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Associations between metabolic dysregulation and circulating biomarkers of fibrosis: the Cardiovascular Health Study

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ABSTRACT

Aim. Fibrosis is one postulated pathway by which diabetes produces cardiac and other systemic complications. Our aim was to determine which metabolic parameters are associated with circulating fibrosis-related biomarkers transforming growth factor-β (TGF-β) and procollagen type III N-terminal propeptide (PIIINP).

Methods. We used linear regression to determine the cross-sectional associations of diverse metabolic parameters, including fasting glucose, fasting insulin, body mass index, fatty acid binding protein 4, and non-esterified fatty acids, with circulating levels of TGF-β (n = 1559) and PIIINP (n = 3024) among community-living older adults in the Cardiovascular Health Study.

Abbreviations: TGF-β, transforming growth factor-β; PIIINP, procollagen type III N-terminal propeptide; DAG-PKC, diacylglycerol-protein kinase C; BMI, body mass index; FABP-4, fatty acid binding protein 4; NEFA, non-esterified fatty acids; CHS, Cardiovascular Health Study; ISI, insulin sensitivity index; CML, carboxymethyl lysine; OGTT, oral glucose tolerance test; ELISA, enzyme-linked immunosorbent assay; CV, coefficient of variation; SBP, systolic blood pressure; CRP, c-reactive protein; eGFR, estimated glomerular filtration rate; NHLBI, National Heart, Lung, and Blood Institute; NINDS, National Institute of Neurological Disorders and Stroke; NIA, National Institute on Aging.

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Results. Among the main metabolic parameters we examined, only fasting glucose was associated with TGF-β ($P = 0.03$). In contrast, multiple metabolic parameters were associated with PIIINP, including fasting insulin, body mass index, and non-esterified fatty acids ($P<0.001$, $P<0.001$, $P=0.001$, respectively). These associations remained statistically significant after mutual adjustment, except the association between BMI and PIIINP.

Conclusions. Isolated hyperglycemia is associated with higher serum concentrations of TGF-β, while a broader phenotype of insulin resistance is associated with higher serum PIIINP. Whether simultaneous pharmacologic targeting of these two metabolic phenotypes can synergistically reduce the risk of cardiac and other manifestations of fibrosis remains to be determined.

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1. Introduction

Emerging evidence suggests that fibrosis may play a role in mediating the association between diabetes and cardiovascular disease [1,2]. In *in vitro* models, high glucose concentrations have been shown to activate the diacylglycerol-protein kinase C (DAG-PKC) pathway [3]. This pathway stimulates the production of pro-fibrotic matrix cytokines such as transforming growth factor-β (TGF-β), and the downstream release of collagen byproducts such as procollagen type III N-terminal propeptide (PIIINP). TGF-β and PIIINP are novel and complementary biomarkers of fibrosis [4–6] that have been independently associated with risk of incident heart failure, myocardial infarction, and stroke in multiple large, community-based cohorts [7–10]. In humans, TGF-β levels are elevated in diabetes compared to normoglycemia [11]. Whether this elevation is due to hyperglycemia *per se* or other correlates of metabolic dysregulation is unknown.

Knowledge of the specific metabolic parameters associated with fibrosis could enable a targeted approach to prevent vascular and myocardial fibrosis. To our knowledge, no studies have examined whether metabolic parameters other than hyperglycemia are associated with TGF-β. Two studies, both conducted in middle-aged populations, have attempted to establish the specific metabolic parameters associated with PIIINP [12,13]; however, the first [12] was conducted in a relatively small cohort of 160 individuals, and the second [13] was conducted without in-depth, fasting and post-challenge measurements of metabolic disturbance. Neither study included a second, complementary biomarker of fibrosis such as TGF-β.

The aim of this study was to determine the cross-sectional associations of diverse indicators of metabolic disturbance, including diabetes status, fasting glucose, fasting insulin, body mass index (BMI), fatty acid binding protein 4 (FABP4), and non-esterified fatty acids (NEFA), with circulating levels of TGF-β and PIIINP among community-living older adults in the Cardiovascular Health Study (CHS). In the subset of our cohort in which measurements were available, we additionally assessed the associations of 2-hour glucose and insulin, Gutt insulin sensitivity index (ISI), and carboxymethyl lysine (CML; a marker of advanced glycated end products) with TGF-β and PIIINP.

2. Methods

2.1. Study Design

The design, rationale and details of the examinations in CHS have previously been published [14]. In brief, 5201 participants were recruited in 1989–1990 from Medicare eligibility lists in four US communities: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. A supplemental cohort of 687 mostly African-American participants was added in 1992–1993 and is also included in this analysis. Eligible individuals were at least 65 years old, living in the community, and expected to remain in that community for at least three years after baseline. Individuals were excluded if they were under active cancer treatment or unable to provide written informed consent. Follow-up interviews to ascertain incident events were conducted at annual study visits through 1998–1999. All participants in our study provided written informed consent, and the institutional review board at each center approved the study protocol.

2.2. Exposure Assessment

We collected serum samples at the 1996–1997 visit after an 8–12 hour overnight fast, and again 2 hours after a 75-g oral glucose tolerance test (OGTT) [15]. Fasting and 2-hour glucose were measured with a standard clinical chemistry analyzer (Eastman Kodak, Rochester, NY). Fasting and 2-hour insulin were measured by competitive radioimmunoassay (Diagnostic Products Corporation, Malvern, PA) [16]. We defined impaired fasting glucose as fasting glucose 100–125 mg/dL, and diabetes as fasting glucose ≥ 126 mg/dL or use of insulin or oral hypoglycemic medications. We calculated the Gutt ISI ($mg{\cdot}L^2/mmol{\cdot}mU{\cdot}min$) as $\textit{insulin sensitivity} = m/(G \times I)$, where m is a measure of glucose uptake during the OGTT calculated from body weight and fasting and 2-hour glucose, G is the mean of fasting and 2-hour glucose, and I is a $\log_{10}$ transformation of the mean of fasting and 2-hour insulin [17]. We used technician-measured height and weight from the 1996–1997 visit to calculate BMI (the weight in kilograms divided by the square of the height in meters). CML was measured from 1996–1997 serum samples using a photometric enzyme-linked immunosorbent assay (ELISA) (Microcoat, Penzberg, Germany) [18]. Because 1996–1997 data were unavailable, we measured plasma FABP4 and NEFA from plasma collected at the 1992–1993 visit. FABP4 concentration was measured using ELISA (Biovendor ELISA); NEFA concentration was measured by the Wako enzymatic method [19].

2.3. Outcome Assessment

TGF-β and PIIINP were measured from stored 1996–1997 EDTA plasma samples in 2011–2012. TFG-β was measured by ELISA (Quantikine Human TGF-β1 Immunoassay; R&D Systems,

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