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Relation between fibroblast growth factor–21, adiposity, metabolism, and weight reduction

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Abstract

Fibroblast growth factor–21 (FGF-21) has been proposed as a novel metabolic regulator, and animal experiments suggested that FGF-21 may affect energy balance. In humans, FGF-21 was correlated with obesity. Until now, no data exist regarding the relationship of FGF-21 and weight reduction in humans. We therefore investigated whether FGF-21 is modified by a moderate intended weight loss in a human trial. Thirty obese individuals (24 female, 6 male) participated in a weight reduction program for 6 months. In addition to several anthropometric and metabolic parameters, FGF-21 was measured before and after weight loss. Baseline serum FGF-21 was independently associated with markers of lipid metabolism and waist circumference. The multimodal intervention induced a moderate weight loss (97.4 ± 3.1 vs 92.2 ± 3.1 kg, $P < .001$), which was accompanied by a significant improvement of lipid and glucose metabolism. However, FGF-21 levels were not modified by moderate weight reduction; and FGF-21 levels at baseline were not a predictive marker for subsequent weight loss. The results presented here confirmed that FGF-21 levels are associated with markers of lipid metabolism and an estimate of abdominal adiposity. The finding that moderate weight loss did not induce changes of FGF-21 levels in humans suggests that FGF-21 is not directly regulated by fat mass under those conditions.

1. Introduction

Fibroblast growth factor–21 (FGF-21) is a recently discovered metabolic regulator of fasting metabolism, which activates glucose uptake in mouse adipocytes as well as in differentiated human adipocytes. FGF-21 also stimulated lipolysis in adipose tissue [1]. It protects animals from diet-induced obesity when overexpressed in transgenic mice and lowers blood glucose and triacylglycerol levels when administered to diabetic rodents [1-3]. Comparable glucose- and triacylglycerol-lowering effects were observed in diabetic rhesus monkeys during long-term FGF-21 treatment [4]. Therefore, FGF-21 was assumed to be a novel target with potential antidiabetic properties that might be useful in the treatment of hyperglycemia, insulin resistance, and hyperlipidemia.

However, human data did not directly support these assumptions because serum FGF-21 levels were found to be increased in obesity, type 2 diabetes mellitus, and metabolic syndrome [5-7]. Circulating FGF-21 levels correlated positively with estimates of adiposity but also with several parameters of the metabolic syndrome like fasting insulin and triacylglycerol levels [5]. Furthermore, increased FGF-21 messenger RNA expression was found in obese individuals, at least in visceral adipose tissue [7]. Thus, the effects and regulation of FGF-21 in humans seem to differ from animal models; and precise relations are not elucidated yet. Given the existing human data, it seems reasonable to hypothesize that FGF-21 might influence body fat stores or vice versa might itself be affected by the degree of obesity.

Current data support a regulation of FGF-21 in humans by several metabolic processes. Prolonged fasting over 7 days increased FGF-21 in a peroxisome proliferator-activator receptor (PPAR) α−dependent fashion, whereas a fasting

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period of 48 hours did not influence FGF-21 levels [3]. Free fatty acids (FFAs) were described as physiologic stimulators of FGF-21 secretion in humans, an effect which was also mediated via PPARα, whereas rosiglitazone, a PPARγ agonist, did not modify FGF-21 in humans [8]. Supraphysiologic hyperinsulinemia increased FGF-21 levels, suggesting that insulin itself might have a modulatory function on FGF-21 [8]. The function of FGF-21 in lipid metabolism and energy balance was recently underlined by Potthoff and coworkers [9], who described the effect of FGF-21 on fatty acid oxidation and on PPARγ coactivator protein-1α, a key regulator of energy homeostasis. Despite these studies suggesting that FGF-21 may contribute to energy balance and body weight, data in humans are basically missing; and specifically regarding the relationship of FGF-21 and weight reduction, no data exist yet in humans.

2. Research design and methods

2.1. Setting and participants

A total of 30 obese individuals (24 female, 6 male) participated in a weight reduction program for 6 months. Mean age was 51.8 ± 2.4 years. Mean starting weight was 97.4 ± 3.1 kg, body mass index (BMI) was 35.3 ± 1.0 kg/m^2, and waist to hip ratio (WHR) was 0.91 ± 0.02. All participants were screened for serious health problems and the intake of medication and were excluded if vascular diseases or hepatic or renal diseases were found. Regarding the results of oral glucose load, 8 subjects had type 2 diabetes mellitus. Individuals with insulin-dependent diabetes or oral antidiabetic drugs were excluded. One subject had newly diagnosed type 2 diabetes mellitus after weight loss period, whereas type 2 diabetes mellitus was dissolved in 4 subjects.

All subjects finished a 6-month weight loss program as previously described [10,11]. In brief, this weight loss program was based on a hypocaloric diet (50% carbohydrates, 30% fat, 20% protein) and at least 60 minutes of physical activity per week. All volunteers documented their eating behavior for 3 days before intervention. Based on eating protocols, an individual consultation was performed, with the recommendation of a daily calorie intake of 400 to 600 kcal less than the total energy expenditure. The diet was composed according to the guidelines of the German Association of Nutrition, with the following distribution of macronutrients: carbohydrates, 50%; fat, 30%; and protein, 20% of the daily energy intake. Meetings for all volunteers took place once a week over the 6 months. In the first 90 minutes at the first 10 dates, nutrition consultants accomplished group workshops with practical cooking exercises. At 9 dates, the workshop was done by a psychologist with relaxation exercises. One workshop was done by a physician with medical hints and advice. At all dates, moderate exercise with gymnastics or aqua fitness was performed during the last 60 minutes. At baseline and after 6 months, physical examination was performed; and fasting blood was taken. Skinfold thickness measurements were carried out by the same physician using a skinfold caliper (Lange skinfold caliper; Beta Technology, Cambridge, MD). Suprailiac, triceps, biceps, and subscapular skinfold thickness measurements were done triply, and the respective mean was calculated. An oral glucose tolerance test was carried out at baseline and after 6 months. In a subgroup of 17 subjects, a hyperinsulinemic-euglycemic clamp and, in 12 subjects, a bioimpedance analysis were performed at baseline and after weight loss.

2.2. Power calculation

A type I error of less than or equal to 5% and a type II error of less than or equal to 20% were defined for power calculation. A standard deviation for FGF-21 was approximately 23% as observed at baseline in the subjects investigated here and in previous studies. Assuming a sample size of 30 participants, this study was sufficiently powered to detect a difference in FGF-21 levels of 12%. Previous metabolic interventions in humans, that is, elevation of FFAs, increased FGF-21 by approximately 20% [8]. We therefore assumed that this weight reduction trial including 30 individuals should be sufficiently powered to detect physiologic changes induced by weight loss.

The study protocols were approved by the Institutional Review Board of the Charité Medical School, Campus Benjamin Franklin; and all subjects gave written informed consent.

2.3. Measurement and laboratory parameters

The following measurements and laboratory parameters were determined in all participants before the intervention and at the end of 6 months. Anthropometry was performed as previously described [12,13]. Bioelectric impedance measurement was performed on resting participants. After attaching the electrodes to the right hand and the right foot, 3 measurements were conducted; and the mean value was calculated. Oral glucose tolerance test and hyperinsulinemic-euglycemic clamp were performed as previously described [14]. After sampling in EDTA or serum tubes, blood was immediately chilled on ice and centrifuged; and aliquots were immediately frozen at −80°C until assayed. Blood samples were analyzed for glucose, insulin, hemoglobin A_{1c}, FFAs, total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, and triacylglycerols as described previously [11,15]. In brief, measurements of insulin and FFAs were performed using Cobas Mira (Roche, Lörrach, Germany). The HDL cholesterol and total cholesterol were detected by ABX Pentra 400 (ABX Diagnostics, Montpellier, France), whereas LDL was calculated according to the Friedewald formula. Hemoglobin A_{1c} was measured by high-performance liquid chromatography (Menarini HA8140, Florence, Italy).

Serum FGF-21 levels were measured at baseline and after 6 months. Serum FGF-21 levels were determined by

radioimmunoassay (Phoenix Europe, Karlsruhe, Germany) using 125 I-labeled FGF-21 as tracer. The linear range of the assay was 0.5 to 8.5 ng/mL, and the standard range was 0.234 to 30 ng/mL. The interassay and intraassay coefficients of variation were 5.0% and 14%, respectively.

2.4. Statistical analysis

All statistical procedures were performed using SPSS version 15.0 (SPSS, Chicago, IL). Data were compared by paired Student *t* test for normally distributed data and Wilcoxon test for skewed data. Correlations between variables were investigated by Pearson coefficient of correlation and adjusted for age, sex, BMI, and fasting insulin. Skewed variables were logarithmically transformed for statistical analysis. Multiple linear regression analysis with stepwise variable selection was performed to assess the independent variables. Insulin sensitivity (M, in milligrams per kilogram of body weight per minute) during the steady-state period (from 120-180 minutes) of the hyperinsulinemic-euglycemic clamp was calculated from the amount of glucose infused to maintain euglycemia. The insulin sensitivity index (ISI_{clamp}) was calculated as ratio of glucose metabolized during the steady-state period (M) to a mean serum insulin concentration (I, in milliunits per liter) during the steady state period in the euglycemic clamp. Insulin sensitivity was additionally assessed by homeostasis model of assessment of insulin resistance (HOMA-IR), which was calculated as previously described [16]. Results were considered to be significant if the 2-sided α was $< .05$. Data are presented as the mean ± SEM unless otherwise mentioned.

3. Results

Metabolic parameters and parameters of body composition at baseline, like bioelectric impedance measurement or skinfold thickness, are presented in Table 1. As expected, after 6 months of the intervention, a moderate but highly significant decrease in body weight and BMI was detected. This was associated with the expected significant changes in several anthropometric parameters and improved fat and glucose metabolism, as it was suggested by a decrease in subcutaneous adipose tissue, waist and hip circumference, and fat mass; an increased fat-free mass; and improved FFAs, HDL cholesterol, and fasting glucose, respectively (Table 1). The HOMA-IR, a parameter of global insulin sensitivity, was also improved by weight loss (Table 1), whereas M value (2.98 ± 0.30 vs 3.28 ± 0.24 mg/[kg min], P = not significant [NS]) and ISI_{clamp} (0.048 ± 0.007 vs 0.047 ± 0.006 ($mg \cdot kg^{-1} \cdot min^{-1}$)/($mU \cdot L^{-1}$), P = NS) were not significantly changed during weight reduction.

Fibroblast growth factor–21 was not correlated with body weight; BMI; WHR; hip circumference; fasting insulin and fasting glucose; insulin and glucose at 30, 60, 90, and 120 minutes after oral glucose load; HDL cholesterol; HOMA-IR; M value; and ISI_{clamp}. A significant correlation was found to several other metabolic and anthropometric parameters, which, at least in part, relate to the metabolic syndrome. This includes FFAs ($r = 0.450$, $P < .05$), total cholesterol ($r = 0.479$, $P < .005$), LDL cholesterol ($r = 0.404$, $P < .05$), triacylglycerols ($r = 0.561$, $P < .001$), and suprailiac skinfold ($r = 0.450$, $P < .05$). The correlation of FGF-21 and waist circumference slightly failed significance ($r = 0.355$, $P = .066$).

Interestingly, the correlations between FGF-21 and total cholesterol ($r = 0.421$, $P < .05$), LDL cholesterol ($r = 0.403$, $P < .05$), and triacylglycerols ($r = 0.451$, $P < .05$) were robust, even after adjustment for the additional confounders age, sex, fasting insulin, diabetes mellitus, and waist circumference; and the correlation between FGF-21 and waist circumference ($r = 0.399$, $P < .05$) was significant after adjustment for age, sex, fasting insulin, and diabetes mellitus (Fig. 1).

Despite the rather strong relation of FGF-21 to parameters of lipid metabolism and waist circumference at baseline, FGF-21 levels were not modified by weight loss (Table 1). Comparably, the anthropometric and metabolic changes induced by weight reduction did not correlate with baseline FGF-21 levels or changes in FGF-21 levels (difference between FGF-21 after weight loss and FGF-21 at baseline). No correlation was found between change of FGF-21 or baseline FGF-21 levels and one of the following parameters: change of WHR, BMI, body cell mass, fat mass, fat-free mass, FFAs, total cholesterol, LDL cholesterol, HDL

Table 1
Baseline characteristics of the participants

	Before weight reduction	After weight reduction
Weight (kg)	97.4 ± 3.1	92.2 ± 3.1‡
BMI (kg/m^2)	34.8 ± 1.0	32.8 ± 1.0‡
Hip circumference (cm)	121.4 ± 2.3	113.8 ± 2.1‡
Waist circumference (cm)	110.0 ± 2.6	102.6 ± 2.5‡
WHR	0.91 ± 0.02	0.90 ± 0.02
Biceps skinfold (mm)	36.8 ± 3.0	29.2 ± 2.4†
Triceps skinfold (mm)	39.5 ± 3.0	34.2 ± 1.5*
Suprailiac skinfold (mm)	45.4 ± 2.1	38.8 ± 1.7†
Subscapular skinfold (mm)	46.8 ± 2.0	41.6 ± 2.1†
Body cell mass allotment (%)	32.0 ± 0.7	33.6 ± 1.0*
Fat mass allotment (%)	40.0 ± 1.0	36.8 ± 1.0†
Fat-free mass allotment (%)	60.0 ± 1.0	63.2 ± 1.0†
Total cholesterol (mmol/L)	5.40 ± 0.20	5.57 ± 0.20§
LDL cholesterol (mmol/L)	3.24 ± 0.16	3.36 ± 0.19
HDL cholesterol (mmol/L)	1.34 ± 0.07	1.37 ± 0.05*
Triacylglycerols (mmol/L)	1.44 ± 0.10	1.53 ± 0.17
FFA (mmol/L)	0.67 ± 0.05	0.55 ± 0.04†
Fasting glucose (mg/dL)	99.4 ± 2.3	93.9 ± 2.4†
Fasting insulin (mU/L)	13.7 ± 1.9	12.7 ± 1.9
HbA_{1c} (%)	5.37 ± 0.14	5.36 ± 0.16
HOMA-IR	3.49 ± 0.56	3.01 ± 0.50†
FGF-21 (ng/mL)	1.22 ± 0.05	1.21 ± 0.05

Results are expressed as means ± SEM. HbA_{1c} indicates hemoglobin A_{1c}.
* $P < .05$ vs before weight reduction.
† $P < .01$ vs before weight reduction.
‡ $P < .001$ vs before weight reduction.
§ $P = .072$ vs before weight reduction.

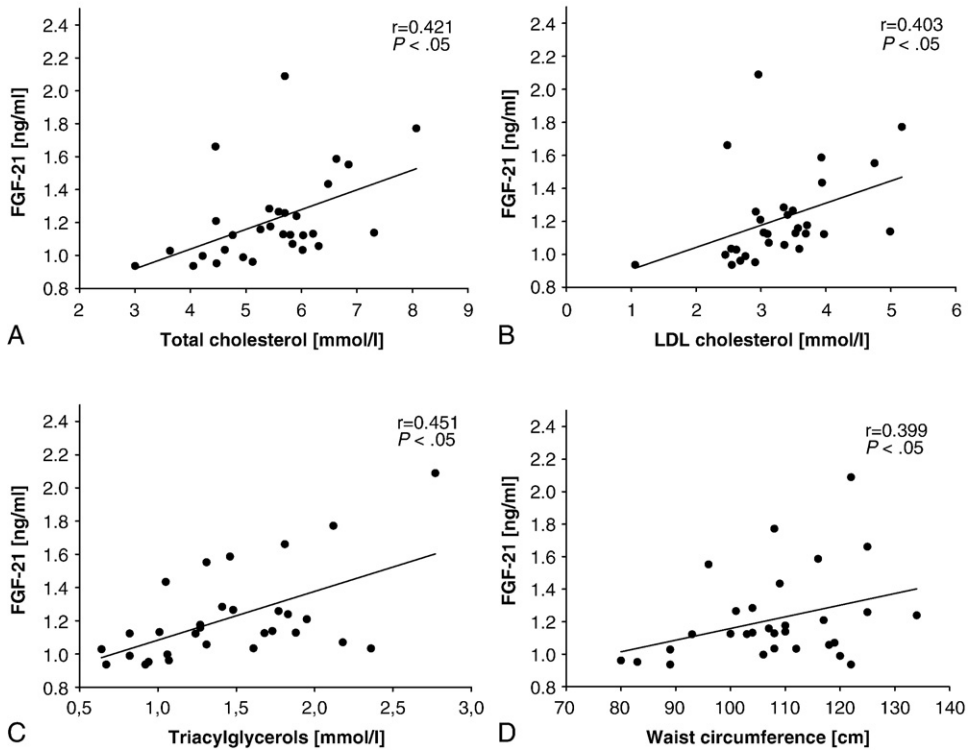

Fig. 1. Simple linear correlation between FGF-21 and several parameters of lipid metabolism and waist circumference. The *r* and *P* values are given for partial correlation after adjustment for age, sex, fasting insulin, diabetes mellitus (D), and additionally waist circumference (A-C).

cholesterol, triacylglycerols, ISI_{clamp}, M value, HOMA-IR, and all skinfold thickness parameters, suggesting that neither FGF-21 itself nor change in FGF-21 levels during weight loss predicts the change in one of the other parameters. There was furthermore no sex difference in FGF-21 levels at baseline (men: 1.20 ± 0.13 ng/mL, women: 1.22 ± 0.05 ng/mL; *P* = NS) and after weight loss (men: 1.20 ± 0.12 ng/mL and women: 1.23 ± 0.06 ng/mL, *P* = NS). Neither the FGF-21 levels at baseline nor the FGF-21 levels after weight loss differed significantly between subjects without and with diabetes mellitus (1.21 ± 0.05 vs 1.22 ± 0.13 ng/mL and 1.19 ± 0.06 vs 1.27 ± 0.12 ng/mL, *P* = NS), and the FGF-21 levels were not changed by weight reduction both in subjects without diabetes mellitus as well as in subjects with diabetes mellitus (*P* = NS).

Despite the negative results of the crude analyses, a potential prognostic value of FGF-21 on weight reduction was further evaluated by a multiple linear regression including several metabolic and anthropometric parameters (WHR, BMI, body cell mass, fat mass, fat-free mass, FFAs, total cholesterol, LDL cholesterol, HDL cholesterol, triacylglycerols, HOMA-IR, fasting glucose, fasting insulin, age, sex, diabetes mellitus, and all skinfold thickness parameters, creatinine, leukocytes). However, no model suggested independent predictive effects of FGF-21 or an interaction of FGF-21 with one of the additionally analyzed confounders. In summary, basal serum FGF-21 was not predictive for subsequent weight loss.

4. Discussion

Weight loss is accompanied by a modification of several hormonal and metabolic parameters [11,17]. One possible candidate that might be a modulatory player in regulation of body weight is FGF-21, which was recently described to be involved in several metabolic processes like increased adipose glucose uptake [2], increased lipolysis in adipocytes [18], and finally increased hepatic ketone body production [1] at least in vitro or in animals. Transgenic mice overexpressing FGF-21 gained significantly less weight under a high-fat diet [2], and FGF-21 administration resulted in a slight reduction in body weight as well as an improved metabolic pattern in monkeys [4]. In summary, animal data support a role of FGF-21 in energy balance [9], although the precise mechanism and a potential role in humans are yet unclear. Indeed, an association of FGF-21 levels and BMI was found in some [5,19,20] but not in all [6,21] human studies. Even if such a relation exists, the direction of that relation would be unclear. Thus, a circulating FGF-21 might affect body weight; but vice versa, body weight might also affect circulating FGF-21. Given this partially unclear situation in humans, we evaluated the effects of moderate weight reduction by a lifestyle intervention program on FGF-21 levels.

As expected, the weight loss was accompanied by an improvement of several metabolic and anthropometric parameters including lipid metabolism, which was comparable to previous findings [22,23]. Despite previous animal

and human data, which suggested a strong correlation between BMI and FGF-21, FGF-21 levels were not modified by a moderate weight reduction. One recent study demonstrated a decrease in FGF-21 levels during ketogenic diet that was accompanied by weight loss [24]. However, the weight loss within this trial was more pronounced than in our subjects (9.2% vs 5.3%), suggesting that the degree of weight loss may be an important confounder in this setting. Furthermore, in the aforementioned study, only 7 subjects were included [24], whereas we investigated a slightly larger cohort (n = 30). Considering our sample size, we would not expect that the study was underpowered. Considering the sample size of our study, theoretically, a difference of 12% of FGF-21 levels was detectable. Therefore, the 42% difference of FGF-21 observed by Christodoulides and coworkers [24] during weight loss (induced by ketogenic diet) should have been detectable in any case. Despite sufficient power, this was not seen in the current trial. Therefore, FGF-21 may not be directly regulated by a moderate change in fat mass and body weight. Nevertheless, a difference in FGF-21 levels less than 12% cannot be excluded by our sample size. Otherwise, the diet used in our intervention was not designed to induce pronounced ketosis, a fact that might also contribute at least in part to the differences between ours and the data of Christodoulides et al, as FGF-21 seems to play a crucial role in ketogenesis [25]. However, notably, a trial analyzing the effects of a ketogenic diet in children also did not demonstrate changes in FGF-21 levels [3].

Actually, Mraz and colleagues [7] observed increased circulating FGF-21 levels after 3 weeks of very low calorie diet, an intervention that was also accompanied by a moderate weight loss. However, very low calorie diet usually leads to an extreme catabolism that may be responsible for the observed changes in FGF-21. Because of those catabolic conditions, the results might not be directly comparable to our data, which indicated that circulating FGF-21 levels are unchanged after a moderate weight reduction without periods of excessive negative energy balance. Indeed, this difference suggests that any mechanisms related to the degree of negative energy balance may contribute to the regulation of FGF-21 rather than fat mass per se. In addition, there may be a considerable variance between individuals in relation to the response of other hormones to regulation of energy balance. This study was underpowered to address such questions, although this would be highly desirable.

Furthermore, it should be mentioned that our cohort was not equally distributed among sexes; and some of the investigated women were in the perimenopausal phase, a situation characterized by several other hormonal and metabolic changes. This could have at least in part influenced the present results.

Given the existing animal data and the positive correlations between FGF-21 and estimates of adiposity in observational studies (including the correlation between abdominal obesity and FGF-21 at baseline presented here), our results of the weight reduction trial suggest that FGF-21 does not substantially contribute to the endocrine response counterbalancing a period of negative energy balance and reduction of fat mass. However, our results cannot exclude that indirect and direct consequences of a negative energy balance and body weight loss may have an opposite effect on circulating FGF-21. Thus, data of correlation analysis indicated that FGF-21 levels were influenced by many other factors, including lipids and waist circumference, which are also affected by body weight reduction. The role of FGF-21 on lipid metabolism was already extensively analyzed in several previous studies from our and other groups [1,2,18,19,24,26], and our actual data strongly support this relation between FGF-21 and lipid metabolism. Considering these findings, it seems reasonable to speculate that FGF-21 may not be directly regulated by obesity and weight reduction itself. Indeed, accompanying metabolic disturbances such as elevated FFAs or triacylglycerol levels in obesity or acute catabolism during weight loss may cause the observed modifications seen in some but not all studies [3,7,24]. In that context, the slightly decreased FFAs and the constant levels of insulin as well as triaclyglcerols in our subjects may account for the unchanged FGF-21 levels.

In accordance to recent data, we observed comparable circulating FGF-21 levels in obese subjects with and without diabetes [7]. However, the number of individuals with diabetes was rather small in our study; and this study is therefore not able to exclude moderate difference between subjects with and without diabetes with respect to the regulation of FGF-21.

As FGF-21 administration evoked weight reduction at least in monkeys [4], we speculated that FGF-21 levels at baseline may predict weight loss in humans. However, neither FGF-21 nor any other of the metabolic parameters analyzed here predicted weight loss. This supports that FGF-21 may not be a major factor in the regulation of energy homeostasis in humans, although effects may depend on period of negative energy balance, degree of weight loss, or nutritive and behavioural parameters. We can also not exclude that tissue-specific concentrations may be relevant and that the FGF-21 system may be additionally regulated at the receptor or postreceptor level. Finally, the predictive effect may be too small to be detected in our cohort.

In summary, our data indicate that FGF-21 levels are associated with markers of lipid metabolism and abdominal adiposity. However, FGF-21 is not directly regulated by moderate change in fat mass and body weight; and baseline levels of FGF-21 do not predict subsequent weight loss. Therefore, it is unlikely that FGF-21 has a predominant role in the regulation of energy balance in humans, although clearly more detailed functional studies will be required to further analyze that relation.

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