Impaired postprandial fullness in Type 2 diabetic subjects is rescued by acute exercise independently of total and acylated ghrelin

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Submitted 14 February 2013; accepted in final form 17 June 2013

Knudsen SH, Karstoft K, Solomon TP. Impaired postprandial fullness in Type 2 diabetic subjects is rescued by acute exercise independently of total and acylated ghrelin. J Appl Physiol 115: 618–625, 2013. First published June 20, 2013; doi:10.1152/japplphysiol.00204.2013.—Ghrelin levels are suppressed in obese subjects and subjects with Type 2 diabetes mellitus (T2DM). Exercise-stimulated decreases in plasma ghrelin are a proposed mediator of exercise-induced satiety in healthy subjects. However, exercise-induced satiety and the impact of impaired ghrelin levels in obesity-related disease are poorly understood. Therefore our objective was to investigate exercise-induced postprandial satiety and ghrelin responses in overweight subjects with T2DM (N = 8) and healthy controls (N = 7). Visual analog scale satiety questionnaires (assessing hunger, thirst, food that could be eaten, nausea, and fullness) and circulating levels of glucose, insulin, and total and acylated ghrelin were measured at baseline and in response to a 75 g oral glucose load, provided immediately after an aerobic exercise bout (1 h at 50% HRmax) or no exercise (rest trial), on two separate occasions. Baseline levels of total (284.4 ± 15.9 and 397.6 ± 35.2 pmol/l) and acylated ghrelin (7.9 ± 1.0 and 13.7 ± 1.2 pmol/l) were lower in subjects with T2DM compared with healthy subjects (P < 0.05). In the rest trial, post- vs. preprandial feeling of fullness increased in healthy subjects but decreased in subjects with T2DM (healthy vs. T2DM; P < 0.05). Exercise increased postprandial fullness in the T2DM group (P < 0.05), while plasma ghrelin levels were unaffected. Our data suggest that the presence of T2DM likely drives suppressed ghrelin levels and poor appetite regulation, but a single exercise bout is sufficient to restore oral glucose-induced fullness independently of ghrelin.

EXERCISE HAS BEEN ARGUED by some not to mediate weight loss due to compensatory energy intake (8, 25). However, a single exercise bout does not increase hunger or energy intake (37, 41), although energy balance is altered by an increased energy expenditure. In fact, exercise can increase satiety and suppress hunger (1–4, 21, 23, 24, 28), arguing the potential importance of exercise in weight loss and maintenance. Whether exercise and satiety are causally related is not well defined but may involve satiety-regulating gut hormones.

Ghrelin is secreted by P/D1 cells in the stomach (16) and exists in two isoforms: active acylated ghrelin and des-acylated ghrelin (15). Plasma ghrelin concentrations rise preprandially and decline during the postprandial period (5), indicating that ghrelin is involved in the acute regulation of satiety. In addition, increasing evidence suggests that ghrelin is also linked to the energy status of the body. While fasting levels of ghrelin are increased in patients with anorexia nervosa (18), levels have been found to be decreased in obese subjects (9, 38) and obese patients with Type 2 diabetes mellitus (T2DM) (9, 20, 33, 34). Some studies suggest that this decrease in ghrelin is associated with the presence of hyperinsulinemia, insulin resistance, and T2DM (20, 33). On the other hand, obese T2DM subjects elicited lower levels than lean T2DMs (34), supporting evidence that the degree of obesity drives the impairment of ghrelin levels (9, 38). Nevertheless, the functional relevance of the disruption of ghrelin levels in obesity and T2DM is not clear.

Weight loss increases plasma ghrelin levels (12, 13) and exercise-induced weight loss has been associated with convincing weight maintenance (17), which might be due to improved appetite control (29) and no compensatory increase in energy intake during an exercise intervention (6). So, a link between weight loss and satiety could be speculated. Also, exercise-induced satiety appears in the presence of decreased circulating levels of ghrelin (1–3, 21, 23), independent of changes in body weight. Additionally, acute aerobic exercise only decreases acylated ghrelin (1–3, 21, 23, 30) without affecting total ghrelin levels (4, 28, 35). That said, such exercise studies have focused on healthy subjects, and the exercise effects on satiety-regulating mechanisms in obesity-related diseases, such as T2DM, are poorly understood. With impaired ghrelin levels in nondiabetic obese subjects as well as lean and obese subjects with T2DM, the impact of the diabetic state on ghrelin levels is not clear. Therefore the first aim was to examine the immediate effects of a single exercise bout on ghrelin and satiety responses in overweight T2DM subjects and healthy controls that did not differ with respect to age and body mass index (BMI), controlling for the influence of body composition. Only a few studies have addressed the functional relevance of the exercise-induced satiety suggesting that exercise can also affect postprandial satiety (3, 22). Therefore the second aim was also to investigate the exercise-induced satiety in response to an oral glucose load.

EXPERIMENTAL PROCEDURES

Subjects. Sixteen sedentary overweight males (N = 8 with T2DM and N = 8 healthy controls) participated in the study. One healthy subject was excluded from all statistical analysis due to incomplete data collection during one of the trials. Subjects were recruited from the local area and underwent a full medical screening (medical history, physical exam, and blood profile). Enrolled subjects underwent dual-energy x-ray absorptiometry (DXA) scan to determine whole body adiposity and fat-free mass and an exercise test on a bicycle ergometer to determine maximal aerobic capacity [oxygen consumption (VO2 max)], power output (Wmax), and heart rate (HRmax). Grouping of T2DM and healthy controls with normal glucose tolerance (NGT) was based on World Health Organization definitions of 2-h glucose values during oral glucose tolerance tests.
Subjects were recruited with the intention to match mean age and BMI between groups. Individuals were included for participation if they were between 45 and 65 years old and had BMI between 25 and 35 kg/m² and excluded if they 1) were treated with insulin, 2) were weight unstable (>5 kg in previous 6 mo), 3) had an illness that contraindicated physical activity, or 4) had hematological, renal, hepatic, cardiovascular, or pulmonary disease. All T2DM subjects were treated with antidiabetic drugs (metformin N = 7, DPP4 inhibitors, and sulfonylureas N = 1) and two were treated with antihyper- tensive drugs. Furthermore, one healthy control and three T2DM subjects were treated with statins. The study was approved by the Scientific Ethics Committee of the capital region of Denmark (file H-3-2010-127) in accordance with the Helsinki Declaration and subjects provided written informed consent to participate.

Experimental design. On two occasions, in a randomized order, subjects underwent an oral glucose tolerance test (OGTT) combined with blood sampling and satiety questionnaires after an hour of rest (Rest trial) or exercise (Exercise trial). Exercise consisted of 1 h of cycle ergometry (Monark 839E, Monark, Sweden) at 50% of Wmax and 60–90 rpm. Power output was fixed during the entire trial. HR was measured continuously and all trials were supervised by the same educated trainer. For 3 days prior to each trial, subjects were instructed by the same study investigator to complete diet records to ensure that daily energy intake (measured as the mean number of calories consumed per day during the 3 days prior to each trial) and daily macronutrient composition (measured as the mean percentage of energy derived from carbohydrate, fat, or protein ingestion during the 3 days) were not different between trials. Also, subjects were informed to refrain from physical activity and to pause antidiabetic, antihypertensive, or statin drugs in these pretrial days.

Experimental protocol. Trials were performed after an overnight fast (~10 h). When arriving at the laboratory, a catheter was placed in an antecubital vein for blood sampling. Immediately after 1 h of rest/exercise, a 180-min OGTT began (75 g glucose in 300 ml water). Blood was drawn at baseline (T = −90) as well as after exercise/rest (T = 0) and during the OGTT (T = 30, T = 60, T = 90, T = 120, and T = 180 min) for measures of glucose, insulin, and total and acylated ghrelin. Furthermore, to monitor plasma volume, hematocrit (Hct) and hemoglobin (Hb) were measured at T = −90 and T = 0. Samples for plasma glucose were collected into heparin-containing syringes and immediately analyzed. Blood samples were collected into EDTA-containing tubes for Hct and Hb analysis, into EDTA + aprotinin (10,000 kIU/ml) tubes for plasma ghrelin analysis (14), and into tubes without coagulation inhibitors for serum insulin analysis. Blood samples for plasma collection were immediately placed on ice and subsequently centrifuged (3,500 g, 15 min, 4°C). Samples were then aliquoted and stored at −80°C until analyses. Samples for serum collection were left at room temperature for 30 min before centrifugation and immediately sent for analysis of insulin at the hospital laboratory. Satiety was measured using visual analog scale questionnaires at T = −90, T = 0, T = 30, T = 60, T = 120, and T = 180 min.

Measurement and determinations. Plasma glucose was measured by the glucose-oxidase method (ABL 700, Radiometer). The analyses of serum insulin, Hct, and Hb were performed at the Department of Clinical Biochemistry, Rigshospitalet [insulin was measured using electrochemiluminescent immunoassay, Hct was measured in duplicate with a microHct centrifuge, and Hb was measured using a co-oximeter (Sysmex XE-2100)]. Total and acylated ghrelin levels were measured in duplicate using a radioimmunoassay (RIA) (Millipore) with an intra-assay coefficient of variation (CV) of 5.2 ± 0.5 and 4.1 ± 0.4, respectively. Diet records were analyzed by the same investigator using DanKost Sport 2000 software (Danish Catering Centre, Herlev, Denmark). A previously validated visual analog scale questionnaire was used to assess satiety (11). Participants indicated their perceived level of satiety by placing a mark on a 100-mm line separating “not at all” (0 mm) and “very” (100 mm) that best represented how hungry they felt, how thirsty they felt, how much food they could eat, how nauseated they felt, and how full they felt. All satiety questionnaires were analyzed by the same person.

Calculations. Responses of each satiety marker, total and acylated ghrelin, insulin, and glucose to the 180-min OGTT were calculated as area under the curve (AUCOGTT) by using the trapezoidal method. The preprandial phase was calculated as the difference between mean values of T = −90 and T = 0 and the initial postprandial phase as the mean of T = 30 and T = 60. The postprandial response of each satiety marker was calculated as the difference between pre- and postprandial phase, indicated as the delta (Δ) value of the means.

Statistics. On the basis of effect sizes calculated from previously published data (2, 3), using G*Power v3 (http://wwwpsycho.uni-duesseldorf.de/abteilungen/aap/gpower3), we determined that a sample size of 6 would achieve adequate statistical power (0.80) for the effect of exercise on satiety and that a sample size of 7 would be sufficient to determine a significant effect of exercise on ghrelin. Student’s t-tests were used to assess differences between baseline and postexercise values, AUC and Δ values of satiety markers, total and acylated ghrelin, and serum and plasma levels of metabolites (glucose, insulin, Hb, and Hct). Unpaired t-tests were used to compare NGT with T2DM groups and paired t-tests were used to compare exercise and control variables within each of the groups in these markers. Repeated-measures ANOVA was used to test the main effects and the interactions of time, group, and trial for satiety parameters, ghrelin, glucose, and insulin. Post hoc analyses with adjustment for multiple comparisons using the Bonferroni method were used to examine differences between groups, trials, and time points. Linear regression was also used to examine relationships between variables. All data are presented as means ± SE and Δ ± SE. All analyses were conducted using Prism v4 (GraphPad, San Diego, CA). Statistical significance was accepted when P < 0.05.

RESULTS

Subjects. Subject characteristics are presented in Table 1. Group means for age, BMI, VO2 max, body fat, and fat-free mass were not different between the T2DM (n = 8) and healthy control (n = 7) groups. T2DM subjects elicited higher fasting and 2-h OGTT glucose values compared with healthy controls.

Diet. Daily energy intake and macronutrient composition were not different between the rest and exercise trials in either of the groups.

Exercise responses. All subjects completed the 1 h of cycle ergometry exercise. This was performed at 49.7 ± 0.5% of Wmax and 60–90 rpm giving a mean work load of 116.8 ± 7.7 W and a mean heart rate of 116.5 ± 3.7 beats/min. There were no differences between groups.

Satiety responses. Fasting satiety ratings (hunger, thirst, food could be eaten, nausea, and fullness) were similar be-
between rest and exercise trial in both healthy and T2DM subjects and there were no differences between groups (Fig. 1A). Also, none of the satiety ratings were changed immediately after rest or exercise (T = −90 vs. 0 min; Fig. 1A). Furthermore, repeated-measures ANOVA revealed no main effect of group or trial in any of the satiety markers throughout the two trials, while hunger, thirst, and food that could be eaten differed over time in both groups during rest and exercise trial (Fig. 1A; \( P < 0.001, P < 0.01, \) and \( P < 0.001, \) respectively). However, in the rest trial, while the postprandial feeling of fullness (determined as the difference between the pre- and postprandial phase; \( \Delta \)) was increased in healthy subjects (Fig. 1E; \( \Delta = +8.4 \pm 5.1 \) VAS mm), it was decreased in subjects with T2DM (Fig. 1E; \( \Delta = -3.9 \pm 2.0 \) VAS mm; healthy vs.

Fig. 1. Following an overnight fast, \( N = 8 \) subjects with Type 2 diabetes mellitus (T2DM; circles and thin lines) and \( N = 7 \) healthy controls (Healthy; squares and thick lines) underwent oral glucose tolerance tests (OGTTs) (ingested at \( T = 0 \) min) after a 1-h period of rest (filled) or exercise (open). Subjects completed visual analog scale questionnaires to determine various parameters of satiety. The data show total response (A) and postprandial response (B) (difference between pre- and postprandial phase, \( \Delta \)) of the five satiety parameters: hunger (0 not full - 100 very full), thirst (0 not thirsty - 100 very thirsty), food you could eat (0 no food - 100 very much food), nausea (0 not nauseated - 100 very nauseated), and fullness (0 not full - 100 very full). Data are presented as means ± SE. A: repeated-measured ANOVA revealed a main effect of time for hunger, thirst, and food could be eaten in both groups during rest and exercise trial (\( P < 0.001, P < 0.01, \) and \( P < 0.001, \) respectively) but no effect of group or trial. Paired \( t \)-tests showed that exercise significantly increased postprandial thirst in healthy subjects and postprandial fullness in subjects with T2DM: \( *P < 0.05; \) area under the curve (AUC) 0–180 min during rest trial vs. exercise trial. B: unpaired \( t \)-tests showed that during the resting trial the postprandial response (difference between pre- and postprandial phase) for nausea was significantly greater in T2DM subjects and that fullness was significantly lower in T2DM subjects: \( *P < 0.05, -90 \) to 0 min vs. 0 to 60 min.
T2DM, \( P < 0.05 \)). This indicates an impaired glucose-induced fullness in T2DM. Furthermore, \( \Delta \) nausea was higher in T2DM compared with healthy controls (Fig. 1B; \( P < 0.05 \)), while no between-group differences in the postprandial responses of hunger, thirst, or food that could be eaten were found.

In the exercise trial thirst was increased during OGTT in healthy subjects (Fig. 1A: AUC: 6,773 ± 480 vs. 8,206 ± 526 VAS min-180 min, \( P < 0.05 \)). Furthermore, the feeling of fullness in response to the OGTT was increased in T2DM compared with the rest trial (Fig. 1A: AUC: 4,870 ± 1,004 vs. 6,003 ± 1,075 VAS min-180 min, \( P < 0.05 \)). Also, \( \Delta \) fullness was not different between groups in exercise trial (Fig. 1B; \( P > 0.05 \)).

**Total ghrelin.** Levels of total ghrelin in healthy and T2DM subjects during the rest and exercise trials are presented in Fig. 2. Fasting plasma total ghrelin was lower in T2DM subjects compared with healthy subjects (284.4 ± 15.9 vs. 397.6 ± 35.2 pmol/l, \( P < 0.001 \)). Repeated-measures ANOVA revealed that there was a main effect of time (\( P < 0.0001 \), both) and group in the rest and exercise trial (\( P < 0.05 \) and \( P < 0.001 \), respectively), indicating that during both trials ghrelin levels were lower in subjects with T2DM compared with healthy controls (Fig. 2A). However, no main effect of trial was found by repeated-measures ANOVA in either of the groups (Fig. 2A, \( P > 0.05 \)). Across groups, post hoc analyses revealed no significant differences at any of the time points. The response (AUC) to the OGTT was also lower in T2DM compared with healthy controls (Fig. 2B, \( P < 0.05 \)); however, there was no difference between trials in any of the groups. Also, the postprandial response (pre- vs. postprandial phase, \( \Delta \)) was not different between groups or between trials.

**Acylated ghrelin.** Levels of acylated ghrelin in healthy and T2DM subjects during the rest and exercise trials are presented in Fig. 3. Fasting plasma acylated ghrelin was lower in T2DM subjects compared with healthy controls (7.9 ± 1.0 vs. 13.7 ± 2.9 pmol/l, \( P < 0.001 \)). Repeated-measures ANOVA revealed a main effect of time (\( P < 0.0001 \), both) and group in rest and exercise trial (\( P < 0.01 \) and \( P < 0.001 \), respectively), showing that during both trials acylated ghrelin levels were lower in subjects with T2DM (Fig. 3A). No main effect of trial was found by repeated-measures ANOVA (Fig. 3A, \( P > 0.05 \)). Post hoc analyses showed that levels were lower in T2DM subjects at \( T = 0 \), 90, and 120 min in the rest trial and at all time points except 120 min in the exercise trial. The acylated ghrelin response (AUC) to the OGTT was also lower in the T2DM group (Fig. 3B, \( P < 0.05 \)); however, there was no difference between trials in any of the groups. Also, the postprandial response (pre- vs. postprandial phase, \( \Delta \)) was not different between groups or between trials.

**Blood and plasma volume.** Hct and Hb were increased by exercise in healthy subjects (\( \Delta \)Hct: 2.6 ± 0.4%, \( P < 0.001 \); \( \Delta \)Hb: 0.7 ± 0.1 mmol/l, \( P < 0.0001 \)) and in subjects with T2DM (\( \Delta \)Hct: 3.5 ± 0.4%, \( P < 0.0001 \); \( \Delta \)Hb: 0.8 ± 0.1 mmol/l, \( P < 0.001 \)), likely indicative of a decrease in plasma volume.

**Glucose and insulin.** Levels of glucose and insulin in healthy and T2DM subjects during the rest and exercise trials are presented in Fig. 4. As expected, T2DM subjects elicited higher fasting glucose and insulin levels compared with the healthy (\( P < 0.05 \) and \( P < 0.01 \), respectively, Table 1). Also, the glucose (Fig. 4A, T2DM vs. healthy, \( P < 0.001 \)), but not insulin (Fig. 4), response to the oral glucose load was higher in T2DM. Fasting levels of insulin did not differ between the rest and exercise trials in either of the groups. In contrast, fasting glucose levels were higher in T2DM subjects in the exercise trial compared with rest (8.1 ± 0.9 vs. 8.9 ± 1.1 mmol/l, \( P < 0.05 \) and tended to be lowered by exercise (\( T = -90 \) vs. 0: 8.9 ± 1.1 vs. 7.6 ± 0.9 mmol/l, \( P = 0.08 \)). Repeated-measures ANOVA revealed a main effect of time (\( P < 0.0001 \), both) and group for plasma glucose (\( P < 0.001 \) and \( P < 0.05 \) for the rest and exercise trials, respectively) but no main effect of trial in either healthy or T2DM subjects (Fig. 4, \( P > 0.05 \)). A main
The effect of time was found for serum insulin by repeated-measures ANOVA in both trials in healthy and T2DM (P < 0.0001, both) but no group or trial differences. Glucose and insulin responses (AUC) to the OGTT were not different between trials in either healthy (P = 0.05, rest vs. exercise trial: glucose: 1,267 ± 51 vs. 1,391 ± 83 mmol/l-180 min; insulin: 38,112 ± 6,184 vs. 34,578 ± 3,000 pmol/l-180 min) or T2DM subjects (P > 0.05, rest vs. exercise trial: glucose: 2,390 ± 205 vs. 2,401 ± 278 mmol/l-180 min; insulin: 53,675 ± 9,709 vs. 47,362 ± 6,355 pmol/l-180 min).

**Correlations.** Neither total nor acylated ghrelin correlated with any of the satiety parameters, glucose, insulin, BMI, or percentage of body fat.

**DISCUSSION**

The novel finding arising from this study is that impaired postprandial feeling of fullness is rescued by a single bout of exercise in T2DM and that this occurs independently of changes in total and acylated ghrelin. Our study confirmed that ghrelin levels are suppressed in overweight T2DM subjects both at baseline and in the postprandial state (9, 20, 34, 38) and furthermore showed that this was accompanied by a reduced glucose-induced feeling of fullness. The reduction of basal ghrelin secretion in response to an increased energy surplus seems to be a reasonable negative-feedback mechanism that...
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helps prevent further energy intake (9, 34). However, it is less obvious why the basal secretion is lower in T2DM than their healthy controls with the same degree of obesity. We did not include a nonobese diabetic group, but the fact that fasting ghrelin levels were lower in the overweight T2DM compared with the overweight healthy controls suggests that the diabetic state could be a contributing factor to the impairment in ghrelin levels. This is in accordance with the findings of Erdmann and colleagues (9) where T2DM subjects had lower ghrelin levels in the fasting and postprandial state compared with healthy obese subjects.

The present study is the first to examine exercise-induced postprandial satiety and levels of total and acylated ghrelin in T2DM and healthy controls, which are not different with respect to age and BMI. However, several studies have investigated the effects of exercise on satiety and ghrelin in healthy subjects. These studies indicate that exercise suppresses hunger and induces satiety (1–4, 21, 23, 24, 28) and some have shown that this happens in the presence of suppressed ghrelin levels (1–3, 21, 23). Even though satiety was not altered immediately after exercise in either of the two groups, our study confirms that satiety is not reduced immediately following exercise. In fact, the postprandial feeling of fullness was increased by exercise in T2DMs. In accordance with previous studies this was without any changes in the levels of total ghrelin either during exercise or in the postprandial phase (4, 28, 35). However, in contrast to recent studies where exercise-induced satiety has been found together with a suppression of acylated ghrelin (1–3, 21, 23), these levels were also unchanged in the present study. Acylation of ghrelin is thought to be essential for appetite regulation because only the acylated form of the hormone can cross the blood-brain barrier (32). This argues that potential changes related to exercise-induced satiety are mediated by the acylated ghrelin. In our study we measured both total and acylated ghrelin, but as stated above neither of these levels were affected by exercise. In the rest trial, ghrelin responses were impaired in our T2DM group, and when Marzullo and colleagues (30) tested obese subjects with impaired ghrelin levels they found that levels of acylated ghrelin decreased during exercise in parallel with satiety ratings. Because this relationship was absent in our T2DM subjects, it appears that exercise-induced satiety is independent of a further suppression of already impaired circulating ghrelin in T2DM subjects. We did not include a lean healthy group; however, baseline ghrelin levels were not suppressed in our overweight healthy controls compared with data reported in lean subjects from previous studies (4, 9). This further supports the proposed role of diabetes in the impairment of ghrelin metabolism, independently of the degree of obesity.

Both glucose and insulin have been found to elicit a suppressing effect on ghrelin levels (9, 10, 31, 34, 36). The fasting hyperglycemic and hyperinsulinemic levels in T2DM subjects compared with healthy controls can explain the baseline differences in ghrelin levels (20). In contrast to the postprandial glucose responses, the insulin responses were similar in healthy and T2DM, indicating that chronic hyperglycemia may be a driving factor in the loss of postprandial suppression of ghrelin levels. This is in line with the findings of Erdmann and colleagues (9) where postprandial ghrelin levels were suppressed in both obese nondiabetic normal and hyperinsulinemic subjects. Neither glucose nor insulin levels were elevated following exercise; in fact, glucose levels tended to decrease in T2DM. This is in accordance with the literature where glucose levels have been found to decrease during exercise in hyperglycemic individuals (19, 27) in contrast to healthy subjects in whom levels usually increase (1, 2, 27). The lack of changes in glucose levels in healthy subjects and the decrease in those with T2DM can explain why ghrelin levels and therefore appetite was not suppressed immediately after exercise in either of the two groups. Furthermore, this could suggest that glucose-derived suppression of ghrelin is not the mediator of exercise-induced satiety in T2DM. Also, postprandial glucose and insulin responses were not affected by exercise in either of the groups, explaining the lack of exercise-induced changes in postprandial ghrelin levels. However, the higher postprandial feeling of fullness following exercise found in T2DM remains unexplained.

Exercise-mediated increases in Hct and Hb could be due to a reduction in plasma volume caused by a reduced hydration status of the subjects induced by sweating (7). This can explain changes in plasma metabolites seen during exercise. However, no significant exercise-derived changes were found in the metabolic measures of the current study. When correcting for the change in Hct and Hb, postprandial total ghrelin levels, but not acylated ghrelin levels, tended to be lower after exercise compared with rest (AUC: 44,324 ± 3,164 vs. 37,761 ± 3,705 pmol/l, rest vs. exercise, P = 0.056). From this it could be speculated that a decrease in plasma volume may have masked a small decrease in total ghrelin levels. Even so, the measured concentration is what the relevant receptor is exposed to and thus elicits the cellular function. Furthermore, the change in blood volume occurred in both T2DM subjects and healthy controls. So the potential change in blood volume is most likely not responsible for changes in metabolites or hormones that could have explained the exercise effect on satiety in T2DM.

Exercise was performed with a duration similar to studies finding exercise-induced satiety (2–4). However, the intensity of ~50% of Wmax giving a mean work load of ~117 W and a heart rate of 116 beats/min is below intensities (167–179 beats/min) performed in these previous studies. Owing to the absence of a confirmation of exercise-induced satiety and suppression of acylated ghrelin levels in our healthy control group, it could be argued that the intensity of the exercise in our study was not sufficient to mediate such suppression and therefore also an insufficient stimulus to affect satiety. However, while levels of ghrelin were not affected, the postprandial feeling of fullness was increased by exercise in T2DM. Since the exercise intensity did not differ between groups, we perceive the exercise intensity to be sufficient to induce an effect on satiety at least in T2DM. This further supports that exercise-induced satiety is mediated by a mechanism besides ghrelin in T2DM subjects. However, since ghrelin is also released in small amounts within the central nervous system acting directly on the appetite-regulating neurons in the hypothalamus (26), it is possible that altered central ghrelin levels would potentially explain the exercise-induced increase in satiety in T2DM subjects. Nevertheless, our finding that aerobic exercise can improve the postprandial feeling of fullness may extrapolate to an improvement in the regulation of energy intake and therefore help improve glycemic control in T2DM patients. That said, owing to the nature of our study design, we did not
objectively measure such outcomes; however, exercise-induced increment in satiety has previously been shown to reduce energy intake in lean and obese young healthy males (39–41). Future studies are needed to determine whether exercise-induced changes in satiety directly affect energy intake and glycometric control in subjects with T2DM.

Summary. Our study confirms existing findings by showing that postprandial fullness is not reduced by exercise. Furthermore, our novel data show that the presence of T2DM likely drives suppressed ghrelin levels and poor appetite regulation but that a single exercise bout is sufficient to restore glucose-induced satiety independently of ghrelin. Also, our results suggest that low ghrelin levels in T2DM do not prevent exercise-induced satiety. While we have not determined the mechanism, because a relationship between exercise-induced reduction in plasma ghrelin and increased satiety was not demonstrated in our T2DM subjects, we suggest that other mediators are responsible for the exercise-induced rescue of glucose-induced satiety in subjects with T2DM. Future studies should determine the physiological relevance of impaired nutrient-induced satiety in T2DM and further elucidate the mechanisms underlying exercise-induced reversal of this impair-ment.

ACKNOWLEDGMENTS

We express our gratitude to Lisbeth Andreasen for her technical assistance with clinical biochemistry assays.

GRANTS

This study was funded by a Paul Langerhans program grant from the European Foundation for the Study of Diabetes (T. P. J. Solomon). The Centre of Inflammation and Metabolism is supported by a centre grant from the European Foundation for the Study of Diabetes (T. P. J. Solomon). The Centre of Inflammation and Metabolism is supported by a centre grant from the Danish National Research Foundation and is part of the UNIK Project: Food, Fitness and Pharma for Health and Disease, supported by the Danish Ministry of Science, Technology, and Innovation.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: S.H.K. and T.P.S. approved final version of manuscript. S.H.K., K.K., and T.P.S. performed experiments; S.H.K. analyzed data; K.K. and T.P.S. contributed reagents and/or materials; S.H.K., K.K., and T.P.S. approved final version of manuscript.

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