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RESEARCH ARTICLE

High-dose thiamine supplementation may reduce resting energy expenditure in individuals with hyperglycemia: a randomized, double – blind cross-over trial

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Abstract

Background Despite the crucial role of thiamine in glucose and energy metabolism pathways, there has been no published study examining the impact of thiamine on energy metabolism in humans.

Objective To assess the effects of thiamine supplementation on resting energy expenditure (REE) in individuals with hyperglycemia.

Methods Twelve hyperglycemic patients completed this double-blind, randomized trial, where all participants received both thiamine (300 mg/day) and matched placebo for 6 weeks in a cross-over manner. REE was assessed by indirect calorimetry. Anthropometric measurements, fasting and 2-h plasma glucose, and glucose-induced thermogenesis were also assessed at the beginning and on the completion of each six-week phase.

Results Participants consuming thiamine supplements experienced a significant decrease in the REE assessed at week six compared to the baseline [mean (SE): 1478.93 (73.62) vs.1526.40 (73.46) kcal/d, $p = 0.02$], and the placebo arm ($p = 0.002$). These results did not change significantly after adjusting for the participants' body weight and physical activity as potential confounders. Six-week intervention had no significant effect on the participants' body weight or waist circumference, in either supplement or placebo arms (all p values>0.05). However, correlation analysis highlighted significant positive relationships between the changes in REE, and those in fasting ($r_s = 0.497$, $p = 0.019$) and 2-h plasma glucose ($r_s = 0.498$, $p = 0.018$) during the six-week intervention period.

Conclusion Supplementation with high-dose thiamine may attenuate REE in patients with impaired glucose regulation. Our findings suggest that the impact of thiamine on REE may in part be explained by improved glycemic control.

Trial registration Australian New Zealand Clinical Trials Registry ACTRN12611000051943. https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12611000051943

Keywords Thiamine · Vitamin B1 · Diabetes mellitus · Hyperglycemia · Glucose intolerance · Blood glucose · Energy expenditure · Energy metabolism · Body weight

Introduction

Diabetes has reached epidemic proportions, affecting around half a billion people worldwide. Additionally, over 370 million adults in the world are estimated to have impaired glucose tolerance, according to the 2019 data from the International Diabetes Federation [1]. It is known that hyperglycemia, in either diabetic or pre-diabetic ranges, can induce various biochemical disturbances at the cellular level, leading to both vascular and tissue damages [2, 3].

Existing evidence reveals that individuals with hyperglycemia may have a higher resting energy expenditure (REE) compared to normal people [4]. This could be in part due to an increased rate of hepatic gluconeogenesis, which is an energetically expensive process [5, 6]. Reciprocally, improving hyperglycemia has been proposed to induce a reduction in the energy expenditure in this group of patients [7].

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Thiamine is a water soluble vitamin playing a crucial role as a co-enzyme in the pathways involved in glucose homeostasis and energy metabolism [8, 9]. Emerging evidence indicates that thiamin may modify specific mechanisms involved in hyperglycemic complications [10–12]. Accordingly, thiamine supplementation has been implicated to have an array of benefits for people with hyperglycemia [13–15]. Supplementation with high-dose thiamine was reported to decrease fasting plasma glucose in drug-naïve patients with T2D [13], and improve glucose tolerance in hyperglycemic individuals [16]. Considering the association of hyperglycemia and energy metabolism mentioned above, the effects of thiamine on blood glucose could be hypothetically accompaneed by the changes in the energy metabolism as well.

There is also evidence indicating that administration of thiamine-deficient diets can reduce food intake and increase resting energy expenditure in experimental animals [17]. Despite these preliminary findings, there has been, however, no published study examining the impact of thiamine on energy metabolism in humans. Thus, the present study investigated the effect of high-dose thiamine supplementation on energy expenditure in patients with hyperglycemia.

Methods

This was a randomized, double-blind crossover design trial, conducted from May 2009 to March 2011 at Curtin University, Australia. This study was approved by the Curtin University Human Research Ethics Committee, and all participants provided written informed consent.

Subjects

Seventeen hyperglycemic patients, comprising 14 individuals with pre-diabetic hyperglycemia and 3 new cases of T2DM, with a BMI 19–40 kg/m^2 and aged 18–75 years participated in the study. Participants were diagnosed as pre-diabetic (fasting plasma glucose in the range 110–125 mg/dl, and/or 2-h plasma glucose in the range of 140–199 mg/dl) or diabetic (fasting plasma glucose ≥126 mg/dl and/or 2-h plasma glucose ≥200 mg/dl) based on the WHO/IDF cut-offs for diagnosis of diabetes mellitus and intermediate hyperglycemia [18]. Individuals with known impaired renal or liver function; major cardiac, neurologic or gastrointestinal disorders; and known allergy or intolerance to thiamine as well as current smokers and women who were pregnant or breast feeding were excluded from this study. No subject was on medications affecting the study outcomes or thiamine metabolism. Participants who were on dietary supplements containing thiamine, or those who consumed more than 2 standard alcoholic drinks per day were instructed not to take the supplement and reduce the alcohol intake during the study period, starting 4 weeks before the first clinical assessment.

Study design and procedure

Hyperglycemic participants were randomly assigned to two groups; to receive either 100 mg thiamine (as thiamine hydrochloride) three times a day (300 mg/day) or a matched placebo for 6 weeks. Clinical measurements were performed at baseline, week 3 and week 6. After completing the first phase and a 14-week wash-out period, participants received alternative capsules for another 6 weeks. The measurements were then repeated on the other three separate visits, similar to the first part (Fig. 1). All participants and investigators who were involved in data collection and analyses were blinded to the treatment allocation. The thiamine capsules contained thiamine hydrochloride and the inactive ingredients starch and lactose (Betamin, Sanofi-Aventis Australia Pty Ltd., Australia). The capsules provided as placebo were matched with the supplement and contained only the inactive ingredients included in the thiamine capsules (starch and lactose).

Participants were instructed to keep to their usual diet and level of physical activity throughout the study. To monitor participants' dietary habits, they were instructed to record all food and drinks consumed over three consecutive days, including 2 week-days and one weekend day, before baseline

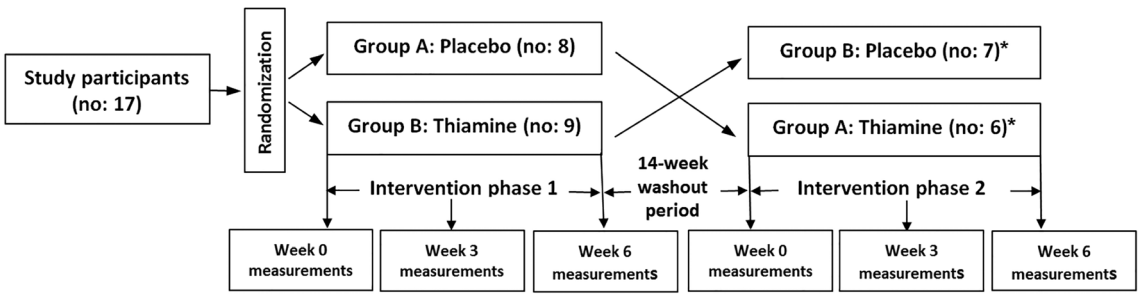

Fig. 1 Study design. *, Seventeen hyperglycemic participants commenced this randomized, double-blind crossover trial. Of those, four subjects dropped out after completing the first phase (two participants from each group) because of the time involved or starting the medication for treatment of hyperglycemia. Another participant was excluded later, due to the lack of compliance during the study. Data of twelve hyperglycemic patients were included for final analysis, where all participants received both thiamine and matched placebo for 6 weeks in a crossover manner

and week six clinical visits. They were also asked to consume an unrestricted carbohydrate diet of at least 150–200 g of carbohydrate/day for the 3 days before the glucose load, and a standard meal provided by the investigators on the evening before each clinical visit. On these days, participants attended the out-patient clinic, School of Public Health, Curtin University in the morning, following a 10–12 h overnight fast. Anthropometric measurements were taken with participants dressed in a gown with empty bladder and no shoes. The participants' body weight and height were measured to the nearest 0.1 kg and 0.5 cm, using a calibrated body composition monitor (Model BC 541, Tanita Corporation, China) and a portable stadiometer, respectively. Waist circumference was measured at mid-exhalation, midpoint between the lateral lower rib margin and the ileac crest using a non-elastic tape. Fasting blood samples were then collected via venipuncture into serum and plasma tubes. All participants also underwent a 75-g oral glucose tolerance test at the baseline and completion of each 6-week phase. The second blood sample was collected 2 h after ingestion of the glucose beverage. Aliquots of plasma, serum and red blood cell (RBC) samples were frozen at −80 °C until analysis.

Measurements of energy expenditure

The impact of thiamine supplementation on the energy expenditure was assessed by indirect open-circuit calorimetry (hood system) using a Deltatrac II machine (Datex, Helsinki, Finland).The performance of the Deltatrac II metabolic monitor was checked by alcohol burn tests as per the manufacturer's instructions. Four alcohol burning tests were carried out intermittently during the study period. The mean (±SD) RQ value for the last 15 min of each test was 0.66 (± 0.02) with a CV of 3.03% and within the acceptable range for RQ of 0.64–0.69. REE was measured in the participants following an overnight fast and an initial 30 min mandatory rest in a temperature-controlled room (22 ± 2 °C).The duration of measurement was 30 min and the average oxygen consumption rate (VO2) and carbon dioxide production rates (VCO2) over the last 25 min was used to calculate REE (kcal/24 h) by the abbreviated Weir equation [19]. During the clinical visits at baseline and week six, postprandial energy expenditure was also measured for a period of 20 min just before taking the second blood sample at 120 min. Change in 2 h EE was then defined as the absolute increase of energy expenditure after the glucose load.

Biochemical measurements

RBC thiamine pyrophosphate (RBC-TPP) was determined by high-performance liquid chromatography (HPLC) with fluorescent detection (pre-column derivatisation) using the Chromsystems reagent kit (Chromsystems Instruments and Chemicals GmbH, Munich, Germany) validated for RBC samples [14]. Plasma glucose concentrations were measured by the hexokinase method, using the Abbott diagnostic kits (Abbott Laboratories, IL, USA) with an inter- and intra-run coefficient of variation of <4.3%.

Compliance evaluation

In this study, the participants' compliances were assessed by 1) capsule count and 2) participant self-report. If there was any discrepancy between the participants' compliances assessed though the two described ways, the lesser value was reported as the participant's minimum compliance.

Statistical analysis

Statistical analyses were performed using SPSS for Windows version 19 (IBM Corp. Released 2010. Armonk, NY: IBM Corp USA). A paired samples t-test was used to compare the metabolic characteristics of participants at the baseline in placebo and supplement arms. The effects of treatment (thiamine supplement) on clinical variables (energy expenditure and biochemical measurements) were assessed using a linear mixed-model analysis, with treatment, week and interaction between treatment and week (treatment*week) as fixed effects. The relationships between the change in REE and other variables of interest were assessed using Spearman's rank-order correlation coefficients (r_s). To test the robustness of the findings, we also performed an intention to treat analysis, in which imputation was done for the missing values. Namely, where the missing data occurred within a phase of the study (Fig. 1), we used a last observation carried forward method. If they occurred before the baseline of the second phase, missing data in different visits of the second phase were inputted by the means of the variable in the participants who completed the study in the same arm and clinical visit. All tests were two-tailed, and a $p < 0.05$ was considered as statistically significant. Based on previous study [20], and the formula using for calculating the sample size in clinical research [21], a sample size of 12 participants in a cross-over study provides sufficient power (80%) to detect a 8% change in REE at a 5% significance level.

Results

Of seventeen participants who were recruited initially, four subjects dropped out after completing the first phase (two participants from each group) because of the time involved or starting the medication for treatment of hyperglycemia. Another participant was excluded later, due to the lack of compliance during the study. Twelve participants (5 men and 7 women) including ten cases of IGT and two new cases of

T2DM, with a mean (SE) BMI of 28.8 (1.2) kg/m^2 and age of 57.2 (3.7) years completed the study. All twelve participants received both placebo and thiamine capsules in a cross-over design, with a compliance rate of at least 88% for the provided treatment. There was no significant difference between clinical characteristics of participants at baseline before they embarked on the placebo or supplement arms of the cross-over design (Tables 1 and 2). No adverse effects were reported following either placebo or treatment arms of the trial.

Supplementation with thiamine increased the participants' RBC-TDP levels from 49.07 (3.2) μg/l at the baseline to 86.60 (3.2) μg/l at week six ($p < 0.001$), with no significant change in RBC-TDP levels of participants in the placebo arm [52.33 (3.2) vs. 52.02 (3.2) μg/l; $p = 0.92$]. While participants consuming thiamine supplement experienced a significant decrease in the REE assessed at week six compared to the baseline [mean (SE):1478.93 (73.62) vs.1526.40 (73.46) kcal/d, $p = 0.02$], there was no significant change in the REE between week 6 and week 0 for those who received placebo [1487.44(73.61) vs. 1500.91(73.46) kcal/d, $p = 0.51$] (Table 2). There was also a significant difference between supplement and placebo arms for the changes in the REE during the six-week intervention period ($p = 0.002$). The trend and significance of these outcomes remained the same even after adjusting for the participants' weight and physical activity levels as potential confounders [within supplement arm (week 6 vs. week 0): $p = 0.01$; within placebo arm (week 6 vs. week 0): $p = 0.18$; between arms: $p = 0.003$]. Furthermore, similar results were observed following the analysis of the intention-to-treat population in the supplement (week 6: 1463.71 vs. week 0: 1514.55 kcal/d, $p = 0.038$) and placebo (week 6: 1515.35 vs. week 0:1519.54 kcal/d, $p = 0.868$) arms. Six-week intervention had no significant effect on the participants' weight or waist circumference in either supplement or placebo arms (Table 1). Similarly, no significant change was found in the supplement or placebo arms for fasting and 2-h respiratory quotient or glucose induced thermogenesis (all p-values>0.05). Subsequent correlation analysis highlighted significant positive relationships between the change in REE with the changes in fasting ($r_s = 0.497$, $p = 0.019$), and 2-h plasma glucose ($r_s = 0.498$, $p = 0.018$) during the six-week intervention period (Fig. 2).

Discussion

In the present study, supplementation with high-dose thiamine for 6 weeks resulted in a significant decrease in REE compared to the baseline and placebo. As indicated before, to our knowledge there has been no clinical trial evaluating the impact of thiamine supplementation on energy metabolism in humans. However, our findings are partially in line with an experimental study indicating that administration of a thiamine - deficient diet for 25 days increased REE (by approximately 10 folds) in an animal model. Subsequent thiamine re-supplementation then rapidly attenuated REE to the control level [17].

It was demonstrated that patients with type 2 diabetes or impaired glucose tolerance may have higher rates of REE compared to normoglycemic people [4, 20, 22–24]. There is evidence suggesting that an increase in fasting hepatic gluconeogenesis as well as glycosuria resulting from hyperglycemia may be behind the high REE observed in diabetic patients [22, 25]. Up-regulation of energy expenditure by hyperglycemia has been proposed to be partially mediated via AMP-

Table 1 Characteristics of participants in different visits by the study arms

	Placebo arm					Thiamin arm					Between arms p value
	Week 0	Week 3	Week 6	P[a]	P[b]	Week 0	Week 3	Week 6	P[a]	P[b]	
Weight (kg)	83.13 (4.2)	83.55 (4.2)	83.49 (4.2)	0.37	0.88	83.50 (4.2)	83.35 (4.2)	83.30 (4.2)	0.62	0.90	0.22
WC (cm)	97.62 (2.9)	97.83 (2.9)	97.66 (2.9)	0.90	0.63	98.04 (2.9)	98.10 (2.9)	97.9 (2.9)	0.72	0.60	0.65
FPG (mg/dl)	105.7 (3.7)	105.7 (3.7)	109.9 (3.7)	<0.01	<0.01	108.4 (3.7)	107.7 (3.7)	108.1 (3.7)	0.82	0.77	<0.01
2-h PG (mg/dl)	170.1 (11.7)	–	173.1 (11.7)	0.64	–	178.0 (11.7)	–	158.1 (11.7)	<0.01	–	<0.01
RBC-TDP (μg/l)	52.33 (3.2)	–	52.02 (3.2)	0.92	–	49.07 (3.2)	–	86.60 (3.2)	<0.001	–	<0.001
Dietary thiamine intake (mg/d)	1.84 (0.32)	–	1.89 (0.32)	0.86	–	1.69 (0.32)	–	1.19 (0.32)	0.12	–	0.66
Physical activity (MET-Min/Week)	2295.2 (534.8)	–	2427.5 (534.8)	0.66	–	2636.8 (534.8)	–	2167.7 (534.8)	0.13		0.10

Data are presented as mean (SE); a, linear mixed model analysis: compare difference between week 0 and week 6; b, Linear mixed model analysis: compare difference between week 3 and week 6; compare between arm difference; FPG, fasting plasma glucose; 2-h PG, plasma glucose 2 h after glucose load

Table 2 Indirect calorimetry measurements in different visits by the study arms

	Placebo arm					Thiamin arm					Between arms p value
	Week 0	Week 3	Week 6	P^a	P^b	Week 0	Week 3	Week 6	P^a	P^b	
REE (kcal/d)	1500.91 (73.46)	1502.67(73.46)	1487.44 (73.61)	0.51	0.46	1526.4(73.46)	1504.36 (73.62)	1478.93 (73.62)	0.02	0.23	0.002
REE† (kcal/d)	1498.99 (47.25)	–	1474.31 (47.46)	0.18	–	1512.45 (47.35)	–	1462.94 (47.51)	0.01	–	0.003
FastingVO2 (ml/min)	211.16 (10.80)	213.50 (10.80)	209.76 (10.83)	0.67	0.27	218.50 (10.80)	214.36 (10.83)	209.90 (10.83)	0.01	0.19	0.002
Fasting VCO2 (ml/min)	189.95 (8.42)	182.75 (8.42)	186.46 (8.50)	0.48	0.45	179.83 (8.42)	180.77 (8.50)	180.68 (8.50)	0.86	0.98	0.45
Fasting RQ	0.90 (0.01)	0.87 (0.01)	0.88 (0.02)	0.64	0.59	0.83 (0.01)	0.87 (0.02)	0.86 (0.02)	0.22	0.97	0.08
Change in 2 h EE following glucose (kcal)	115.48 (36.94)	–	185.15 (38.65)	0.17	–	53.09 (36.94)	–	115.00 (38.65)	0.22	–	0.91
2-h RQ	0.94 (0.02)	–	0.91 (0.02)	0.14	–	0.87 (0.02)	–	0.90 (0.02)	0.28	–	0.09

Data are presented as mean (SE); a, linear mixed model analysis: compare difference between week 0 and week 6; b, Linear mixed model analysis: compare difference between week 3 and week 6; †, Adjusted for weight and physical activity; REE, resting energy expenditure; Fasting RQ, fasting respiratory quotient ($fVCO_2/fVO_2$); Change in 2 h EE following glucose, energy expenditure assessed 2 h after glucose load minus resting energy expenditure; 2-h RQ, respiratory quotient assessed 2 h after glucose load (2-h VCO_2/ 2-h VO_2)

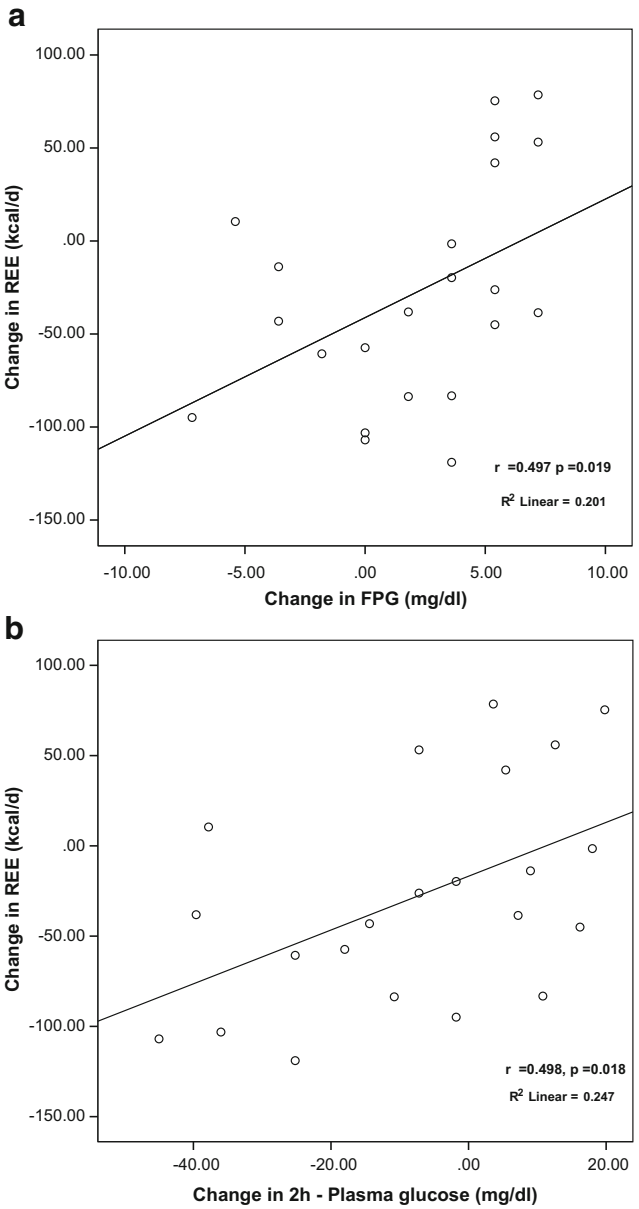

Fig. 2 Scatterplot of the changes (week 6 – week 0) in fasting plasma glucose (FPG) (**a**) and change in 2 h-plasma glucose (**b**) vs. resting energy expenditure (REE)

activated protein kinase (AMPK), which is a crucial energy-sensing enzyme [26]. AMPK is activated when cells are exposed to a variety of metabolic stresses including energy deprivation or hypoglycemia [27, 28]. Upon activation, AMPK inhibits ATP-consuming pathways such as gluconeogenesis, and stimulates ATP-producing pathways including fatty acid oxidation and glucose uptake by cells [26]. On the contrary, AMPK activity/phosphorylation has been shown to decrease in the presence of high glucose concentration [29] or an increase in the cellular glycogen stores [30].

Emerging evidence indicates that thiamine may influence the pathways involved in glucose – AMPK – energy axis. In

an experimental study by Tabidi et al. [31], incubation of cardiac myocytes with 5 mM glucose resulted in an 82% decrease in AMPK activity. The addition of thiamine to the incubation buffer could then attenuate the effect of glucose on AMPK activity, and increase AMPK phosphorylation in the myocytes. The exact mechanisms by which thiamine improves AMPK activity under hyperglycemic condition are not fully elucidated. However, considering the key role of thiamine as the precursor of the TDP (thiamine diphosphate) an essential coenzyme for transketolase in the pentose phosphate pathway, it was proposed to modify some intermediates of the pentose phosphate pathway triggering the inactivation of AMPK by glucose [12, 31].

As mentioned previously, individuals with hyperglycemia are known to have a relatively higher resting energy expenditure compared to healthy people [4], and existing evidence confirms a reciprocal decrease in the basal metabolic rate following an improvement in the glycemic control [7]. Given the positive effects of thiamine on hyperglycemia reported in both diabetic [13, 32] and pre-diabetic patients [16], it seems that, apart from modulating glucose effect on AMPK activity discussed above, thiamine therapy may also primarily reduce REE as a result of controlling blood glucose; this notion is supported by the significant correlation between the six-week change in REE and the changes in the fasting and 2-h plasma glucose observed in the present study. In this context, it should be also noted that this study included participants with hyperglycemia mostly at the pre-diabetic ranges, expecting to have a REE higher than normal but not as high as those in individuals with diabetes [20]. Accordingly, supplementation with high-dose thiamine may hypothetically induce more significant changes in REE of diabetic patients. Further research is required to explore this assumption more definitely.

In the present study, decreases in the REE of participants in the supplement arm were not associated with significant changes in their body weight or waist circumference. An experimental study showed that the reduced REE resulted from thiamine re-supplementation in thiamine deficient mice was accompanied by stimulation of hypothalamic AMPK activity and increased appetite and food intake, causing an overall body weight gain [17]. However, the findings of human studies investigating the effect of thiamine on the body weight have been controversial: in a clinical trial conducted by Wilkinson et al. [33] thiamine supplementation (10 mg/d) for 3 months resulted in a considerable decrease in the weight of older participants with persistent subclinical thiamine deficiency confirmed on two occasions, but not in those with just an isolated low thiamine concentration. No exact explanation was offered by Wilkinson et al. for this finding. However, they explained a likely improvement in the heart failure of participants taking Furosemide and a subsequent weight loss resulting from diuresis as a notable point. By contrast, Smidt et al. [34] reported a significant increase in the body weight of elderly participants with marginal thiamin deficiency taking thiamine supplement (10 mg/d) for 6 weeks, which was accompanied by significant improvements in their appetite and energy intake. In another study, dietary intake of thiamine (mg/kcal) was significantly correlated with the body mass index, on the basis of a gender difference (positive and negative correlations in men and women, respectively) [35]. The inconsistency between our results for the body weight and the findings of previous studies may be in part due to the fact that those studies were mainly conducted on normoglycemic people with subclinical/marginal thiamine deficiency. However, all participants of our study were hyperglycemic and had a normal thiamine status at the baseline. More comprehensive studies investigating the association of thiamine with the body weight in normal and hyperglycemic people / with or without underlying thiamine deficiency would be worthwhile.

The strength of the present study is that it is the first to examine the effect of thiamine on energy expenditure in humans. However, this study has some limitation as well. First of all, the sample size of the study is relatively small, limiting us to evaluate the impact of thiamine on REE in men and women, or in the subgroups of diabetics and pre-diabetics, separately. In the present study, we were also unable to evaluate the participants' body composition. Therefore, although the thiamine-induced decrease in REE was not associated with a significant change in body weight, it is not possible to identify an impact on body composition.

In conclusion, this study provided evidence indicating that high-dose thiamine supplementation may attenuate REE in patients with hyperglycemia at an early stage. We also found a positive correlation between the change in REE and amendments in fasting and 2-h plasma glucose, suggesting that the impact of thiamine supplementation on REE may partly result from improving hyperglycemia. Considering the lack of previous research on this topic, further research with a larger sample size is required to confirm these results and elucidate the possible mechanisms. Moreover, future clinical studies exploring the effect of thiamine on food intake, energy metabolism and body composition in normal individuals as well as patients with hyperglycemia, in either diabetic or pre-diabetic ranges, may provide a novel insight into the regulation of body weight and new preventive/therapeutic strategies.

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Authors' contributions FAS, JS and MJS were involved in the conception and design of the study, and contributed to the final version of the manuscript. Data were collected, analyzed and interpreted by FAS. ML was involved in drafting the manuscript. YZ provided the support with statistical analysis. All authors read and approved the final manuscript

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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