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Attenuated fibroblast growth factor 21 response to acute aerobic exercise in obese individuals

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Abstract *Background and aim:* Fibroblast growth factor 21 (FGF21) is positively associated with body mass index, potentially as a compensatory mechanism to mediate obesity related metabolic and inflammatory insult due to chronic low-grade elevations of the pro-inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α). Therefore, FGF21 response in obese subjects and the associations with increased pro-inflammatory cytokines, insulin resistance, and energy utilization warrants investigation.
Methods and results: Twenty four untrained subjects (12 obese and 12 normal-weight) performed 30 min of continuous submaximal aerobic exercise. Following exercise, obese subjects exhibited a blunted FGF21 response to exercise compared to normal-weight subjects as indicated by area-under-the-curves "with respect to increase" (AUCi) analyses ($p = 0.005$). Furthermore, while exercise-induced plasma FGF21 was not associated with any inflammatory cytokine (IL-6 and TNF-α) response, FGF21 AUCi was positively correlated with glucose AUCi ($r = 0.495$, $p = 0.014$), total relative energy expenditure ($r = 0.562$, $p = 0.004$), and relative maximal oxygen consumption (VO_{2max}; $r = 0.646$, $p = 0.001$) in all subjects.
Conclusion: Impaired cardiorespiratory fitness may influence the sensitivity of FGF21 response to acute exercise in obese individuals, potentially contributing to the attenuated metabolic response (e.g., glucose) and total exercise energy expenditure. Therefore, exercise training aimed at improving cardiorespiratory fitness and/or body composition may augment cardioprotective properties against obesity-associated CVD through enhanced FGF21 flux.

Introduction

In the United States, obesity is reaching epidemic proportions as adult prevalence rates are currently 34.9% [1]. Obesity is characterized as a low grade, chronic inflammatory state significantly increasing the risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2D) [2,3]. These obesity-associated illnesses are marked by elevated levels of pro-inflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [4] through the migration of blood monocytes into white adipose tissue as classically activated (M1), macrophages [5]. Therefore, the identification of possible

Abbreviations: AUCi, area-under-the-curve with respect to increase; BMI, body mass index; CVD, cardiovascular disease; FFA, free fatty acids; FGF21, fibroblast growth factor 21; HOMA-IR, homeostasis model assessment estimate of insulin resistance; IL-6, interleukin-6; IR, insulin resistance; REE, relative energy expenditure; TNF-α, tumor necrosis factor alpha; T2D, type 2 diabetes mellitus; VO_{2max}, cardiorespiratory fitness levels.

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mediators contributing to obesity-associated inflammation is essential for early detection, prevention, and treatment of chronic inflammatory diseases.

Fibroblast growth factor 21 (FGF21) is a member of the fibroblast growth factor superfamily expressed by hepatocytes, adipocytes, and skeletal muscle [6]. Circulating FGF21 concentrations are positively associated with body mass index (BMI) [7] and elevated in patients with T2D [8], potentially as a compensatory mechanism to mediate obesity related metabolic and inflammatory insult [9,10]. For example, plasma FGF21 concentrations as well as skeletal muscle mRNA expression were increased following 3–4 h of insulin infusion [10]. Increased FGF21 expression in adipose tissue and skeletal muscle also serves as an acute phase response in mice, protecting cells from inflammatory stimuli such as lipopolysaccharide [9]. Furthermore, infusion of FGF21 has been shown to decrease pro-inflammatory cytokine production via the inhibition of NF-κB in human myotubes [11]. However, the exact role of FGF21 in mediating an anti-inflammatory response still remains unknown.

Aerobic exercise training has been shown to decrease the risk of chronic inflammatory diseases [12]. For example, Steensberg et al. [13] found an elevation in plasma IL-6 concentrations following acute intense exercise in young healthy subjects. This exercise-induced IL-6 production has been found to be exacerbated in obese compared to normal-weight individuals [14]. However, it is important to note that elevated concentrations of IL-6 following exercise may also act as an anti-inflammatory mediator. In a follow-up study, Steensberg et al. [15] infused IL-6 to attain intense exercise-induced concentrations in human subjects and found an elevation in the anti-inflammatory cytokine IL-10 after 1 h of IL-6 infusion. Collectively, these findings suggest that an elevation in circulating IL-6 following exercise may initiate a reciprocal anti-inflammatory response that can promote recovery.

Interestingly, recent studies have shown that exercise training up to 3 months decreased circulating FGF21 concentrations in overweight and obese individuals [16,17]. In response to acute exercise, elevations in circulating FGF21 concentrations have been demonstrated in an intensity-dependent manner up to 4 h into recovery in normal-weight subjects [6,18]. While FGF21 may act as a metabolic regulator controlling glucose uptake [11], obese individuals are more resistant to FGF21 fluctuations postprandially as well as during periods of negative energy balance compared to normal-weight individuals [19]. Given these findings, it remains unclear whether acute exercise would elicit an elevation in circulating FGF21, thus contributing to the regulation of inflammatory responses, insulin resistance (IR), and substrate utilization in obese individuals compared to those of normal-weight.

Therefore, the primary objective of this study was to examine the effect of acute intense exercise on plasma FGF21 response and its relationships with inflammatory cytokines (IL-6 and TNF-α), IR, and energy utilization in obese and normal-weight subjects. We hypothesized that following acute exercise, plasma FGF21 response in obese subjects would be attenuated compared to normal-weight subjects, accompanied by an exacerbated elevation in plasma IL-6, impaired improvement in IR, as well as substrate utilization.

Methods

Subjects

Twenty four untrained subjects (12 obese [5 males; 7 female] and 12 normal-weight [6 male; 6 female]) aged 18–35 participated in the study. Previous studies have demonstrated that FGF21 concentrations do not differ between males and females [20] and that female sex hormones do not influence FGF21 concentrations [21]. Subjects with a BMI above 30 kg/m^2 were classified as obese, and those with a BMI between 18.5 and 24.9 kg/m^2 were classified as normal-weight. The study was approved by Florida Atlantic University's Institutional Review Board and all subjects provided informed written consent, completed a medical history questionnaire prior to participation. To limit the effect of training on physiological response to acute exercise, those who reported more than 150 min of moderate and high physical activity levels per week as determined by a 7-day physical activity recall questionnaire were excluded from participation.

Subjects were excluded from participation if they possessed any known inflammatory diseases/conditions, were under current administration of medication that may influence inflammatory or metabolic processes, and/or were currently pregnant or nursing. Subjects were also excluded from the study if they were users of tobacco products or if they consumed an average of ten or more alcoholic beverages per week. Subjects were instructed to undergo an 8 h overnight fast and to abstain from alcohol, caffeine intake, and intense physical activity 24 h prior to each laboratory visit.

Procedures

Subjects arrived at the laboratory between 7:00 and 9:00 on the morning of the testing sessions. Session one consisted of completion of informed consent following full explanation of the research and familiarization with testing procedures. A maximal graded exercise test on a treadmill to assess maximal oxygen consumption (VO_{2max}) was then administered beginning with a 3 min warm-up at 3 mph with 0% grade. Speed was subsequently increased to elicit 80% ± 5 bpm of the subject's age predicted maximal heart rate (HR). After 4 min, grade was increased 2% every 2 min while speed remained constant until voluntary exhaustion resulted within 12–15 min. Criteria for attaining VO_{2max} included attainment of two of the following criteria: a plateau in O_2 consumption (defined as a failure to increase oxygen uptake by 150 ml/min with increased workload), respiratory exchange ratio ≥1.15, HR within 10 bpm of subject's age-predicted maximum heart rate (220-age), and a rating of perceived exertion ≥19.