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GDF15 Is a Novel Biomarker for Impaired Fasting Glucose (*Diabetes Metab J* 2014;38:472-9)

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Growth differentiation factor-15 (GDF15) is widely distributed in mammalian tissues and has been shown to play multiple roles in inflammation, cancer, and cardiovascular diseases [1,2]. It has protective roles in tissue injury or inflammation [1,3,4]; acute tissue injury induces GDF15 level increased compensatively [5,6]. In addition, the fact that overexpression of GDF15 results in improved insulin sensitivity [7,8] and resistance to both genetic and dietary-induced obesity [8], whereas genetic deletion of GDF15 increases glucose level in diabetic rat model [9] supports its favorable effect on metabolic diseases.

Despite its beneficial role in experimental studies, subjects with chronic diseases such as cancer, cardiovascular diseases, and metabolic disorders showed paradoxically elevated level of GDF15 [1]. GDF15 level was also increased in subjects with diabetes or prediabetes [10,11]; however, its level in other chronic diseases (e.g., cardiovascular disease) is glucose-independent [12,13]. Cardiovascular disease has been consistently reported to be associated with elevated GDF15 level [6,12,14], and GDF15 is an independent risk factor of cardiovascular disease even after adjusting for glucose level [12,13].

Hong et al. [11] showed that GDF15 levels were elevated in impaired fasting glucose (IFG) and diabetic groups compared with normal glucose tolerance (NGT) group and suggested GDF15 as a novel diagnostic marker for IFG. Considering the increasing epidemiology of IFG or impaired glucose tolerance (IGT) and their impact on cardiovascular disease risk, clinically easier screening tools for the detection of IFG or IGT might be important. However, several things should be considered to address whether GDF15 is a useful diagnostic marker for IFG. First, the main determinant of GDF15 should be investigated. Hong et al. [11] showed the significant correlates of GDF15 levels in monovariate analysis. I wonder what the independent determinants of GDF15 level are in multivariate model including glucose, homeostasis model assessment of insulin resistance (HOMA-IR), and lipid profile. Even in the Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) trial which showed high GDF15 level is a risk factor for the progression of glucose intolerance, GDF15 concentration was higher only in individuals with IGT but not in those with IFG compared with those with NGT [10]. IGT state has been reported to show higher peripheral insulin resistance [15] and higher cardiovascular risk as compared with IFG [16]. The results of XENDOS trial [10] and the phenotype of transgenic mouse model [7,8] implied that GDF15 concentration might reflect insulin resistance rather than glucose level itself. HOMA-IR is a very useful marker for insulin resistance; however, it is not a diagnostic marker of IFG or IGT. Second, measurement of hemoglobin A1c (HbA1c) along with glucose level is a better validated tool than measuring GDF15 for the diagnosis of prediabetes. What is the strength of GDF15 in the diagnosis of IFG compared with HbA1c? The area under the receiver operating characteristic curve of GDF15 for detection of IFG was less than 0.7 in Hong's study [11], which implied GDF15 is not a useful diagnostic marker for IFG [17].

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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