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Editorial

Fibroblast growth factor-21 levels in metabolic syndrome: Another instrument in a widening tool belt?

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The metabolic syndrome (MetS) is a clustering of metabolic abnormalities including insulin resistance, obesity, atherogenic dyslipoproteinemia, elevated blood pressure, and abnormal glucose [1]. Patients with the MetS are at increased risk for developing diabetes, cardiovascular disease and mortality [2,3]. MetS has become increasingly prevalent, more so because of the global obesity epidemic [4,5]. Hence, studies that identify biomarkers that associate with the development of MetS may be potential risk markers or therapeutic targets not only for MetS and obesity but also for cardiovascular disease.

One such novel endocrine biomarker, fibroblast growth factor-21 (FGF-21), a member of the fibroblast growth factor family, is a 210-aminoacid containing polypeptide protein that is mainly expressed in the liver [6] and to a lesser extent in skeletal muscle [7], adipocytes, and beta cells [8]. It is a metabolic hormone with beneficial effects on glucose, lipid, and energy homeostasis in humans and animals. Prior studies, done mostly in racially homogenous human populations, have found significant associations for FGF-21 with the MetS and associated disorders including diabetes mellitus, renal progression in diabetes [3], and coronary artery disease. No previous studies have prospectively examined this relationship in a large, racially and ethnically diverse population as was done in the study by Ong et al. in this issue of *Atherosclerosis* [20].

In genetically engineered mice, Kharitonenkov et al. identified FGF-21 as a regulator of insulin-independent glucose uptake in adipocytes, lowering triglycerides and protecting against diet-induced obesity [9]. Overexpression of this protein in transgenic vs. control mice improved metabolic profiles in terms of weight, glucose clearance, increased brown adipose tissue and insulin sensitivity [9]. Subsequently, recombinant FGF-21 administration in diabetic rhesus monkeys significantly improved lipoprotein and glycemic indices without inducing hypoglycemia [10]. FGF-21 also improves pancreatic β-cell function by activating extracellular response kinase 1/2 and Akt signaling pathways [7,8]. Interestingly, the beneficial metabolic effects of FGF-21 in mice are dependent on adiponectin [11]. In addition, FGF-21 is a key downstream target for peroxisome proliferator-activated receptor alpha (PPARα)- a regulator of energy homeostasis, and may partially mediate the metabolic benefit of PPARα agonists [12].

Paradoxically, serum FGF-21 levels are often elevated in obesity-related conditions such as the MetS and diabetes mellitus. It is unclear whether this is a compensatory response or a state of relative resistance as seen in hyperinsulinemia and hyperleptinemia. Adipose tissue contributes to the elevation of serum FGF-21 levels in obese individuals, and hence FGF-21 is an adipokine. Prior studies found that elevated FGF-21 levels associated with increased risk of MetS independent of important factors such as age and MetS components. However, these prior studies were mostly cross-sectional and done in small, racially homogenous populations [12–16]. In a study of 232 Chinese individuals, FGF-21 was markedly increased in patients with overweight/obesity or MetS and associated with adverse cardiometabolic factors independent of BMI [12]. A corollary study examining FGF-21 mRNA expression in the adipose tissue of 29 Chinese women found correlation between mRNA expression in adipose tissue and serum protein concentration [12]. Another prospective cohort study done in white adults found significant association of FGF-21 with incident MetS [17]. Yet another study showed genetic linkage between FGF-21 and MetS [18].

More recently, in a longitudinal one-year follow up study of obese children who participated in a lifestyle weight loss intervention, serum FGF-21 concentrations significantly correlated with BMI but not MetS [19]. However, FGF-21 serum concentrations reversibly decreased with weight loss in this study, which suggests a compensatory upregulation of FGF-21 in obesity-related disorders.

In a broader approach, Ong et al. investigated the longitudinal relationship of FGF-21 and MetS in a prospective U.S. multi-ethnic cohort over a longer follow-up period of 9.2 years [20]. In a total of 5783 participants from the Multi-Ethnic Study of Atherosclerosis, FGF-21 levels were positively associated with both prevalent and incident

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MetS, with adjusted odds ratios of 2.80 (2.30–3.40) for the top vs. bottom quartile FGF-21 levels for prevalent MetS, and 1.76 (1.42–2.12) for incident MetS. Furthermore, while there were no significant interactions with race/ethnic groups for this association, risk prediction beyond standard risk factors for MetS was improved with the addition of FGF-21 amongst two specific ethnic groups (non-Hispanic White and Chinese Americans). Another interesting finding was that FGF-21 did not predict the development of hyperglycemia in the prospective analysis, which deserves further investigation in future studies.

The strength of this study lies in its large sample size, long follow-up period, generalizability to a broad population, and detailed phenotyping of various biomarkers of risk. In their elegant analysis, the authors were also able to delineate the metabolic risk of FGF-21 from concomitant cardiovascular risk factors, including biomarkers of inflammation and nonalcoholic fatty liver disease. While it is possible that single measurements of FGF-21 and a one-time diagnosis of a reversible syndrome such as MetS could cause misclassification bias, such misclassification would not change the study conclusions.

In summary, this well-designed and timely study suggests that FGF-21 should be investigated further as a promising diagnostic or potentially therapeutic target for cardiometabolic and obesity-related diseases.

Conflict of interest

Dr. Ajala has no disclosures.

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Oluremi Ajala
Center for Lipid Metabolomics, Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Samia Mora*
Center for Lipid Metabolomics, Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
E-mail address: smora@bwh.harvard.edu.

* Corresponding author. Center for Lipid Metabolomics, 900 Commonwealth Avenue E, Boston, MA, 02215, USA.