation, plaque burden, and altered cardiac parameters may likely represent an endogenous protective mechanism, trying to limit the cardiovascular damage. If so, this might imply a potential therapeutic role of GDF-15, a hypothesis that should be assessed in future studies.

Finally, another consideration concerns the potential influence of medications on several cardiovascular parameters considered, i.e. endothelial function, carotid atherosclerosis, and cardiac mass. In the study by Lind et al.,\textsuperscript{11} almost half of the cohort recruited was reporting the use of cardiovascular therapy, mainly anti-hypertensive drugs and statins. It is well accepted that among blood pressure-lowering agents, calcium-antagonists represent the class of cardiovascular drugs with more solid evidence of restoration of endothelial dysfunction in several vascular districts, including the forearm microcirculation, an effect mainly due to their antioxidant property.\textsuperscript{14} In addition, and likely by the same mechanism, their ability to slow down the progression of vascular atherosclerosis has been recognized.\textsuperscript{15} Angiotensin-converting enzyme (ACE)-inhibitors represent another fundamental class of cardiovascular drugs, and a large amount of data showed that ACE-inhibitors, through the blockade of the angiotensin II-dependent vascular inflammation and smooth muscle cell proliferation and migration, are able to induce a regression of vascular structural changes.\textsuperscript{16} Considering the different peculiarities of these two drug classes towards the vessel wall, it is conceivable that the association of them, largely used in clinical practice, may provide an optimal vascular protection. Moreover, calcium-antagonists and ACE-inhibitors have a great beneficial impact on left ventricular mass.\textsuperscript{17} With respect to statins, originally introduced into the clinical practice to lower blood cholesterol levels, these drugs have then displayed their ability as anti-oxidant and anti-inflammatory compounds, thus offering endothelial and more in general vasculoprotective effects.\textsuperscript{18} Unfortunately, in the study by Lind et al.,\textsuperscript{11} the percentage of individuals taking calcium-antagonists, ACE-inhibitors, or their association, if any, was missing. In addition, the distribution of cardiovascular compounds among GDF-15 quartiles was not reported. These additional data might further help to extrapolate the exact relationship between GDF-15 and cardiovascular disease.

**Conclusions**

Growth differentiation factor-15 is a stress-responsive cytokine that is emerging as a useful biomarker of cardiovascular disease. Elevated circulating levels of GDF-15 are in relationship to several indices of cardiovascular dysfunction and clinical manifestation of cardiovascular disease. In particular, elevated GDF-15 values are in a strict relationship with high-risk individuals, including patients with stable coronary artery disease, acute coronary syndrome, and chronic heart failure. The association of GDF-15 with clinical outcomes in such patients is independent of traditional...
clinical risk factors and established biomarkers, including NT-proBNP. There is no doubt that these interesting findings, together with many previous others coming from the PIVUS Study, contribute to our understanding of the complex pathophysiology of cardiovascular disease. Of importance, the majority of such information has been collected from a population sample of elderly individuals, likely not representative of the general population. Therefore, future larger studies will allow to clarify whether these conclusions may be extended to younger populations. At present, GDF-15 appears to be a promising biomarker of cardiovascular disease, while its role as a prognostic indicator needs further clarification. In clinical practice, the potential utility of biomarkers is to better stratify the cardiovascular risk and, hopefully, to better assess the efficacy of treatment. In this direction, priority aims of future studies will be to define GDF-15 cut-off values and to establish whether its plasma values will be definitively useful as a tool of therapeutic decision-making by physicians.

**Conflict of interest:** none declared.

**References**