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Original Article

The impact of thiamine supplementation on blood pressure, serum lipids and C-reactive protein in individuals with hyperglycemia: a randomised, double-blind cross-over trial

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ABSTRACT

Background: The adverse effects of hyperglycemia may be potentiated when it is accompanied with hypertension and dyslipidemia. This study assessed the effects of high dose thiamine on blood pressure, serum lipids and C-reactive protein (hs-CRP) in individuals with impaired glucose metabolism.
Methods: This was a double-blind, randomised trial, where 12 hyperglycemic subjects (10 cases of impaired glucose tolerance and 2 new cases of type 2 diabetes mellitus) received both placebo and thiamine capsules (3×100 mg/day) for six weeks in a cross-over manner. Anthropometric measurements, systolic and diastolic blood pressure (SBP & DBP), serum cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, hs-CRP and thiamine status were evaluated at the start, after three weeks and on the completion of each arm.
Results: DBP was significantly decreased in participants consuming thiamine supplements for six weeks (67.9 ± 5.8 mm Hg) relative to baseline (71.4 ± 7.4 mm Hg, $p = 0.005$) and week 3 ($70.9. \pm 5.8$ mm Hg, $p = 0.02$). This was accompanied with a tendency toward a lower SBP at week six relative to baseline (116.5 ± 11.0 vs. 120.7 ± 15.3 mm Hg, $p = 0.06$). Also, mean arterial pressure (MAP) determined in the supplement arm after six weeks was significantly lower than baseline (84.1 ± 6.5 vs. 87.8 ± 9.0, $p = 0.005$). These variables did not change in the placebo arm. No significant change was detected in the supplement or placebo arms when lipid profile and hs-CRP were assessed.
Conclusion/interpretation: High dose thiamine supplementation may have beneficial effects on the blood pressure of individuals with hyperglycemia at early stages, and may have a role in the prevention of further vascular complications.
Trial registration: Australian New Zealand Clinical Trials Registry ACTRN12611000051943

1. Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide. Hyperglycemia, in either diabetic or pre-diabetic ranges, is an important factor contributing to the increased risk of CVD [1]. Evidence indicates that the adverse effects of hyperglycemia may be potentiated when it is accompanied with hypertension. Moreover, hyperglycemia itself enhances the development of hypertension through several mechanisms [2].

Thiamine is a water-soluble vitamin playing an essential role as a co-enzyme in metabolic pathways involving glucose. There is convincing evidence that thiamine can modify specific mechanisms implicated in abnormalities associated with hyperglycemia [3]. Abnormality in the renin-angiotensin system is one of the mechanisms suggested to play a role in the pathogenesis of hypertension in diabetic patients [2]. Thiamine repletion was shown to reduce blood pressure in experimental hypertensive rats via down – regulating the expression of mRNAs implicated in the renin – angiotensin system [4]. Furthermore, thiamine supplementation was reported to reduce blood pressure of elderly people with subclinical thiamine deficiency [5]. There is evidence that individuals with hyperglycemia are similarly prone to thiamine deficiency, due to an increased urinary excretion [6]. Therefore,

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supplemental thiamine may also have beneficial effects on the blood pressure of hyperglycemic patients from this perspective. Given these findings, the main objective in this study was to assess the effect of high dose thiamine supplementation on systolic and diastolic blood pressure (SBP & DBP) in patients with hyperglycemia at early stages. Additionally, the effects of supplemental thiamine on serum lipids, high-sensitive C-reactive protein (hs-CRP) and thiamine status were assessed at baseline and after each intervention period.

2. Material and methods

2.1. Subjects

Seventeen hyperglycemic adults (14 IGT and 3 new cases of T2DM) with a BMI between 19 and 40 kg/m^2 and aged 18–75 years started the study. Exclusion criteria were: smoking; known impaired renal or liver function; major cardiac, neurologic or gastrointestinal disorders; known allergy or intolerance to thiamine and women who were pregnant or breast feeding. No subject was receiving medications affecting blood pressure, lipid profile, blood glucose or thiamine metabolism. Subjects taking any supplements or consuming more than two standard alcoholic drinks per day were instructed to cease the supplement and decrease the alcohol consumption throughout the study period, starting four weeks leading up to their first clinical visit.

2.2. Study design and procedure

This was a randomised, double-blind study, with a cross-over design. Hyperglycemic participants were randomly assigned to consume either 100 mg thiamine (as thiamine hydrochloride) or placebo three times a day (300 mg/d) for six weeks. Anthropometric measurements, SBP, DBP, serum lipids, hs-CRP and thiamine status were evaluated at baseline, week 3 and week 6. After completion of the first part and a 14-week wash out period, participants received alternative capsules for another six weeks. Subsequently, clinical measurements were made on another three separate visits according to the same protocol as the first part. All participants and investigators involved in data collection and analysis were blinded to the treatment assignments. The thiamine capsules contained thiamine hydrochloride and the inactive ingredients of starch and lactose (Betamin, Sanofi-Aventis Australia Pty Ltd., Australia). The capsules provided as placebo were matched with the supplement and contained the same inactive ingredients.

Participants were instructed to maintain their usual diet and level of physical activity during the study period, and to consume a standard meal provided by the investigators on the evening before the clinical days. On these days, subjects attended the out-patient clinic, School of Public Health, Curtin University in the morning, after a 10–12 h overnight fast. Anthropometric measurements were taken with subjects dressed in a gown with no shoes and empty bladder. After a mandatory rest period of 30 min, SBP and DBP were measured on subjects' right arms in supine position, using a vital signs patient monitor (Cardiocap II, Datex, Helsinki, Finland). Three blood pressure measurements, with 2 min intervals, were recorded in the fasting state and the average value was reported. Fasting blood samples were then collected via venipuncture. Aliquots of separated serum, plasma and red blood cell (RBC) were stored at −80 °C until analysis.

Plasma glucose was measured with the hexokinase method. 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. Enzymatic colorimetric assays were used to determine the levels of serum triglyceride and total cholesterol. Concentrations of HDL-cholesterol were directly measured in the serum samples by the Ultra HDL assay. These analyses were performed using the Abbott diagnostic kits (Abbott Laboratories, IL, USA) with a within- and between-run coefficient of variation of <4.3%. LDL-cholesterol was calculated using a modified version of Friedewald equation [7] with quantities in mmol/l. Serum hs-CRP was measured by nephelometry using a BNII system (Siemens Healthcare Diagnostic inc. Newwark, DE, USA) with between- and within-run coefficient of variation of 8.35% and 5.7%, respectively.

This study was approved by the Curtin University Human Research Ethics Committee (Approval number HR 161/2008) and all participants provided written informed consent.

2.3. Statistical analysis

Statistical analyses were conducted using IBM SPSS for Windows (Version 19.0. Released 2010. Armonk, NY: IBM Corp USA). The metabolic characteristics of subjects at the baseline between placebo and supplement arms were compared using a paired samples *t*-test. The effects of treatments (supplement and placebo) on cardiovascular risk factors were tested using a linear mixed-effects modelling analysis, with treatment, treatment × week interaction and week as fixed effects. All tests were two-tailed and a $p < 0.05$ was considered as statistically significant.

Sample size was calculated based on a change of 5 mm Hg reduction in DBP after intervention, assuming a standard deviation of 6 mm Hg [8]. Using a clinical trial formula [9], a sample of 12 subjects in the cross-over study provides sufficient power (80%) to detect significant changes at the 5% significance level. The sample size required for detecting other endpoints was equal or lower. A total of 17 subjects were recruited to allow for drop out/non-compliance.

3. Results

Thirteen participants completed the study, with four subjects dropping out after completing the first part (two subjects from each group) due to the time involved or starting the medication for treatment of hyperglycemia. Data of another subject were excluded later, because of a lack of compliance during the study. Thus, data of 12 subjects (5 males and 7 females), 10 cases of IGT and 2 new cases of T2DM, with a BMI between 21.46–36.30 kg/m^2 and aged 29–71 years were included in the final analysis.

There was no significant difference in the mean SBP, DBP, serum lipids or hs-CRP between placebo and supplement arms at the baseline (Table 1). Also, the mean BMI and blood glucose of subjects were not different at the baseline of placebo and supplement arms. The present investigation has been a part of a clinical study examining the potential effects of thiamine on different CVD risk factors. The fasting glucose levels at the three time points in each arm have been described elsewhere [10].

Thiamine supplementation for six weeks resulted in a significant increase in RBC-TPP compared with the baseline (256.7 ± 50.7 vs. 145.5 ± 25.3 nmol/l, $p < 0.001$). There was no significant change in RBC-TPP of subjects in the placebo arm (154.2 ± 22.0 vs. 155.2 ± 26.0 nmol/l, $p = 0.92$). DBP of subjects consuming thiamine supplement decreased significantly after week six (67.9 ± 5.8 mm Hg) compared with those at the baseline (71.4 ± 7.4 mm Hg, $p = 0.005$) and week three ($70.9. \pm 5.8$ mm Hg, $p = 0.02$). This was accompanied by a tendency toward a lower SBP at week six relative to baseline (116.5 ± 11.0 vs. 120.7 ± 15.3 mm Hg, $p = 0.06$). Also, mean arterial pressure (MAP) determined in the supplement arm after six weeks was significantly lower than that at