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Research Paper

Circulating levels of fibroblast growth factor-21 increase with age independently of body composition indices among healthy individuals

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ABSTRACT

Background: Circulating FGF21 levels are commonly elevated in disease states. There is limited information regarding concentrations of circulating FGF21 in the absence of disease, as well as age-related differences in body composition that may contribute to FGF21 regulation across groups.
Objective: The objectives of this study were to assess FGF21 levels across age groups (childhood to elder adulthood), and investigate whether body composition indices are associated with age-related differences in circulating FGF21.
Materials and methods: We cross-sectionally analyzed serum concentrations of FGF21 in 184 healthy subjects aged 5–80 y (45% male). Multiple linear regression was performed to assess the independent association of categorical age (children: 5–12 y, young adults: 20–29 y, adults: 30–50 y, older adults: 55–64 y, elder adults: 65–80 y) with FGF21 concentration taking into account DXA-measured body composition indices [bone mineral density (BMD) and percent lean, trunk, and fat mass]. We also stratified analysis by tertile of FGF21.
Results: Incremental increases in FGF21 levels were observed across age groups (youngest to highest). Age group was positively associated with FGF21 level independent of body composition indices (age group variable: $\beta = 0.25, 0.24, 0.24, 0.23$, all $P < 0.0001$, controlling for percent lean, BMD, percent fat, and percent trunk fat, respectively). By FGF21 tertile, age group was associated with FGF21 in the lowest tertile only ($\beta = 13.1, 0.19, 0.18$, all $P \leq 0.01$, accounting for percent lean, fat and trunk fat, respectively), but not when accounting for BMD.
Conclusions: Our findings in a healthy population display an age-related increase in serum FGF21, highlighting a potential age effect in response to metabolic demand over the lifecourse. FGF21 levels increase with age independently of body composition. At lower levels of FGF21, BMD, but not other body composition parameters, attenuates the association between FGF21 level and age, suggesting the metabolic demand of the skeleton may provide a link between FGF21 and energy metabolism.

Abbreviations: FGF-21, Fibroblast growth factor 21; BMD, bone mineral density; BMI, body mass index; DXA, dual-energy x-ray absorptiometry; ELISA, enzyme-linked immunosorbent assay; CV, coefficient of variation.

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Introduction

Fibroblast growth factor 21 (FGF21) has garnered significant interest in recent years, given its emerging role in intermediary metabolism involving glucose and lipid utilization. FGF21 is released into the circulation from the liver, adipose tissue, and skeletal muscle where it is involved in adaptations to energy demand across tissues. FGF21 expression by the liver and adipose tissue is largely controlled by peroxisome proliferator activated receptor (PPAR) α and λ, respectively [1,2], and in skeletal muscle by the insulin/Akt pathway [1]. An insulin-signaling pathway-dependent mechanism has been suggested to be the primary action in skeletal muscle [1], and in adipose tissue, an insulin-independent mechanism promotes glucose uptake by enhancing the expression of GLUT1 [3]. The metabolic effects of FGF21 in adipocytes are also mediated by β-Klotho, a single-pass transmembrane protein induced during adipogenesis [4]. FGF21 has been shown to improve pancreatic β-cell function and survival by activation of extracellular signal-regulated kinase 1/2 and Akt signaling pathways [5]. In the liver, down-regulation of FGF21 leads to fatty liver, dyslipidemia, and reduced serum ketones due to the altered expression of key genes involved in hepatic lipid and ketone metabolism, potentially linking FGF21 to metabolic disease [6]. Moreover, increased production of FGF21 in transgenic mice has been associated with body weight maintenance and longevity [7]. These findings in animal-based studies suggest FGF21 is a potent metabolic regulator with beneficial independent effects on glucose, lipid and overall energy metabolism. However, the extent to which metabolic regulation by FGF21 is modified with aging has not been explored.

Changes in accumulation, degeneration and metabolic activity of various body tissues, well-accepted as part of the aging process, may affect synthesis and release of FGF21. Adipocytes have been shown to be an important source of FGF21 production, whereas the liver has been previously considered as the main source of FGF21 in circulation [8]. More recently, skeletal muscle expression and secretion of FGF21 have been shown to lead to a fivefold increase in circulating FGF21 concentration [9]. Because the aging process is associated with reciprocal modification of body composition – adiposity increases, muscle mass decreases, in general – the synthesis and secretion of FGF21 by these tissues into the circulation may change concomitant to age-related alterations in body composition.

In humans, serum FGF21 concentrations appear to vary between individuals and across age groups, but to-date there is no single dataset across age groups. In separate studies, higher circulating values have been reported in adults compared to children, but an underlying explanation has not been elucidated. Further, values have been reported to vary widely (e.g., 250-fold) among healthy normal-weight adults ages 20–80 y, ranging from 21 to 5300 pg/ml [10]. While less studied in children, a recent investigation in a healthy, non-obese pediatric Danish cohort, including subjects ages 8–16 y, reported a range from below level of detection (30 pg/ml) to 1715.1 pg/ml [11]. To our knowledge no studies have examined FGF21 across age groups in healthy individuals. Thus, the two-fold objective of this study was to assess fasting FGF21 concentrations across age groups, ranging from 5 to 70 y, and to assess whether body composition indices (fat, lean or bone mass) may account for any age-related differences.

Materials and methods

Subjects

Fasting blood samples were obtained from the compilation of several pediatric and two adult studies conducted at University of Alabama at Birmingham (UAB). Specific study inclusion criteria have been published elsewhere for pediatric [12–15] and adult cohorts [16,17]. While the cited studies include interventional components, the current investigation is limited to cross-sectional analyses of baseline data for all participants. For each of these studies, subjects were recruited using newspaper advertisements, posted flyers, by word-of-mouth and through local radio advertisements. All measurements were performed at the Clinical Research Unit (CRU), UAB Center for Exercise Medicine and the Human Physiology Core at UAB. All study protocols were approved by the Institutional Review Boards (IRBs) of UAB and/or the Birmingham Veterans Affairs Medical Center, and all subjects provided written, informed consent and assent (where appropriate) prior to participation to utilize samples collected for future research.

Children/adolescents

The pediatric population included participants enrolled in a variety of clinical studies conducted at UAB investigating metabolic changes during growth and maturation [12–15]. The total pediatric sample included 69 healthy children ages 5–12 y (Tanner stage < 4), who underwent DXA scans and fasting morning venipuncture over the period of 2009–2014. Exclusionary criteria for each of the studies were medical diagnoses and/or current use of medications known to affect body composition, lipid or glucose metabolism, or blood pressure (e.g., diabetes; impaired fasting glucose; use of thyroid medication, diuretics, beta-blockers, thiazolidinediones, etc.); an allergy to lidocaine (used for topical anesthesia prior to venipuncture in study participants); and history of an eating disorder(s). The study physician conducted an overall health assessment for each of the participants to rule out medical diagnoses.

Adults

The de-identified data and samples from adults $20–80^{+}$ yr derived from fasting morning venipuncture encompassing the baseline assessments in one of two studies [16,17]. For each of these studies, subjects were free of any musculoskeletal or other disorders that could potentially affect their ability to complete testing. Subjects were non-obese (BMI < 30) and none of the participants were treated with pharmacological interventions thought to influence body composition or glucose metabolism.

Body composition and fat distribution

Body composition indices [percent lean mass, bone mineral density (BMD), total percent fat mass, and percent trunk fat] were determined using dual energy x-ray absorptiometry (DXA) scans (GE Lunar Corporation, Madison, WI, USA) and encore 2002 software (version 6.10.029) according to manufacturer's instructions (pediatric version where appropriate). Subjects were scanned in light clothing, lying flat on their back with arms at their sides.

Serum assay

For all participants, blood was drawn in the morning after an overnight fast. Serum concentrations of FGF21 were measured using a commercially-available, enzyme-linked immunosorbent assay (ELISA; Millipore Corporation, Billerica, MA). All samples were processed immediately upon completion of blood draw to extract serum samples and subsequently stored at -80° until measurement of the analytes of interest in batched assays in accordance with assay specifications. The inter-assay coefficient of variation (CV) was $<11\%$ and intra-assay CV was $<5\%$. The minimum sensitivity was 31.3 pg/ml. Four participants (all children)