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Reduction of atherogenic risk in patients with type 2 diabetes by curcuminoid extract: a randomized controlled trial☆

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Abstract

Curcumin is a phytocompound found in the root of turmeric, a common herbal ingredient in many Asian cuisines. The compound contains anti-inflammatory activity, which is mediated through an up-regulation of adiponectin and reduction of leptin. Consumption of curcumin was shown to prevent some deteriorative conditions caused by inflammation, such as ulcerative colitis, rheumatoid arthritis and esophagitis, and so on. Inflammation-associated cardiovascular conditions such as atherosclerosis are common in diabetes patients. The anti-inflammation effect of curcumin might be beneficial to prevent such condition in these patients. We aim to evaluate an antiatherosclerosis effect of curcumin in diabetes patients. Effects of curcumin on risk factors for atherosclerosis were investigated in a 6-month randomized, double-blinded and placebo-controlled clinical trial that included subjects diagnosed with type 2 diabetes. An atherosclerosis parameter, the pulse wave velocity, and other metabolic parameters in patients treated with placebo and curcumin were compared. Our results showed that curcumin intervention significantly reduced pulse wave velocity, increased level of serum adiponectin and decreased level of leptin. These results are associated with reduced levels of homeostasis model assessment-insulin resistance, triglyceride, uric acid, visceral fat and total body fat. In summary, a 6-month curcumin intervention in type 2 diabetic population lowered the atherogenic risks. In addition, the extract helped to improve relevant metabolic profiles in this high-risk population.

Keywords: Curcuminoid extract; Atherogenic risk; Pulse wave velocity (PWV); Abdominal obesity (visceral fat and total body fat); Insulin resistance; Type 2 diabetes

1. Introduction

Type 2 diabetes mellitus (T2DM) is a cluster of abnormal metabolic conditions that is primarily composed of insulin resistance (IR). Other associated metabolic conditions are abdominal obesity, dyslipidemia, hyperuricemia, high blood pressure and cardiovascular complications. Recent findings indicated that T2DM/IR is not only associated with cardiovascular conditions but also is a driver for atherogenesis [1,2]. Marfella et al. [3] pointed out that inflammation often found in T2DM patients is likely the cause of the diabetes-associated atherosclerosis. Circulating markers of inflammation, as well as monocyte gene expression of proinflammatory mediators, are elevated in type 2 diabetes [4,5]. In addition, a balanced level between a proinflammatory cytokine, leptin and an anti-inflammatory cytokine, adiponectin is often disrupted in T2DM patients; specifically, leptin is up-regulated, while adiponectin is down-regulated [6–8]. The imbalanced levels of these inflammatory-regulating adipocytokines are shown to contribute to the atherosclerosis [9]. It is believed that adiponectin induction, or leptin suppression, in general, should reduce a risk for atherosclerotic diseases in type 2 diabetes patients [10,11]. Other metabolic parameters, known to promote atherogenesis, commonly coexist in the T2DM patients. Such conditions are abdominal obesity [visceral fat (VF) and total body fat (TBF)] [12,13], dyslipidemia [(high triglyceride and low high-density lipoprotein cholesterol (HDL-C)] [14,15] and high uric acid [16,17].

Curcumin is a principal curcuminoid compound found in turmeric (*Curcuma longa* Linn.), a popular spice in Asian cuisine. It is widely consumed and believed to be beneficial for human health [18]. Curcumin extract was shown, in animal models [19–23] and in human [24], to contain positive effects on several metabolic syndromes. It was also shown to contain anti-inflammation [25], antioxidative stress

☆ This trial was registered at clinicaltrials.gov as NCT01052597.

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activities and reduce aortic fatty streak development in rabbits [26]. In addition, daily treatment of curcumin extract can decrease significantly the low-density lipoprotein (LDL) and apoB levels and increase the HDL and apoA in healthy subjects [27]. Due to these positive indications, a trial in human patients of curcumin treatment for prevention of arteriosclerosis has been proposed.

In this study, we aim to study an efficacy and safety of curcumin extract as an intervention agent for reducing the risks for atherogenesis in T2DM, by conducting an evidence-based, double-blind, placebo-controlled clinical trial to access the possibility of using curcumin as an intervention agent for such condition.

2. Subjects and methods

2.1. Subject screening

This simple randomized, double-blinded, placebo-controlled trial with parallel design was conducted at HRH Princess Maha Chakri Sirindhorn Medical Center of Srinakharinwirot University, Nakornnayok, Thailand. Two hundred forty patients with type 2 diabetes were selected by inclusion and exclusion criteria (for the trial profile and consort information, see Online Supplemental Material in Figure 1). The subjects were enrolled in a 9-month-long study. Nutritionists educated all subjects by having the participants to attend a one-on-one consultation, to perform the same pattern of diet and exercise through course of this study after the enrollment (during a 3-month period before the randomization). Standard lifestyle and diet recommendations were provided for all subjects in written form after understanding in educated program from nutritionists. Because all the subjects were recruited from the same geological background with a very similar ethnicity, we assumed that the type of the dietary intake is not dissimilar. To avoid any interference from other medications, during the recruitment process, we excluded all of patients who were taking any other medicines, as indicated in the exclusion criteria. Only type 2 diabetic subjects at the age of ≥35 years, the typical age range in which T2DM normally develops, were included in this study. Type 2 diabetes was diagnosed following the American Diabetes Association (ADA) practice guidelines [28,29]. Briefly, subjects who fit into at least one of these three criteria were included: subjects with a fasting plasma glucose (FPG) ≥126 mg/dl, an oral glucose tolerance test (OGTT) plasma glucose at 2 h post-glucose load (OGTT at 2 h) ≥200 mg/dl and a glycated hemoglobin (HbA1c) ≥6.5%. Diagnosis of type 2 diabetes was confirmed by second repeating tests of all of the above-listed criteria on a different day.

Subjects diagnosed with prediabetes conditions according to the new ADA guidelines [28] were excluded from the study (subjects who are positive for one of these following criteria: FPG between 100 and 124 mg/dl, OGTT at 2 h between 140 and 199 mg/dl, and HbA1c range from 5.7% to 6.4%). The following subjects were also excluded from the study: subjects receiving oral antidiabetes (biguanide, thiazolidinediones and dipeptidyl peptide-4 inhibitors) or insulin injection; subjects receiving antiplatelet drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, fenofibrate, atorvastatin, rosuvastatin and fluvastatin; subjects with serum creatinine ≥2.0 mg/dl or dialysis; subjects with liver enzyme alanine aminotransferase (ALT) ≥3 folds of upper limit of normal value range; subjects receiving other herbal medicine; subjects with secondary causes of hyperglycemia (receiving steroid or with pancreatic cancer); subjects with acute infections or chronic inflammatory diseases (cancer, rheumatoid arthritis); and subjects with a gall bladder disease or history of cholecystectomy. This study (clinical trial registration no. NCT01052597) was approved by the Ethic Committee of Faculty of Medicine, Srinakharinwirot University, Bangkok, Thailand (serial number: SWUEC 30/2550) in accordance with the Declaration of Helsinki and to the guideline by the Consolidated Standards of Reporting Trials (CONSORTs) [30]. Participants were informed and gave their consent before enrollment.

2.2. Randomization procedures

After steps of screening, consenting, and diet and lifestyle training, all subjects were randomly assigned to either the curcumin-treated group (intervention condition) or the placebo-treated group (control condition) using a fixed randomization scheme with assignment based on computer-generated random numbers performed by an independent researcher. The allocation scheme was sealed in opaque and consecutively numbered envelopes. Envelopes were opened sequentially by an independent person. The participants were informed that two types of interventions were being compared.

2.3. The intervention

All participants were instructed to take three capsules with blinded labels of either curcumin or placebo twice a day (total of six capsules per day) for 6 months continuously. Each curcumin capsule has curcuminoid content of 250 mg. Each placebo capsule contains 250 mg of starch. Patients were asked to bring all capsules back when having follow-up visits at 3 and 6 months for assessing their compliance. Numbers of capsules taken by the subjects were recorded in Online Supplemental Material in Table 1.

2.4. Preparation of curcuminoids capsules

Curcumin and identical placebo capsules were manufactured by the Government Pharmaceutical Organization of Thailand. Dried rhizomes of turmeric (*C. longa* Linn.) grown in Kanchanaburi province, Thailand, were ground into powder. The turmeric powder was extracted with ethanol and evaporated at low pressure to obtain ethanol extract in the form of semisolid containing oleoresin and curcuminoids. Oleoresin was then removed to yield curcuminoid extract (total curcuminoids content is between 75% and 85%). The peak ratio of curcumin: demethoxycurcumin and bisdemethoxycurcumin in the extract was determined by high-performance thin-layer chromatography. The extract (calculated for 250 mg of curcuminoids) was capsulated under the Good Manufacturing Procedures standard. Fingerprints of the extract and a detailed analysis of the chemical composition of the preparation in the extract are shown in Online Supplemental Material in Fig. 2.

2.5. Study outcomes

The primary outcome of the antiatherogenic activities was assessed by an average pulse wave velocity (PWV) in the curcumin-treated group and the placebo group. In addition, the changes in the level of anti-inflammatory adipocytokines (increased adiponectin or decreased leptin) were also recorded. Other parameters assessed included IR (HOMA-IR), triglyceride and uric acid levels, and abdominal obesity (VF and TBF).

Indications of adverse effects of curcumin were monitored by elevated creatinine ≥1.2 mg/dl and aspartate aminotransferase (AST)/ALT ≥3 times of the upper limit of normal value range, and any symptoms of patient complaints were recorded [29].

2.6. Data collection and measurement methods

Measurements were performed at the baseline and during the 3 and 6-month visits. We recorded demographic data at the baseline; the researchers administered a questionnaire and measured the medical history, medication, body weight, body height, waist circumference (WC) and vital sign status. The abdominal obesity indicated by WC was measured by a tape in the direction of the horizontal plane, midway between the inferior margin of the wrist and the superior border of the iliac crest [31]. Abdominal obesity indicated by TBF and VF was determined by bioelectrical impedance analysis (body fat analyzer: OMRON HBF-362), and was then analyzed for body fat level and VF level, respectively [32]. Blood was collected at 8:00 AM from the antecubital vein with the patient in the recumbent position, after an overnight fast. Plasma samples for assays of insulin, adiponectin and leptin were frozen and stored at −70°c until the analyses of hormones were performed. FPG, HbA1c, total cholesterol, triglyceride, LDL cholesterol (LDL-C) and HDL-C levels were measured according to the standard procedures. Plasma insulin, adiponectin and leptin concentrations were determined using the radioimmunoassay kits (Millipore, St. Charles, MI, USA). The signals were detected by a gamma scintillation counter calibrated for 125 iodine measurement. HOMA-IR was calculated to assess change in IR [33,34]. PWV was used as an indicator for the arterial stiffness [35,36]. PWV was measured by Colin Medical Technology (VP-1000) and analyzed by pulse wave diagnosis results [37]. Peripheral PWV (baPWV) represented by volume waveforms for the brachium and ankle and was measured using a VP-1000 pulse wave analyzer (Colin Medical Technology), as previously described [38]. In brief, the PWV measurement system recorded electrocardiogram, phonocardiogram and three-pulse waves from the brachial and dorsalis pedis arteries. Pressure pulse sensors were used to measure pulse waves. Amplifier, filter and isolation circuits were used to detect accurate signals. The intersecting tangent algorithm, using the least square mean method, was adapted to determine up stroke points. Regional PWV values, brachial and dorsalis pedis were calculated automatically after collecting 10 s of data. For baPWV, brachial–dorsalis pedis transit time and PWV were calculated from the brachial–dorsalis pedis path length divided by transit time. Path length was estimated from the linear distance from the sternal notch to the dorsalis pedis artery at the point of applanation.

2.7. Sample size

The sample size was statistically calculated to obtain a power of 80%, with an alpha error of .05. In order to demonstrate an effect in levels of PWV levels, consisting of a 60-cm/s reduction with standard deviation of 160 cm/s [39], a sample size of 226 (113 in the curcumin-treated group and 113 in the placebo group) is required. Assuming a 5% loss to follow-up, 238 subjects between the two groups need to be selected. The two groups will be of equal size in order to obtain the greatest statistical power.

2.8. Statistical analysis

Continuous data are presented as the means±SEM, and $P<.05$ was considered statistically significant. Two-tailed Student's t test was used for baseline comparisons and outcome evaluations between two groups, and between means at baseline and 3 or 6 months. Categorical variables were presented in percent and analyzed using chi-square test. Outcome data were analyzed on an intention-to-treat basis, including all randomized patients in the efficacy and safety analyses, according to their randomized treatment group regardless of the treatment received. These exclude patients who