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A pilot study of the effects of niacin administration on free fatty acid and growth hormone concentrations in children with obesity

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Summary

Context: Children with obesity have low spontaneous growth hormone (GH) secretion. High circulating free fatty acid (FFA) concentration is believed to inhibit GH secretion in those with obesity. In adults, lipolytic inhibition with niacin lowers FFA and increases GH, but there are no prior studies in children with obesity.

Objective: The objective of the study was to determine the dose and frequency of niacin administration required to lower FFA and stimulate GH in children with obesity.

Design: Dose-finding study of nondiabetic children ages 6–12 years with body mass index (BMI) ≥ 95th percentile given niacin 250 mg q2h × 3 doses ($n = 2$), 500 mg q2h × 3 doses ($n = 5$) or 500 mg q1h × 4 doses ($n = 5$).

Participants: Eight boys and four girls (age 9.7 ± 1.8 years; BMI 26.4 ± 3.1 kg m^{-2}; BMIz 2.2 ± .25) were studied.

Main Outcome: Percentage of serum FFA values that were below 0.2 mEq L^{-1}. GH, insulin and glucose were also measured serially.

Results: FFA decreased as the dose and frequency of niacin increased ($p = .01$). Niacin 500 mg q1h 4 doses suppressed FFA < 0.2 mEq L^{-1} and significantly increased GH ($p = .04$). Adverse effects were flushing/warmth (100%), tingling (60%) and GI complaints (20–40%).

Conclusions: Niacin 500 mg q1h significantly lowered serum FFA and increased GH. These pilot data suggest that high FFA is an important suppressor of GH secretion in children with obesity.

Keywords: adipose tissue, free fatty acids, growth hormone, lipolysis, obesity, somatotropin.

Introduction

Compared to children with normal weight, children with obesity have lower serum concentrations of growth hormone (GH), whether measured spontaneously (1), after provocative pharmacological stimulation (2) or after exercise (3). Several studies have also documented that, even within the normal range for weight, secretion of GH is negatively associated with body mass (4). See Supporting Information for additional references.

Dys-regulation of factors normally involved in GH secretory regulation may underlie the hyposoma-

totropinemia of obesity, given that GH concentration usually normalizes after weight loss in both adults (5) and children (6), with peak GH response to pharmacologic stimuli correlating with the degree of weight loss (7). In children, even short-term energy restriction leads to a 60% improvement in GH secretion (8).

Growth hormone secretion is a complex process regulated by multiple hormones and substrates. Growth hormone-releasing hormone (GHRH) and somatostatin are important hypothalamic regulators of pituitary GH secretion. Factors believed to influence secretion of these hypothalamic hormones and/or directly affect the somatotrophs include, but are not limited to, GH itself, insulin-like growth factor 1, sex hormones, ghrelin, orexins, leptin, glucose, insulin and free fatty acid (FFA) concentration (9).

Several lines of evidence support the importance of FFA for the inhibition of GH in obesity. First, serum FFA concentration is positively correlated with body weight (10). The rate of FFA turnover is also faster in obese patients, suggesting increased mobilization of these compounds from the adipose tissue (11). Measurements of FFAs in children with obesity have been less frequently performed but overall show elevations compared to controls with normal weight (1). Infusion of fatty acids leads to blunting of GH secretion in animal models (12). In humans, lipid infusion lowers unstimulated GH concentrations and lowers the responsiveness to GHRH stimulation in normal weight and anorexic adult women (13). Finally, there is evidence in adults that inhibiting lipolysis can increase GH secretion. After administration of niacin (vitamin B3) to inhibit lipolysis via its binding to GPR109A, a G_i-G protein-coupled receptor (14), healthy adults of normal weight had increased spontaneous (15), stimulated (16) and post-exercise (17) GH production. When niacin was administered to adults with obesity, the inhibition of lipolysis led to increased spontaneous GH secretion in one study (18) although no effects were seen in a second report (19). A third study found increased spontaneous GH secretion in subjects with diabetes (20). After administration of acipimox, another lipolytic inhibitor that suppresses FFA concentrations, but which is not FDA-approved for use in the USA, adults with obesity had increased spontaneous (21) and stimulated (22) GH production. There are no data in children with obesity demonstrating the effects of inhibition of lipolysis on GH secretion.

We studied the safety and efficacy of niacin for inhibiting lipolysis and increasing spontaneous GH secretion in children with obesity. We hypothesized that, in children with obesity, inhibition of lipolysis by niacin would decrease plasma FFA, increase spontaneous GH serum concentrations and be associated with tolerable adverse effects. Because there were no prior data regarding the dose or frequency of niacin administration needed to suppress FFA in children with obesity, we carried out a dose-establishing pilot study. This represents the first step in determining if niacin could be safely used in GH stimulation tests to increase the sensitivity and specificity of such studies.

Research design and methods

Study overview

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Institutional Review Board approved the trial (clinicaltrials.gov registration NCT01237041).

Potential participants and both parents/guardians provided signed assent/consent, respectively. Financial compensation was provided for subjects' time and inconvenience. Participants were seen at the National Institutes of Health (NIH) Clinical Research Center on two separate occasions. After a baseline screening visit to assess participant eligibility, those who qualified returned for an overnight in-patient stay for niacin administration and serial blood sampling. The dose and frequency of niacin administration was increased according to a pre-specified plan for successive participants to identify a regimen that would inhibit lipolysis (FFA concentration $<200\ \text{uEq L}^{-1}$).

An investigational new drug application was obtained from the US Food and Drug Administration (#111,512) for niacin administration in children. Nicotinic acid 500 mg tablets (Upsher-Smith Laboratories, Inc. Minneapolis, MN) were purchased. These tablets were crushed to a fine powder and repackaged by the NIH Clinical Center Pharmaceutical Development Section in opaque 250 mg capsules for administration. Sterility evaluations, dissolution tests and niacin assay by HPLC were performed per USP 33 NF 28 standards.

Participants

Study participants were recruited between June 2011 and March 2015 via flyers, LISTSERVs, word of mouth and social media from the surrounding geographical area. Inclusion criteria were aged 7–14 years, good general health, body mass index (BMI) ≥95th percentile according to the Centers for Disease Control BMI standards and weight ≥30 kg. Participants were eligible only if prepubertal or in an early stage of puberty (Tanner I, II, or III for breast development in girls and testes <12 mL in boys). Exclusion criteria were short stature, presence of a chronic illness that might impact growth or

development including monogenic or chromosomal causes of obesity, recent use of a medication known to affect growth, body weight, GH secretion or metabolism (e.g. metformin, stimulants, lipid-lowering agents, glucocorticoids or sex steroids), pregnancy, evidence for precocious puberty or other endocrinopathies including impaired fasting glucose, impaired glucose tolerance or Type 2 diabetes, as evidenced by fasting plasma glucose $\geq$100 mg dL^{-1}, 2 h post-dextrose glucose $\geq$140 mg dL^{-1}, or HgbA1C $>$6.4%.

Screening evaluation

Subjects were screened for eligibility at an outpatient screening visit at the NIH Hatfield Clinical Research Center. At this visit, a medical history and physical examination including pubertal staging, weight and height (in triplicate, using a calibrated stadiometer) were obtained.

Participant's fasting blood and urine samples were used to examine metabolic, hematologic, hepatic and renal function. An oral glucose tolerance test was performed (dextrose, 1.75 g kg^{-1} body weight; maximum dose 75 g) with glucose measured at baseline and at 2 h.

Dose-establishing in-patient study

Within 2 months of initial screening, eligible participants returned for an overnight stay at the NIH Clinical Research Center for serial sampling and niacin administration. Participants were asked to discontinue any vitamin supplements for at least 3 days before the admission. Subjects were studied after an overnight fast starting at 10 PM. and ending after completion of testing with niacin. An intravenous catheter was placed for blood sampling during testing. Based on limited applicable data from adult studies (17), the trial design specified a niacin dose increase from 250 q2h $\times$ 3 doses to 500 mg q2h $\times$ 3 doses if, after the first two participants were studied with 250 mg niacin q2h, inadequate suppression of FFA ($>$200 uEq L^{-1}) was observed. Subsequently, the effects of 500 mg niacin administered hourly for four doses were evaluated after inadequate suppression of FFA was observed in five participants treated with 500 mg q2h $\times$ 3 doses. For the q2h niacin administration protocols, niacin was administered at 6 AM, 8 AM and 10 AM. Blood samples were collected every 30 min from 6 AM to 12 NN and were analyzed for FFA, GH, glucose and insulin concentrations. For the q1h 500 mg niacin administration protocol, niacin was administered at 7:30 AM, 8:30 AM, 9:30 AM and 10:30 AM, with blood samples collected from 7:30 AM to 11:30 AM. The NIH Clinical Center Department of Laboratory Medicine assayed the samples for FFA, GH and insulin assay details are given in the Supporting Information. Participants were interviewed hourly with a structured case report form to assess the adverse effects of niacin during testing and were discharged after testing was complete and any adverse effects had resolved.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 19 (IBM Corp., 2010) and GraphPad Prism 6 (GraphPad Software, Inc., San Diego, CA). There were no prior studies on which to base a power calculation for this pilot dose-finding study; empirically, groups of five per dose were selected a priori to be evaluated. The primary efficacy analysis examined the percentage of FFA measurements $<$200 uEq L^{-1} after each dose by contingency table (Pearson Chi Square) analysis. A second analysis was a repeated measures ANOVA with niacin treatment (250 q2h, 500 q2h and 500 q1h) as the between factor, time as the repeated measure and FFA concentration as the dependent variable. An additional secondary outcome analysis was a repeated measures ANOVA with the same independent variables and GH concentration as the dependent variable. Similar analyses for the tertiary outcomes of insulin and glucose concentrations were also performed. Because there were great individual differences in baseline glucose and insulin on the day of niacin testing, glucose and insulin values were compared after converting subjects' values to be a percentage of their baseline glucose and insulin. For ANCOVAs with significant dose or dose x time interaction terms, one-tailed post-hoc Fisher least significant difference tests were used to examine differences at individual time points between those given niacin hourly vs. every 2 h. $p < 0.05$ was considered significant.

Results

Figure 1 presents participant flow through the protocol. Of the 22 children who attended a screening visit, six were not eligible, three withdrew from the study, one opted to participate in another research study and 12 completed study procedures. The cohort given niacin consisted of eight male and four female children (mean age 9.7 $\pm$ 1.8 years; BMI 26.4 $\pm$ 3.1 kg m^{-2}; BMIz 2.2 $\pm$ .25) who were taking no medications other than intermittent treatment for asthma or allergies (Table 1 and Table S1). Two participants were given 250 mg niacin q2h $\times$ 3 doses, five received 500 mg niacin q2h $\times$ 3 doses and five were studied with 500 mg niacin q1h $\times$ 4 doses.

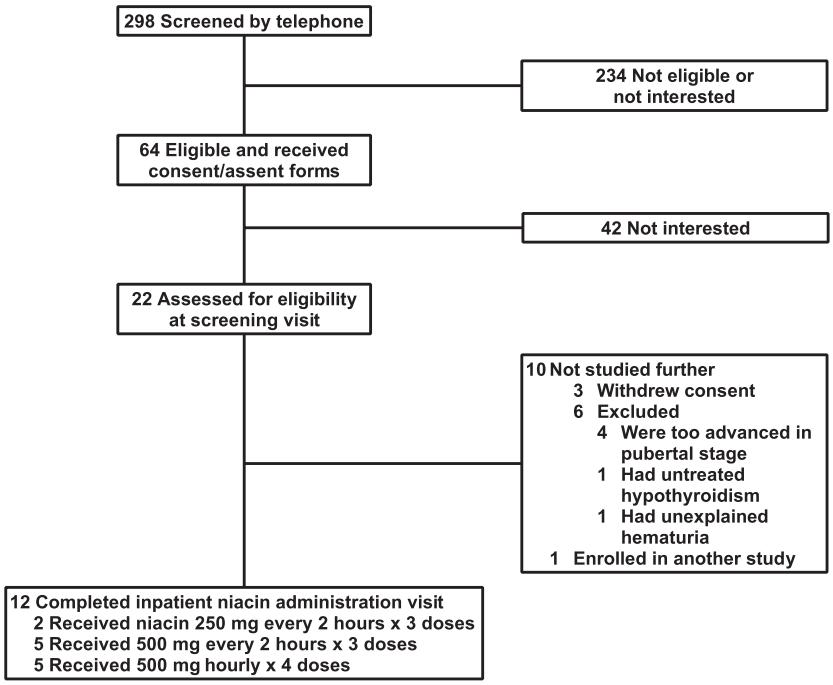

Figure 1 Participant flow through the protocol.

Table 1 Participant characteristics

	250 mg Niacin q2h × 3	500 mg Niacin q2h × 3	500 mg Niacin q1h × 4
Sample size	2	5	5
Age (year)*	10.5 ± 2.2	9.7 ± 1.9	9.3 ± 1.9
Sex	2 Male	2 Male and 3 Female	4 Male and 1 Female
Race	2 NHB	3 NHB and 2 NHW	2 NHB and 3 NHW
Tanner stage			
Prepubertal	1	2	3
Early pubertal	1	2	2
Mid-pubertal	0	1	0
Weight (kg)*	53.6 ± 10.8	58.0 ± 16.0	52.9 ± 17.0
Height (cm)*	143.0 ± 12.2	143.2 ± 12.1	142.6 ± 13.6
Height *z* score*	0.13 ± .08	1.1 ± 0.48	1.28 ± 1.58
BMI (kg/m^2)*	26.0 ± 0.8	27.9 ± 3.2	25.4 ± 3.4
BMI *z* score*	2.09 ± 0.21	2.33 ± 0.24	2.12 ± 0.32
Fasting glucose ($mg\,dL^{-1}$)*	78.5 ± 4.95	89 ± 6.82	80.2 ± 7.89
Glycosylated haemoglobin (%)*	4.8 ± 0.4	5.7 ± 0.2	5.4 ± 0.4
IGF-1 ($ng\,mL^{-1}$)*	241†	259.0 ± 96.4	269.1 ± 131.9

Prepubertal: Tanner I breast development in girls or testes <4 mL in boys; Early pubertal: Tanner II breast development in girls or testes 4–<8 mL in boys; mid-pubertal: Tanner III breast development in girls or testes 8–<12 mL in boys.
*Mean ± SD.
†IGF1 was available in only one of the two participants who received 250 mg niacin q2h.
NHB, non-Hispanic black; NHW, non-Hispanic white; IGF-1, insulin-like growth factor 1.

Effects on free fatty acids

The primary outcome analysis indicated that there was significantly greater suppression of FFA as the dose and frequency of niacin administration increased (Fig. 2a; $p < 0.007$). There were also significant differences in the effects of the different niacin regimens on FFA concentrations by repeated measures ANOVA

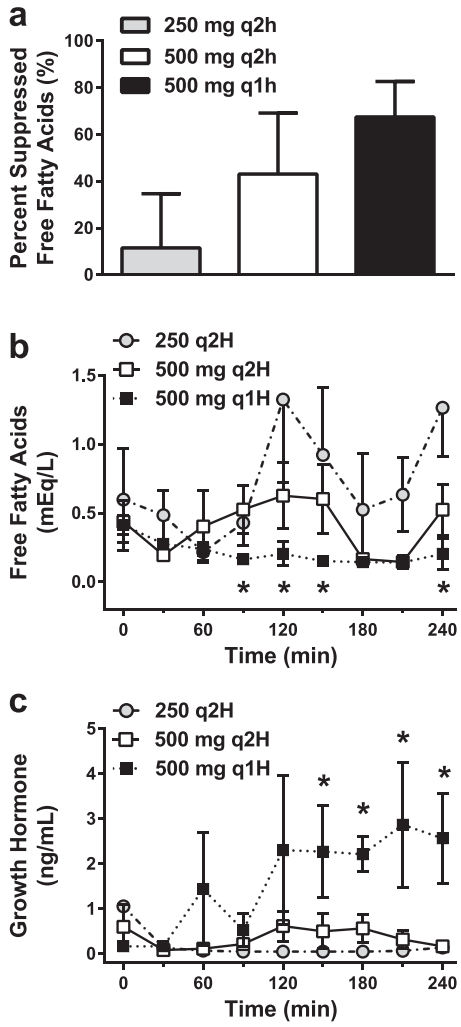

Figure 2 Effects of niacin administration on free fatty acids and growth hormone. (a) Percentage of free fatty acid measurements post-niacin that was suppressed below 0.2 mEq L^{-1}. There was a significant increase in the percentage of suppression with increasing dose and frequency of niacin ($p < 0.007$). (b) Free fatty acid concentrations at baseline (time 0) and after niacin 250 mg q2h, 500 mg q2h and 500 mg q1h. *$p < 0.05$; post-hoc one-tailed Fisher LSD tests between participants given niacin hourly vs. every other hour. (c) Growth hormone concentrations at baseline (time 0) and after niacin 250 mg q2h, 500 mg q2h and 500 mg q1h. *$p < 0.05$; post-hoc one-tailed Fisher LSD tests between participants given niacin hourly vs. every other hour.

(Fig. 2b; dose $p = 0.048$; dose x time interaction $p = 0.018$). The two participants given 250 mg q2h × 3 doses of niacin showed temporary and insufficient suppression of FFA below 0.2 mEq L^{-1} (Fig. 2a, b), with only 11.5% of post-niacin FFA values <0.2 mEq L^{-1}. Among the five participants given 500 mg niacin q2h, there was greater suppression of lipolysis than with 250 mg q2h, but the 2-h interval between niacin doses led to rises in FFA to near baseline concentrations, such that only 43.1% of post-niacin FFA values were <0.2 mEq L^{-1} (Fig. 2a,b). The five children who received niacin 500 mg hourly for 4 h demonstrated the greatest suppression of lipolysis (Fig. 2a,b); all five participants who received 500 mg hourly demonstrated suppression of FFA below 0.2 mEq L^{-1}, with 67.5% of post-niacin values indicative of suppressed lipolysis.

Effects on growth hormone

Niacin administration was associated with dose-dependent effects on GH concentrations (Fig. 2c; $p = 0.019$). GH did not increase significantly after niacin 250 or 500 mg q2h but increased significantly with 500 mg q1h (Fig. 2c). Mean GH for subjects given 500 mg q1h at 210 min was 2.9 ng dL^{-1}.

Both subjects given 250 q2h had peak GH below 3 ng mL^{-1}. One subject given 500 q2h had peak GH between 7 and 10 ng mL^{-1}; two peaked between 2 and 3 ng mL^{-1}, and two were <1 ng mL^{-1}. Two subjects given 500 q1h had peak GH between 7 and 10 ng mL^{-1} and three peaked between 2 and 3 ng mL^{-1}. All peak values were found during the final 2 h of testing.

Effects on insulin and glucose

Analyses for insulin and glucose were performed in the 500 mg q2h and 500 mg q1h groups (Fig. 3). Although insulin decreased significantly during the test in both groups, there were no significant niacin dose or dose*time interactions. However, for glucose, participants receiving 500 mg q1h had an accentuated rise at 60, 90,150 and 240 min when compared with those receiving 500 mg q2h.

Adverse events

There were no serious adverse events involving subjects participating in the protocol. The expected adverse reactions to niacin (based on the adult literature) were, however, frequently observed (Table S2). Flushing and feeling warm were reported in 80–100% of participants after the first dose of niacin. Among those given niacin 500 mg q1h, 60% reported tingling or rash, 20% had emesis and 40% had nausea or abdominal discomfort. For all of these adverse effects, as anticipated based on the extant literature, there was tachyphylaxis such that side effects rapidly abated despite continued niacin administration.

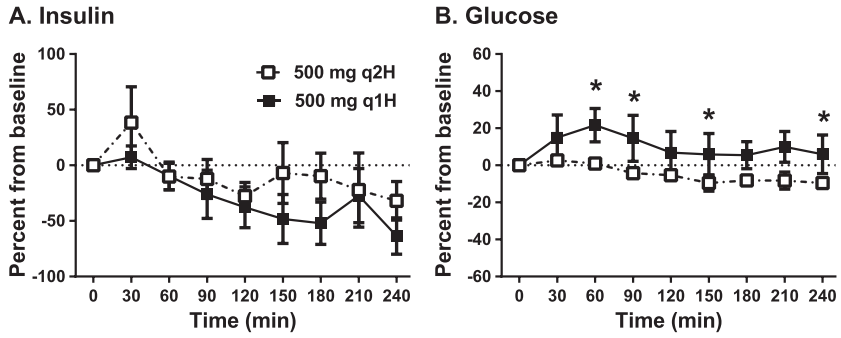

Figure 3 Effects of niacin administration on (a) glucose and (b) insulin.

Symptoms had generally resolved completely by the end of testing.

Discussion

This study, to the best of our knowledge, is the first trial investigating the effects of inhibition of lipolysis on the GH axis in children with obesity. This study provides preliminary evidence regarding a dose of niacin that suppressed FFA in children with obesity and was associated with a rise in serum GH concentrations.

We found that administering niacin 250 or 500 mg every 2 h did not suppress lipolysis sufficiently, although there was evidence for greater suppression of circulating FFAs using 500 mg than 250 mg q2h. Doses administered every 2 h did not increase GH concentrations significantly. However, at a dose of 500 mg hourly for 4 doses, there was significant suppression of FFAs to the pre-specified outcome ($<0.2\,mEq\,L^{-1}$) and detectable increases in GH concentration. Our findings are consistent with previous adult studies that demonstrated increase in spontaneous GH secretion after administration of lipolytic inhibitors including niacin (15) and acipimox (21). Only one previous paediatric study has tested the effects of lipolytic inhibition on GH (23). Lanes *et al*. examined the effects of acipimox vs. placebo after L-dopa infusion in 14 healthy children, finding increased GH secretion after inhibition of lipolysis, but non-significant differences in peak GH concentrations during L-Dopa administration.

In this study, niacin was relatively well tolerated. Although we observed the expected adverse effects of niacin, including flushing, pruritis and nausea, we also found the expected tachyphylactic pattern of response (24), with diminishing adverse events. The anti-lipolytic effects and the flushing of niacin are dependent on its receptor GPR109A, which has also been shown as having a role in insulin secretion in the pancreatic islet cells (25). Insulin is known as a critical suppressor for GH release; thus, it is possible that this elevation of GH by niacin is because of its inhibition of insulin. However, we found no significant differences in the concentrations or patterns of insulin attributable to niacin administration despite an apparent decrease of insulin levels during the time course.

The capillary glucose measurements in the group that received the greatest niacin exposure showed a significant increase when compared with the other doses. Prior studies suggest that long-term use of niacin may increase glucose concentrations (26) and induce other adverse consequences (27). Acute exposure may affect the FFA that become available to muscles and could explain the higher levels of plasma glucose observed (28). It is possible that differences in physical activity, timing of the onset of obesity or in body composition might contribute to the heterogeneity of responses observed.

The mechanisms through which FFA suppress GH remain somewhat unclear. In animal models, infusions that increase FFA can decrease GH secretion, suggesting that FFAs lead to inhibition of the GH axis (29). Decreased GH secretion has been demonstrated *in vitro* with porcine pituitary cells, where linoleic and oleic acid suppress the GH response to GHRH (12). The inhibition of porcine pituitary cells by a lipid-rich environment suggests that FFA may exert their effect directly on pituitary somatotrophs. This theory is supported by one *in vivo* animal study in which FFA inhibition was unable to be reversed by the addition of an antisomatostatin antibody, suggesting FFA do not induce somatostatin release (29). However, another *in vivo* study with similar methodology saw reversal of the effect, perhaps because of different timing of the antisomatostatin antibody in relation to GHRH administration (30).

Further studies are required to elucidate the pathways through which lipolytic inhibition de-repress GH secretory capacity including effects on insulin-like growth factor 1 and ghrelin concentrations.

Despite several adult studies demonstrating that FFA suppression increases GH obtained during GH

stimulation tests (16,17,22); see also Supporting Information, there are no paediatric trials examining the impact of niacin on stimulated GH in children. The high-GH stimulation test failure rate among even normally growing prepubertal children and the low-positive predictive value of failed GH stimulation tests during childhood to predict adult isolated GH deficiency suggest additional approaches to improve the specificity of GH testing could help prevent costly and unnecessary GH treatment. Future studies should investigate the impact of FFA suppression on the accuracy of GH stimulation testing in children both with and without obesity.

This study is limited by its design as a dose-finding trial. As such we empirically selected a small number of consecutively recruited children with obesity to be studied at each treatment dose. This approach meant participants could not be matched for their characteristics. It limited cohort size and rendered the study underpowered for some outcomes. Given the heterogeneity of spontaneous GH secretion, larger studies are needed to determine if niacin 500 mg q1h can reliably increase GH concentrations. There is also a need for more data to assess the mechanisms through which FFA affect the GH axis in children. Two other limitations of this study stem from its design. There was no randomization of subjects to the studied doses and no placebo-treated comparison group. Strengths of the study include the evaluation of three different dose regimens, with escalation to a dose that inhibited FFA. We employed a rigorous in-patient study design, which limited the between-individual variation from test-related differences and eliminated potential confounding factors.

In conclusion, in a small group of children with obesity, administration of Niacin 500 mg q1h per os decreased FFA concentrations below 0.2 mEq L^{-1}. This lipolytic inhibition was associated with a dose-dependent rise in serum GH. Further studies are needed to determine if niacin administration can safely improve the specificity and diagnostic accuracy of GH stimulation tests in children.

Conflict of interest statement

Dr. Yanovski reports grant support from Zafgen Inc. and Rhythm Pharmaceuticals for studies unrelated to growth hormone or niacin.

References

1. Heptulla R, Smitten A, Teague B, Tamborlane WV, Ma YZ, Caprio S. Temporal patterns of circulating leptin levels in lean and obese adolescents: relationships to insulin, growth hormone, and free fatty acids rhythmicity. *J Clin Endocrinol Metab* 2001; 86: 90–6.
2. Pineda J, Dieguez C, Casanueva FF, Martul P. Decreased growth hormone response to dexamethasone stimulation test in obese children. *Acta Paediatr* 1994; 83: 103–5.
3. Oliver SR, Rosa JS, Minh TD, *et al.* Dose-dependent relationship between severity of pediatric obesity and blunting of the growth hormone response to exercise. *J Appl Physiol* 2010; 108: 21–7.
4. Stanley TL, Levitsky LL, Grinspoon SK, Misra M. Effect of body mass index on peak growth hormone response to provocative testing in children with short stature. *J Clin Endocrinol Metab* 2009; 94: 4875–81.
5. Valera Mora ME, Manco M, Capristo E, *et al.* Growth hormone and ghrelin secretion in severely obese women before and after bariatric surgery. *Obesity (Silver Spring)* 2007; 15: 2012–8.
6. Argente J, Caballo N, Barrios V, *et al.* Multiple endocrine abnormalities of the growth hormone and insulin-like growth factor axis in prepubertal children with exogenous obesity: effect of short- and long-term weight reduction. *J Clin Endocrinol Metab* 1997; 82: 2076–83.
7. Savastano S, Angrisani L, Di Somma C, *et al.* Relationship between growth hormone/insulin-like growth factor-1 axis integrity and voluntary weight loss after gastric banding surgery for severe obesity. *Obes Surg* 2010; 20: 211–20.
8. Kasa-Vubu JZ, Barkan A, Olton P, Meckmongkol T, Carlson NE, Foster CM. Incomplete modified fast in obese early pubertal girls leads to an increase in 24-hour growth hormone concentration and a lessening of the circadian pattern in leptin. *J Clin Endocrinol Metab* 2002; 87: 1885–93.
9. Xu R, Wang Q, Yan M, *et al.* Orexin-A augments voltage-gated Ca2+ currents and synergistically increases growth hormone (GH) secretion with GH-releasing hormone in primary cultured ovine somatotropes. *Endocrinology* 2002; 143: 4609–19.
10. Dole VP. A relation between non-esterified fatty acids in plasma and the metabolism of glucose. *J Clin Invest* 1956; 35: 150–4.
11. Bjorntorp P, Bergman H, Varnauskas E. Plasma free fatty acid turnover rate in obesity. *Acta Med Scand* 1969; 185: 351–6.
12. Barb CR, Kraeling RR, Rampacek GB. Glucose and free fatty acid modulation of growth hormone and luteinizing hormone secretion by cultured porcine pituitary cells. *J Anim Sci* 1995; 73: 1416–23.
13. Gianotti L, Fassino S, Daga GA, *et al.* Effects of free fatty acids and acipimox, a lipolysis inhibitor, on the somatotroph responsiveness to GHRH in anorexia nervosa. *Clin Endocrinol (Oxf)* 2000; 52: 713–20.
14. Zhang Y, Schmidt RJ, Foxworthy P, *et al.* Niacin mediates lipolysis in adipose tissue through its G-protein coupled receptor HM74A. *Biochem Biophys Res Commun* 2005; 334: 729–32.
15. Quabbe HJ, Luyckx AS, L'Age M, Schwarz C. Growth hormone, cortisol, and glucagon concentrations during plasma free fatty acid depression: different effects of

nicotinic acid and an adenosine derivative (BM 11.189). *J Clin Endocrinol Metab* 1983; 57: 410–4.
16. Hicks BH, Taylor CI, Vij SK, *et al.* Effect of changes in plasma levels of free fatty acids on plasma glucagon, insulin, and growth hormone in man. *Metabolism* 1977; 26: 1011–23.
17. Stokes KA, Tyler C, Gilbert KL. The growth hormone response to repeated bouts of sprint exercise with and without suppression of lipolysis in men. *J Appl Physiol (1985)* 2008; 104: 724–8.
18. Uccella R, Morenghi R, Agosti C, Saponati G. Possible glucagon-mediated hypocholesterolemic activity of a nicotinic acid derivative (sorbinicate). *Artery* 1983; 11: 400–12.
19. Irie M, Tsushima T, Sakuma M. Effect of nicotinic acid administration on plasma HGH, FFA and glucose in obese subjects and in hypopituitary patients. *Metabolism* 1970; 19: 972–9.
20. Assan R, Tchobroutsky G. Serial plasma growth hormone levels in 33 cases of severe diabetic ketoacidosis – effects of sodium nicotinate. *Horm Metab Res* 1972; 4: 317–21.
21. Kok P, Buijs MM, Kok SW, *et al.* Acipimox enhances spontaneous growth hormone secretion in obese women. *Am J Physiol Regul Integr Comp Physiol* 2004; 286: R693–8.
22. Cordido F, Alvarez-Castro P, Isidro ML, Casanueva FF, Dieguez C. Comparison between insulin tolerance test, growth hormone (GH)-releasing hormone (GHRH), GHRH plus acipimox and GHRH plus GH-releasing peptide-6 for the diagnosis of adult GH deficiency in normal subjects, obese and hypopituitary patients. *Eur J Endocrinol* 2003; 149: 117–22.
23. Lanes R, Lunar L, Carrillo E, Villaroel O, Gunczler P, Palacios A. Acipimox, a nicotinic acid analog, stimulates growth hormone secretion in short healthy prepubertal children. *J Pediatr Endocrinol Metab* 2000; 13: 1115–20.
24. Stern RH, Spence JD, Freeman DJ, Parbtani A. Tolerance to nicotinic acid flushing. *Clin Pharmacol Ther* 1991; 50: 66–70.
25. Chen L, So WY, Li SY, Cheng Q, Boucher BJ, Leung PS. Niacin-induced hyperglycemia is partially mediated via niacin receptor GPR109a in pancreatic islets. *Mol Cell Endocrinol* 2015; 404: 56–66.
26. Sazonov V, Maccubbin D, Sisk CM, Canner PL. Effects of niacin on the incidence of new onset diabetes and cardiovascular events in patients with normoglycaemia and impaired fasting glucose. *Int J Clin Pract* 2013; 67: 297–302.
27. Anderson TJ, Boden WE, Desvigne-Nickens P, *et al.* Safety profile of extended-release niacin in the AIM-HIGH trial. *N Engl J Med* 2014; 371: 288–90.
28. Vega GL, Cater NB, Meguro S, Grundy SM. Influence of extended-release nicotinic acid on nonesterified fatty acid flux in the metabolic syndrome with atherogenic dyslipidemia. *Am J Cardiol* 2005; 95: 1309–13.
29. Alvarez CV, Mallo F, Burguera B, Cacicedo L, Dieguez C, Casanueva FF. Evidence for a direct pituitary inhibition by free fatty acids of in vivo growth hormone responses to growth hormone-releasing hormone in the rat. *Neuroendocrinology* 1991; 53: 185–9.
30. Imaki T, Shibasaki T, Masuda A, *et al.* The effect of glucose and free fatty acids on growth hormone (GH)-releasing factor-mediated GH secretion in rats. *Endocrinology* 1986; 118: 2390–4.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Supplemental Table 1. **Individual participant data**. NHB (Non-Hispanic Black), NHW (Non-Hispanic White), BMI (Body Mass Index), BMI% (Body Mass index Percentile), BMIz (Body Mass Index z score by CDC 2000 standards), A.N. (Acanthosis Nigricans + present, - absent), TC (Total cholesterol), LDL (Low Density Lipoprotein Cholesterol), HDL (High Density Lipoprotein Cholesterol), TG (Triglycerides), FFA (Free fatty acids) PRN (as needed)

Supplemental Table 2: **Adverse Events After Niacin Administration**. Percentage of subjects who-reported expected adverse events of niacin at baseline (time 0) and after niacin administration.