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Original article

FGF19 and FGF21 serum concentrations in human obesity and type 2 diabetes behave differently after diet- or surgically-induced weight loss

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SUMMARY

Background & aims: Fibroblast growth factor 19 (FGF19) and 21 (FGF21) have emerged as key regulators of energy homeostasis. Our aim was to analyze the impact of weight loss (WL) induced either by conventional dietary treatment (CDT) or bariatric surgery on FGF19 and FGF21 concentrations. Furthermore, the diverse effect of sleeve gastrectomy (SG) versus RYGB (Roux-en-Y gastric bypass) as two surgical procedures that affect the gastrointestinal anatomy and physiology differently was also analyzed.
Methods: Serum concentrations of FGF19 and FGF21 were measured in 137 obese patients with different degrees of insulin resistance matched by sex, age and body adiposity and compared to 33 lean individuals. Furthermore, FGF19 and FGF21 were measured in 114 subjects before and one-year after WL induced either by CDT (n = 28), SG (n = 20) or RYGB (n = 66).
Results: Circulating serum FGF19 concentrations were decreased ($P < 0.01$) similarly in obese patients regardless of their degree of insulin resistance, while FGF21 levels were increased in obesity ($P < 0.01$), being further increased in obesity-associated T2D ($P < 0.01$). FGF19 concentrations were increased in obese subjects after surgically-induced WL ($P < 0.01$), but not after WL achieved by CDT, while FGF21 levels were reduced after CDT- ($P < 0.05$) or SG-induced WL ($P < 0.05$), but not after RYGB. The change in FGF21 concentrations emerged as a significant predictor of the change in insulin resistance (HOMA) after WL.
Conclusions: Based on the circulating concentrations and their subsequent pattern of response following WL, we conclude that FGF19 levels are mainly related to body adiposity, in particular visceral adiposity, while FGF21 is mainly related to glucose homeostasis.
ClinicalTrials.gov identifier: NCT01572090.

1. Introduction

Obesity prevalence is increasing alarmingly threatening the health advances achieved in the last decades [1]. Obesity favors the clustering of cardiometabolic alterations such as type 2 diabetes mellitus (T2D), cardiovascular alterations, nonalcoholic fatty liver

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disease (NAFLD) and dyslipidemia leading to an increase in morbidity and mortality in relation to excess adiposity [2].

Fibroblast growth factors (FGFs) constitute a family of proteins comprising at least 22 members involved in the regulation of cell growth and differentiation, development, angiogenesis, wound repair and metabolism [3]. Most FGFs are secreted heparin-binding proteins and function as autocrine or paracrine factors, while FGF19, FGF21 and FGF23 exhibit common unique structural properties which confer them the ability to elicit endocrine actions functioning as hormones [3]. FGF23 regulates phosphate/vitamin D metabolism in a bone-kidney crosstalk. FGF19 is an ileum-derived enterokine that controls bile acid and nutrient metabolism. FGF19 has been reported to play a role in the regulation of glucose and lipid metabolism, as well as in energy expenditure and body adiposity [3,4]. FGF21 is produced mainly in the liver and promotes fatty acid oxidation, improves insulin sensitivity and increases energy expenditure [3,4]. FGF21 is paradoxically increased in obesity, suggesting that obesity is a FGF21-resistant state [5]. Both FGF19 and FGF21 have been involved in the etiopathology of obesity and T2D representing potential therapeutic targets for the treatment of these metabolic diseases [3].

The first therapeutic approach in obese patients is to reduce body adiposity through a decrease in caloric intake and an increase in energy expenditure by lifestyle modification [1]. Weight loss (WL) is associated with an improvement in obesity-associated comorbidities, even if the loss is modest. Bariatric/metabolic surgery is the most effective strategy for achieving significant and sustainable long-term WL in severe obesity, resolving or improving T2D, decreasing cardiovascular events and reducing mortality [6]. Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are the most performed surgical techniques nowadays, substantially improving obesity-associated comorbidities as well as extending life expectancy [6,7].

Studies aimed to analyze the impact of WL on FGF19 and FGF21 in humans are scarce and none of them has compared the different impact of diet-versus surgery-induced WL and the different effect on these hormones of SG and RYGB, two surgical procedures that affect the gastrointestinal anatomy and physiology in diverse ways. Therefore, the aim of the present study was to analyze the impact of WL induced by either conventional dietary treatment or bariatric surgery on FGF19 and FGF21 concentrations. Furthermore, the different effect of SG versus RYGB was also explored.

2. Methods

2.1. Study design

In order to analyze the effect of obesity and T2D on FGF19 and FGF21 concentrations 170 Caucasian subjects [33 lean (LN) and 137 obese (OB), 47% female] aged 43 ± 11 y (18–74 y), were recruited from healthy volunteers and patients attending the Endocrinology & Nutrition and Surgery Departments at the Clínica Universidad de Navarra, Pamplona and the Department of Medicine at the Hospital de la Santa Creu i Sant Pau, Barcelona. Subjects were classified according to body mass index (BMI) (lean < 25 kg/m^2; and obese ≥ 30 kg/m^2). All participants were weight-stable (±2 kg) for the previous 3 months. Patients with signs of acute inflammation or taking any drug potentially influencing insulin production were excluded. Glucose intolerance or T2D of obese subjects was of recent-onset being diagnosed at the baseline visit. Normoglycemia (OB-NG, n = 71), impaired glucose tolerance (IGT, OB-IGT n = 35) and T2D (OB-T2D, n = 31) in obese patients were defined as previously described [8,9] based on both fasting plasma glucose concentrations and plasma glucose 2 h after an oral glucose tolerance test (OGTT). The experimental design was approved by the Hospitals' Ethical Committees responsible for research. Informed consent was obtained from all individual participants included in the study.

In addition, a group of 114 obese Caucasian patients (56 males and 58 females) aged 45 ± 12 y (range 18–74 y) was selected to investigate the effect of WL on circulating concentrations of FGF19 and FGF21 in an interventional, nonrandomized, open-labeled clinical trial (ClinicalTrials.gov identifier: NCT01572090). Participants were recruited from patients attending the Departments of Endocrinology & Nutrition, and Surgery at the Clínica Universidad de Navarra. The WL was achieved either by bariatric surgery (SG, n = 20 or RYGB, n = 66) or by prescription of a diet (n = 28). Surgical procedures were performed by the same surgeon and multidisciplinary team. Patients were prescribed oral vitamin and micronutrient supplements to compensate for their possible reduced intake and absorption. Conventional dietary treatments consisted of an individualized dietary regime prescribed by a physician in collaboration with a dietitian with planned regular follow-up visits to ensure a daily caloric deficit of 500–1000 kcal/d as estimated from the measurement of the resting energy expenditure by indirect calorimetry (Vmax29, SensorMedics Corporation, Yorba Linda, CA) and multiplication by the physical activity level to find out the total energy expenditure. This dietary treatment enables a safe and steady WL supplying 54, 30 and 16% of energy requirements in the form of carbohydrates, fat, and protein, respectively. The study was approved by the Clínica Universidad de Navarra's Ethical Committee. All participants signed the informed consent to participate in the study.

2.2. Anthropometry

Body weight was measured to the nearest 0.1 kg with a digital scale. Height was determined with a Holtain stadiometer (Holtain Ltd., Crymych, UK) to the nearest 0.1 cm. BMI was calculated as weight in kg divided by the square of height in meters. Body fat percentage was estimated by means of air-displacement-plethysmography with the Bod-Pod® (COSMED, Rome, Italy) as previously reported [2]. Blood pressure was measured at least 3 times at the right upper arm after a 5-min rest with the patient in the semi-sitting position with a sphygmomanometer. The mean of the three measurements was used in the study.

2.3. Serum biochemistry

Serum samples were collected after 12-h of fasting in the morning in order to reduce the potential confounding influence of hormonal rhythmicity. Serum glucose and insulin concentrations were determined as previously reported [10–12]. The homeostatic model assessment (HOMA) was calculated as an indirect measure of insulin resistance. Total cholesterol and triglyceride levels were quantified by enzymatic spectrophotometric methods (Roche, Basel, Switzerland). High-density lipoprotein (HDL-cholesterol) was measured by a colorimetric method in a Beckman Synchron® CX analyzer (Beckman Instruments, Ltd., Bucks, UK). The Friedewald formula was used to calculate low-density lipoprotein (LDL-cholesterol).

Uric acid levels were determined by enzymatic tests (Roche). Fibrinogen, homocysteine, von Willebrand factor (vWF) antigen and high-sensitivity C-reactive protein (CRP) concentrations were determined as previously described [10,11]. White blood cells (WBC) count was determined using an automated cell counter (Beckman Coulter, Inc., Fullerton, CA). Leptin measurement was performed by a RIA method (Linco Research, Inc., St. Charles, MO); with intra-and inter-assay coefficients of variation being 5.0% and 4.5%, respectively. FGF19 and FGF21 concentrations were

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