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SHORT COMMUNICATION

Effect of thiamine administration on metabolic profile, cytokines and inflammatory markers in drug-naïve patients with type 2 diabetes

Manuel González-Ortiz · Esperanza Martínez-Abundis · José A. Robles-Cervantes · Viridiana Ramírez-Ramírez · Maria G. Ramos-Zavala

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Abstract
Purpose To evaluate the effect of thiamine administration on metabolic profile, cytokines and inflammatory markers in drug-naïve patients with type 2 diabetes mellitus (T2DM).
Methods A randomized, double-blind, placebo-controlled, pilot-scale clinical trial was carried out in 24 patients with T2DM. Twelve subjects received thiamine orally (150 mg), once daily during a fasting state for 1 month. An additional 12 patients (control group) were given placebo for the same period of time. Before and after the intervention, fasting glucose, A1C, creatinine, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, very low-density lipoprotein, high-sensitive C-reactive protein, interleukin 6, tumor necrosis factor-alpha, leptin and adiponectin levels were estimated. Wilcoxon's signed-rank and Mann–Whitney U test were used for statistical analyses.
Results There were significant decreases in glucose (6.7 ± 1.0 mmol/l vs. 6.0 ± 1.0 mmol/l, $p = 0.024$) before and after the intervention, respectively, and leptin concentrations (32.9 ± 13.3 ng/ml vs. 26.9 ± 12.8 ng/ml, $p = 0.027$) before and after the intervention, respectively, with thiamine administration. There were no changes with the rest of the measurements.
Conclusions Thiamine administration for 1 month decreased glucose and leptin concentrations in drug-naïve patients with T2DM.

Keywords Thiamine · Metabolic profile · Cytokines · Inflammatory markers · Type 2 diabetes

M. González-Ortiz (✉) · E. Martínez-Abundis · J. A. Robles-Cervantes · V. Ramírez-Ramírez · M. G. Ramos-Zavala
Cardiovascular Research Unit, Physiology Department, Health Science University Center, University of Guadalajara and Medical Research Unit in Clinical Epidemiology, Specialties Hospital, Medical Unit of High Specialty, West National Medical Center, Mexican Institute of Social Security, Montes Urales 1409, 44340 Guadalajara, Colonia Independencia, Mexico
e-mail: uiec@prodigy.net.mx

Introduction

Type 2 diabetes mellitus (T2DM) has become a worldwide health problem with a significant impact due to its high prevalence of microvascular complications (nephropathy, retinopathy and peripheral neuropathy) and macrovascular complications (cardiovascular disease and stroke) that decrease quality and expectations of life, as well as being a major financial burden for the family and for healthcare institutions [1].

Inflammation and other pathways of biochemical dysfunction including cytokine increase have been implicated as important etiological factors in the development of both T2DM and the acceleration of its complications. These findings have emerged from recent advances in the understanding of cell biology of diabetes and diabetic complications [2].

Thiamine (vitamin B1) is an essential cofactor in most organisms and is required during several stages of anabolic and catabolic intermediary metabolism such as intracellular glucose metabolism. Thiamine acts as a coenzyme for transketolase and for the pyruvate dehydrogenase and α-ketoglutarate dehydrogenase complex, enzymes that play a fundamental role in intracellular glucose metabolism [3]. Plasma- and tissue-specific thiamine

deficiencies in experimental diabetes have been associated with decreased activity of the thiamine-dependent enzyme of transketolase and increased renal clearance of thiamine [4]. On the other hand, low plasma thiamine concentration in diabetes has been inversely linked to markers of metabolic and vascular dysfunction, increasing the risk of atherosclerosis [5]. High-dose thiamine therapy appears to prevent the development of complications in experimental diabetes [6, 7], independent of glucose control.

We are currently unaware of the effect of thiamine administration on cytokines and inflammatory markers; therefore, the aim of this study was to evaluate the effect of the administration of thiamine on metabolic profile, cytokines and markers of inflammation in drug-naïve patients with T2DM.

Subjects and methods

A randomized, double-blind, placebo-controlled, pilot-scale clinical trial was carried out in 24 patients (30- to 65-year old) with type 2 diabetes, overweight or obesity (body mass index [BMI], 25–40 kg/m^2), fasting glucose level <11.0 mmol/L and A1C level <8% without pharmacological treatment. Subjects were selected from the same geographical location and belonged to a similar socioeconomic status. No participant was excessively sedentary or participated in heavy physical activity. All individuals were non-smokers. They had stable body weight for at least 3 months before the study and with blood pressure <140/90 mmHg. There was no personal history reported of hepatic, renal or coronary artery disease. They admitted to using no medications known to affect carbohydrate or lipid metabolism during the previous 6 months. All subjects consumed an isocaloric diet containing >250 g of carbohydrates/day for 3 days before the study. Nutritional medical therapy in accordance with the American Diabetes Association was prescribed during the study, as confirmed by dietary history.

Patients were evaluated before and after the 1-month study period. Tests were performed at 8:00 a.m. after a 10- to 12-h overnight fast. Height and weight were recorded with the individuals wearing light clothing and without shoes. Height was measured and rounded off to the nearest centimeter with the subjects standing. BMI was calculated as weight (in kilograms) divided by height squared (in meters). Blood pressure was evaluated by the investigator after a 5-min resting period with the individual sitting in a chair and was determined using a standard mercury sphygmomanometer. Systolic and diastolic pressures were based on Korotkoff phases I and V, respectively.

Venous blood was obtained with the subject lying supine in a quiet room. The blood was allowed to clot for 30 min at room temperature and then centrifuged. The resulting serum was placed into two aliquots. The first one was immediately used for measurement of fasting glucose, A1C, creatinine, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), triglycerides (TG) and very low-density lipoprotein (VLDL) concentrations. The second aliquot was frozen at −20° C for measurement of high-sensitive C-reactive protein (hs-CRP), interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-α), leptin and adiponectin levels within the following 30 days.

Pharmacological administration

After randomization, thiamine (Sukrol, Allen, Mexico City, Mexico) (150 mg daily) or placebo was administered orally, once daily during a fasting state for 1 month.

Blood glucose was determined by the glucose oxidase technique. Serum creatinine and lipid levels (TC, HDL-c, LDL-c, TG and VLDL) were measured enzymatically. In particular, HDL-c was assessed after selective precipitation of non-HDL fractions. Determinations were performed with commercially available equipment (Vitros, Ortho-Clinical Diagnostics, Johnson & Johnson Co. Rochester, NY, USA) with an intra- and inter-assay coefficient of variation of <2%. A1C levels were measured with ion-exchange high-performance liquid chromatography technique (Bio-Rad Laboratories, Hercules, CA, USA) with an intra- and inter-assay coefficient of variation of 0.4 and 1.6%, respectively. hs-CRP level was measured with particle-enhanced immunonephelometry using BN system (Dade Behring, Marburg, GmbH) with an intra- and inter-assay coefficient of variation of 3.1 and 3.4%, respectively. Enzyme-linked immunosorbent assay was used to measure IL-6 (Bender MedSystems, Burlingame, CA, USA), TNF-α (Bender MedSystems), leptin (BioVendor LLC, Candler, NC, USA) and adiponectin (R&D Systems, Minneapolis, MN, USA) concentrations with an intra- and inter-assay coefficient of variation for all (<3.5 and <6.7%, respectively).

Statistical analyses

Sample size was calculated using a clinical trial formula [8] with a 95% confidence level, 80% power, standard deviation (SD) of leptin level of 11.9 ng/ml [9] and an expected difference of at least 15.0 ng/ml of leptin level after the intervention, obtaining a total of 12 patients for each group. With other end points, the sample size was equal or lower. Values were converted to SI units and are presented as mean ± SD. Intra- and inter-group

differences were calculated by paired *t*-test and Student's *t*-test, respectively, due to the parametric distribution of the data. χ^2 was used for non-parametric gender data.

Ethical considerations

The study protocol was reviewed and approved by the institutional Ethics Committee, and written informed consent was obtained from all volunteers.

Results

All 24 subjects who were eligible after screening completed 1 month of pharmacological intervention. Placebo group consisted of five women and seven men, and thiamine group was comprised of seven women and five men ($p = 0.414$). There were no significant differences in ages between placebo and thiamine groups (46.0 ± 6.6 vs. 43.7 ± 10.6 years, $p = 0.541$; respectively). There were no significant differences in baseline laboratory measurements between groups (Table 1).

Weight and BMI were not modified with placebo (78.3 ± 11.3 vs. 78.1 ± 12.4 kg, $p = 0.795$ and 29.5 ± 2.9 vs. 29.4 ± 3.0 kg/m^2, $p = 0.685$) or with thiamine (74.1 ± 13.9 vs. 73.3 ± 13.4 kg, $p = 0.116$ and 29.4 ± 3.0 vs. 29.1 ± 3.2 kg/m^2, $p = 0.151$). There were no significant differences in systolic and diastolic blood pressures due to the intervention (114 ± 9 vs. 112 ±10 mm Hg, $p = 0.538$ and 74 ± 6 vs. 75 ± 8 mm Hg, $p = 0.848$ in the placebo group and 118 ± 8 vs. 113 ± 10 mm Hg, $p = 0.143$ and 75 ± 7 vs. 75 ± 8 mm Hg, $p = 0.882$ in the thiamine group).

There was a significant decrease in glucose level after thiamine administration (6.7 ± 1.0 vs. 6.0 ± 0.9 mmol/l, $p = 0.024$); however, this was not demonstrated with placebo (6.4 ± 1.2 vs. 6.4 ± 1.2 mmol/l, $p = 1.000$). A significant decrease in leptin concentration was obtained after thiamine administration (32.9 ± 13.3 vs. 26.9 ± 12.8 ng/ml, $p = 0.027$), but this was not observed in the placebo group (23.9 ± 12.5 vs. 18.9 ± 8.6 ng/ml, $p = 0.113$). There were no changes with the rest of the measurements (Table 1).

Adverse events reported were headache in the placebo group and increased appetite with the administration of thiamine; however, these could not be linked to the drug administration.

Discussion

Low thiamine concentrations in diabetes may be of limited significance. Tissues can up-regulate gene expression, and protein levels of thiamine transporters maintain normal transketolase activity, although this occurs in the normoglycemic state. On the other hand, decreased availability of thiamine in vascular cells in diabetes exacerbates metabolic dysfunction in hyperglycemia [5].

A major health concern of diabetes is achieving good control of blood glucose; however, this is not always attainable because of limitations of current drug therapy, patient compliance and other associated factors. Therefore, any effort to improve glucose level is recommended. In patients with T2DM with microalbuminuria, regression of urinary albumin excretion after 3 × 100 mg of thiamine per day for 3 months without effect on glycemic control,

Table 1 Laboratory measurements before and after the intervention in the studied groups

	Placebo			Thiamine		
	Basal	1 month	*p*	Basal	1 month	*p*
A1C, %	6.3 ± 0.8	5.9 ± 1.0	0.108	6.3 ± 0.3	6.1 ± 0.5	0.086
Creatinine, μmol/l	61.8 ± 8.8	70.7 ± 8.8	0.175	70.7 ± 8.8	70.7 ± 17.6	0.267
Cholesterol, mmol/l	4.8 ± 0.6	4.7 ± 0.6	0.689	4.8 ± 0.7	4.7 ± 1.0	0.795
HDL-c, mmol/l	1.0 ± 0.2	0.9 ± 0.1	0.624	1.1 ± 0.3	1.1 ± 0.2	0.835
LDL-c, mmol/l	2.9 ± 0.7	2.7 ± 0.7	0.353	2.7 ± 0.8	2.7 ± 0.7	0.675
Triglycerides, mmol/l	1.7 ± 0.4	1.7 ± 0.3	0.485	1.6 ± 0.5	1.5 ± 0.5	0.243
VLDL, mmol/l	0.3 ± 0.0	0.3 ± 0.0	0.485	0.3 ± 0.1	0.3 ± 0.1	0.225
CRP, mg/l	4.4 ± 2.2	4.1 ± 2.2	0.438	5.7 ± 2.9	4.6 ± 2.0	0.114
Interleukin 6, pg/ml	4.7 ± 1.5	4.8 ± 1.7	0.731	4.7 ± 1.0	4.4 ± 1.6	0.429
TNF, pg/ml	14.3 ± 9.4	14.2 ± 11.0	0.952	14.2 ± 6.3	12.8 ± 9.0	0.562
Adiponectin, ng/ml	56.7 ± 34.8	59.9 ± 26.5	0.560	73.2 ± 41.2	62.0 ± 31.9	0.187

A1C hemoglobin A1c, *HDL-c* high-density lipoprotein-cholesterol, *LDL-c* low-density lipoprotein-cholesterol, *VLDL* very low-density lipoprotein, *CRP* C-reactive protein, *TNF* tumor necrosis factor

dyslipidemia or blood pressure has been reported [7]. On the contrary, our results in drug-naïve patients showed a decrease in fasting glucose levels, possibly because both genetic and enzymatic mechanisms involved in metabolic control are more preserved. A1C level just showed a tendency to decrease because, in general, A1C allowed the identification of metabolic control of the patients during the last 3 months, and our intervention time was shorter. High-dose thiamine therapy appears to prevent the development of microvascular complications such as nephropathy, neuropathy and retinopathy in experimental diabetes through multiple mechanisms of biochemical dysfunction: activation of protein kinase C, activation of the hexosamine pathway and increased glycation and oxidative stress, without improvement in metabolic control. Besides, both thiamine and benfotiamine appear to produce marked reversals of increased diuresis and glycosuria, without change in glycemic status [6, 10]. Additionally, in endothelial progenitor cells, befotiamine administration has shown to at least partially counteract the effect of glucotoxicity via modulation of Akt/FoxO1 activity, probably decreasing diabetes complications [11].

Leptin is an adipocyte-derived hormone and cytokine that regulates energy balance through a wide range of functions. The leptin axis has functional interactions with elements of metabolism and its abnormalities. Metabolic and inflammatory-mediated injury may result from either resistance to action of leptin in selective tissues or from excess leptin action from adiposity-associated hyperleptinemia. These represent potential novel diagnostic and therapeutic targets in obesity, diabetes and its complications [12]. We found that the beneficial effect of thiamine in reducing leptin concentration may help to regulate energy balance, as well as to explain the tendency for the decrease in weight and BMI observed in our patients.

The results of this study with thiamine, as well as those results reported with benfotiamine, whose bioavailability is fourfold higher than thiamine in non-diabetic subjects [13] and unknown in patients with diabetes, do not show an improvement in inflammatory and endothelial dysfunction markers in the fasting state [14].

One limitation of our study was that we did not evaluate the postprandial state. This provides us with an opportunity to improve the study design in a future investigation. Our findings may be explained by the short treatment duration, which was insufficient to induce baseline changes and/or by the apparent low dose used (dosage commercially available in Mexico and recommended by the producers to other medical indications) compared with higher doses used in other studies with benfotiamine [14, 15].

An alternative explanation is that thiamine probably acts by reducing mechanisms that induce inflammation only in the presence of hyperglycemia. Patients included in the present study had A1C values close to metabolic control with relatively low levels of fasting glucose concentration. The number of subjects studied was relatively small, and the investigation was pilot-scale; therefore, a larger patient cohort to confirm the above-mentioned findings is needed.

We suggest that thiamine may play an important role in preventive therapy of atherosclerosis in patients with diabetes; however, more in-depth studies should be performed before recommending this therapy in clinical practice.

In conclusion, thiamine administration for 1 month decreased glucose and leptin concentrations in drug-naïve patients with type 2 diabetes.

References

1. Blonde L (2007) State of diabetes care in the United States. Am J Manag Care 13(Suppl 2):S36–S40
2. King GL (2008) The role of inflammatory cytokines in diabetes and its complications. J Periodontol 79(Suppl 8):1527–1534
3. Beltramo E, Berrone E, Tarallo S, Porta M (2008) Effects of thiamine and benfotiamine on intracellular glucose metabolism and relevance in the prevention of diabetic complications. Acta Diabetol 45:131–141
4. Babaei-Jadidi R, Karachalias N, Kupich C, Ahmed N, Thornalley PJ (2004) High-dose thiamine therapy counters dyslipidaemia in streptozotocin-induced diabetic rats. Diabetologia 47:2235–2246
5. Thornalley PJ, Babaei-Jadidi R, Al Ali H, Rabbani N, Antonysunil A, Larkin J, Ahmed A, Rayman G, Bodmer CW (2007) High prevalence of low plasma thiamine concentration in diabetes linked to a marker of vascular disease. Diabetologia 50: 2164–2170
6. Thornalley PJ (2005) The potential role of thiamine (vitamin B1) in diabetic complications. Curr Diabetes Rev 1:287–298
7. Rabbani N, Alam SS, Riaz S, Larkin JR, Akhatar MW, Shafi T, Thornalley PJ (2009) High-dose thiamine therapy for patients with type 2 diabetes and microalbuminuria: a randomized, double-blind placebo-controlled pilot study. Diabetologia 52: 208–212
8. Jeyaseelan L, Rao PSS (1989) Methods of determining sample sizes in clinical trials. Indian Pediatr 26:115–121
9. Robles-Cervantes JA, Martínez-Abundis E, González-Ortiz M, Cárdenas-Camarena L, Hernández-Salazar E, Olvera-Ozuna R (2007) Behavior of insulin sensitivity and its relation to leptin and tumor necrosis factor-alpha in obese women undergoing liposuction: 6-month follow-up. Obes Surg 17:1242–1247
10. Babaei-Jadidi R, Karachalias N, Ahmed N, Battah S, Thornalley PJ (2003) Prevention of incipient diabetic nephropathy by high-dose thiamine and benfotiamine. Diabetes 52:2110–2120
11. Marchetti V, Menghini R, Rizza S, Vivanti A, Feccia T, Lauro D, Fukamizu A, Lauro R, Federici M (2006) Benfotiamine counteracts glucose toxicity effects on endothelial progenitor cell differentiation via Akt/FoxO signaling. Diabetes 55:2231–2237
12. Martin SS, Qasim A, Reilly MP (2008) Leptin resistance: a possible interface of inflammation and metabolism in obesity-related cardiovascular disease. J Am Coll Cardiol 52:1201–1210
13. Schreeb KH, Freudenthaler S, Vormfelde SV, Gundert-Remy U, Gleiter CH (1997) Comparative bioavailability of two vitamin B1

preparations: benfotiamine and thiamine mononitrate. Eur J Clin Pharmacol 52:319–320
14. Stirban A, Negrean M, Stratmann B, Gawlowski T, Horstmann T, Götting C, Kleesiek K, Mueller-Roesel M, Koschinsky T, Uribarri J, Vlassara H, Tschoepe D (2006) Benfotiamine prevents macro- and microvascular endothelial dysfunction and oxidative stress following a meal rich in advanced glycation end products in individuals with type 2 diabetes. Diabetes Care 29:2064–2071
15. Du X, Edelstein D, Brownlee M (2008) Oral benfotiamine plus alpha-lipoic acid normalises complication-causing pathways in type 1 diabetes. Diabetologia 51:1930–1932