Effects of Age, Diabetes, and Vascular Disease on Growth Differentiation Factor 11: First-in-Human Study

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Growth differentiation factor 11 (GDF11), a member of the transforming growth factor-β superfamily, has been recently described as a soluble rejuvenation factor for the heart, muscle, and brain. In fact, GDF11 declines in aged mice, while its replenishment improves vascular, brain, muscle, and cardiac function (1–3). As type 2 diabetes (T2D) increases with age and is characterized by accelerated aging (4), we cross-sectionally explored the effects of age, diabetes, and vascular disease on plasma GDF11 concentrations. The study was approved by the local ethics committee and conducted in accordance with the principles of the Declaration of Helsinki. Plasma GDF11 concentrations were measured by ELISA (MBS2502734, MyBioSource) in a previously described cohort of T2D patients and age- and sex-matched control subjects without diabetes (5). As the distribution of GDF11 concentrations was skewed, it was log-transformed before statistical analyses. On average, plasma GDF11 concentrations were higher in T2D patients than in control subjects (1,065 ± 401 vs. 168 ± 62; $P = 0.030$) (Fig. 1*A*), and this difference was exclusively attributable to the very high GDF11 levels in T2D patients with macroangiopathy (Fig. 1*B*). The association between macroangiopathy and GDF11 levels in the T2D group remained significant after adjusting for use of statin and drugs active on the renin-angiotensin system (not shown). Plasma GDF11 was not associated with diabetic microangiopathy (Fig. 1*C*). In control subjects, GDF11 concentrations declined with age ($r = -0.50$; $P = 0.0013$), while there was no correlation between age and GDF11 in T2D patients ($r = 0.03$; $P = 0.865$). The Fisher transformation test showed that the coefficients of correlation between age and GDF11 were significantly different in the two groups ($z = 2.43 \pm 0.24$; $P = 0.015$). After exclusion of patients with macroangiopathy, this difference was amplified (control subjects: $r = -0.64$, $P < 0.0001$; T2D patients: $r = -0.04$, $P = 0.82$; $z = 2.68 \pm 0.28$, $P = 0.007$). GDF11 was not correlated with HbA_{1c}, diabetes duration, or concentrations of interleukin-6 or tumor necrosis factor-α.

Our data show for the first time that plasma GDF11 concentrations progressively decline with age in individuals without diabetes, especially when free from cardiovascular disease. Intriguingly, this correlation was completely lost in T2D patients, and patients with diabetic macroangiopathy had markedly increased levels of plasma GDF11. Though GDF11 is being explored as a target of antiaging therapies, our data provide a note of caution. The reasons whereby GDF11 concentrations did not decline with age in T2D patients and markedly increased in those with cardiovascular disease are presently unclear. These findings may reflect that accelerated aging and vascular disease in T2D occur through "nonphysiological" aging pathways. In fact, GDF11 was able to prevent cardiac hypertrophy induced by age but not by pressure overload (3). Differently from mice, humans rarely age without diseases, such as diabetes, hypertension, heart, lung, and kidney disease. Therefore, regulators of GDF11 in these conditions need to be explored. We acknowledge that the current study is very small. Nonetheless, patients were well characterized and matched, and results are statistically robust. In addition, this is the very first investigation of GDF11 concentrations in humans and the first evidence that GDF11 declines with normal aging. Unfortunately, aging in the diabetic milieu might not benefit from therapies targeting normal aging pathways.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.
Author Contributions. G.P.F. designed the study, researched and analyzed data, and wrote the manuscript. L.M., B.M.B., M.M., S.P., and S.V.d.K. researched and analyzed data. A.A. contributed to discussion and supervised the project. G.P.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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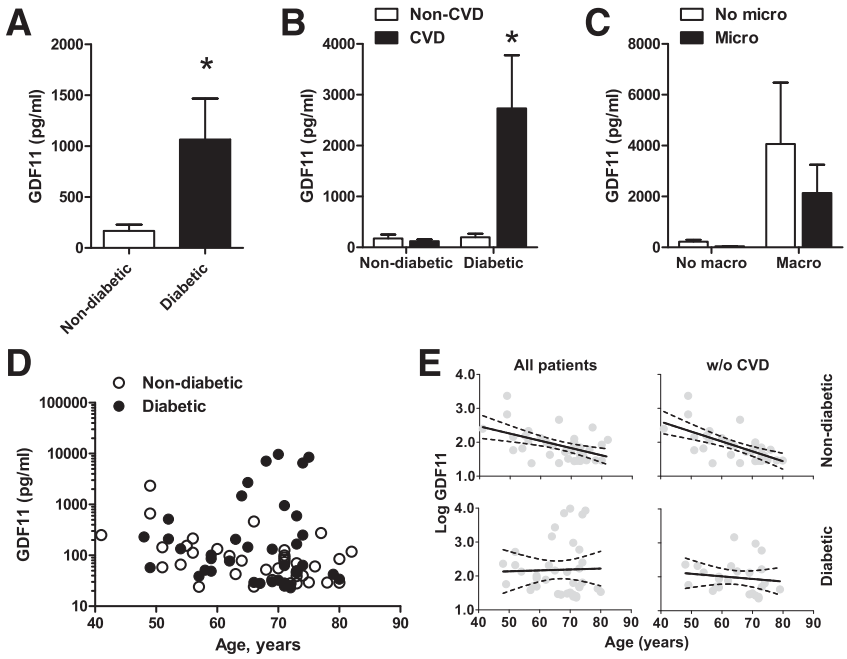

Figure 1—*A*: Plasma GDF11 levels in individuals with vs. without diabetes (*$P < 0.05$). *B*: Plasma GDF11 levels according to the presence or absence of diabetes and cardiovascular disease (CVD) or macroangiopathy (*$P < 0.05$ vs. nondiabetic and vs. non-CVD). *C*: Plasma GDF11 levels in patients with diabetes divided according to the presence of micro- and/or macroangiopathy. *D*: Linear correlation between log plasma GDF11 and age in individuals with (black circles) and without (white circles) diabetes. *E*: Linear correlations between age and log plasma GDF11 levels in all individuals with and without diabetes (left panels) or after excluding those individuals with CVD (right panels). Dashed lines indicate the 95% CI of the solid regression line.

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