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The Story of Growth Differentiation Factor 15: Another Piece of the Puzzle

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The research interest in risk markers in general, and biochemical risk markers in particular, has exploded in the last 2 decades. A Medline search on "cardiovascular risk markers" yields only 21 hits for the publication year 1990. By contrast, for 2010 the figure has risen almost 100-fold to 2032 hits. Despite the high number of new biomarkers examined, only a few have gained widespread use in routine clinical practice. In the cardiovascular area cardiac troponin T (cTnT),[2] cTnI, B-type natriuretic peptide (BNP), and N-terminal proBNP are examples of biomarkers that have been put into widespread use on the basis of their excellent diagnostic properties rather than their similarly excellent prognostic properties. Why then is there such great interest in biomarkers studies for risk prediction? And what criteria must a biomarker fulfill to be accepted clinically? These 2 questions come to the forefront when considering the elegant study by Jennifer Ho and coworkers on biomarkers of cardiovascular stress and incident chronic kidney disease (CKD) presented in this issue of *Clinical Chemistry (1)*. In the Framingham cohort, the authors evaluated 2 new markers, growth differentiation factor 15 (GDF-15) and soluble ST2, and 1 established marker, cTnT, for the prediction of the development of CKD. Convincing associations were shown between GDF-15 concentrations and the development of CKD and rapid decline of renal function. However, no similar statistically significant associations were demonstrated with the 2 other biomarkers. There was a gradual increase in risk with increasing quartiles of GDF-15; following multivariable adjustment, individuals with GDF-15 concentrations in the highest quartile, compared to those with concentrations in the lowest, had 5.65-fold (95% CI, 2.97–10.75) higher odds of incident CKD and 2.51-fold (95% CI, 1.54–4.09) higher odds of a rapid decline in renal function during 9.5 years of follow-up. Thus, another piece is added to the intriguing puzzle of GDF-15.

GDF-15 is a member of the transforming growth factor β superfamily; it is also known as macrophage inhibitory cytokine-1, placental transforming growth factor-β, gene placental bone morphogenic protein, prostate-derived factor, NSAID (nonsteroidal anti-inflammatory drug)-activated gene 1, and placental transforming growth factor-β. The expression of GDF-15 in virtually all tissues suggests its importance in general and basic cellular functions. Although the exact biological functions of GDF-15 are still poorly understood, it has been shown to be involved in regulating inflammatory and apoptotic pathways and its expression is upregulated in many different pathological conditions, including inflammation, cancer, cardiovascular disease, pulmonary disease, and renal disease. GDF-15 exhibits differing and even opposing functions under various circumstances. For instance, GDF-15 may show proapoptosis, antiapoptosis, proangiogenesis, antiangiogenesis, proproliferative, antiinflammatory, and immunosuppressive properties *(2, 3)*. Therefore, GDF-15 exhibits a complex pattern of beneficial and harmful functions. Whether increased serum concentrations can cause direct damage or may represent a protective response to biologic stress is still an open question, and the answer might well depend on the circumstances.

GDF-15 has been shown to be a strong and independent predictor of mortality and disease progression in patients with established disease, such as acute coronary syndromes, angina pectoris, heart failure, stroke, chronic kidney disease, and different types of cancer *(3–6)*. In addition, in community dwellers, higher concentrations of GDF-15 have been associated with increased cardiovascular as well as noncardiovascular mortality, and development and progression of a broad range of diseases, such as coronary artery disease, heart failure, diabetes, cancer, and even cognitive impairment *(7–10)*. The study of Ho et al. now adds CKD to that list *(1)*.

A study on twins indicated that although genetic and environmental factors contributed nearly equally to variations in GDF-15 concentrations, differences in the environmental factors, rather than in the genetic background, were the major determinants of the differ-

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[2] Nonstandard abbreviations: cTnT, BNP, B-type natriuretic peptide; CKD, chronic kidney disease; GDF-15, growth differentiation factor 15.

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ences in GDF-15 concentrations that related to mortality risk *(9)*. Furthermore, recently it was shown in a cohort of community-dwelling elderly individuals that the median GDF-15 concentration increased by 11% over a 5-year period and that the changes were related not only to the baseline renal function but also to the change in renal function over the 5-year period *(11)*. Thus, these observations, along with the findings of Ho et al., indicate an intricate interplay between renal function and GDF-15 concentrations, in which the GDF-15 concentration predicts the change of renal function over time, and vice versa, the renal function predicts the change of GDF-15 value. Not surprisingly, Eggers et al. also showed that the change in GDF-15 concentration during the follow-up period, in addition to the baseline value, was a strong and independent predictor of all-cause mortality *(11)*.

One can imagine that the robust and convincing data on the prognostic value of GDF-15 might have led to rapid implementation of the measurement of GDF-15 in routine clinical practice. However, there are several concerns that prevent the widespread use of GDF-15. First, owing to its lack of tissue specificity compared with markers such as cTnT, cTnI, and BNP, GDF-15 has no useful role as a diagnostic marker. Second, the strong characteristics of GDF-15 as a prognostic marker for a wide range of outcomes paradoxically could turn out to be one of its weaknesses as a clinically useful marker of risk. What action should be taken in response to a given GDF-15 concentration? Can the value be used in targeting treatment and in decision-making for an individual patient? Such information is essential for clinicians, and the answers to these questions determine whether the marker is clinically helpful or is just academically interesting.

In the study by Ho et al., the addition of GDF-15 to established clinical risk factors improved the ability to identify patients at a particularly low risk of developing CKD, rather than identifying high-risk patients. In the analysis of net reclassification improvement, the addition of GDF-15 to clinical risk factors, in fact, slightly impaired the ability to accurately identify people at high risk but improved the correct identification of low-risk patients (resulting in a significant and moderately positive net effect) *(1)*. There is other evidence indicating that finding a low concentration of GDF-15 in a patient might be helpful; in the FRISC-II (Fragmin and Fast Revascularization during Instability in Coronary Artery Disease II) trial, low GDF-15 identified patients who would not benefit from the invasive strategy, even when other risk factors (increased cardiac troponin and ST-segment depression in the electrocardiogram) indicated that an invasive strategy could be beneficial *(12)*. Thus, GDF-15 might be the ideal biomarker for identifying very healthy individuals in the general population who will have a low risk for almost any disease; and in diseased populations for identifying patients with low risk for complications in general and death in particular. Third, there is no supporting evidence so far that GDF-15 is useful for monitoring of treatment effects. There is no convincing evidence of any intervention that can lower the GDF-15 concentration and thus also lower the associated risk. Likewise, proven beneficial interventions, like regular exercise training in patients with stable coronary artery or angiotensin receptor blockade treatment in heart failure, did not affect long-term GDF-15 concentrations *(13, 14)*, and revascularization after an episode of acute coronary syndrome had only a minimal effect on GDF-15 concentrations *(15)*.

The GDF-15 puzzle is a good example of how epidemiological and mechanistic studies can interact successfully. The clinical significance of newly discovered mechanisms can be evaluated and conversely, the mechanisms behind epidemiologically proven associations can be elucidated. This might, at least partly, explain the vastly increased interest in risk marker studies, although very few of the new markers will eventually make it to the clinic.

GDF-15 is a marker that is being considered for introduction to the clinic. What questions remain to be answered to establish GDF-15 as a clinically useful biomarker? First, is GDF-15 a risk marker or a causative risk factor, or more importantly, what are the circumstances under which GDF-15 is just a marker of risk vs a causative factor? Second, can the GDF-15 concentration be used to identify groups of patients who will benefit or will not benefit from various interventions or treatments? Third, are there any treatments for which monitoring of GDF-15 concentrations might be useful to guide the treatment (dose and/or duration)? Finally, given that one or more of the above requirements are fulfilled, can GDF-15 measurement, when added to the current strategy or used as a replacement for the current strategy, be proven cost-effective?

We are eagerly waiting for the next pieces in the exciting puzzle of GDF-15.

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