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The Effects of Bioavailability-Enhanced Curcuminoids on Serum Paraoxonase-1 Activity in Patients with Metabolic Syndrome

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ABSTRACT

Introduction: Metabolic syndrome (MetS) is characterised by a clustering of metabolic cardiovascular disease (CVD) risk factors that include: central obesity, impaired glucose metabolism, dyslipidaemia (hypertriglyceridemia, increased low-density lipoprotein [LDL], decreased high-density lipoprotein [HDL]) and hypertension. Paraoxynase-1 (PON1) is a plasma HDL associated protein that inhibits the oxidation of other lipoproteins. There is some evidence of reduced enzyme activity in subjects with metabolic syndrome. Curcumin is a natural polyphenol, it has been reported that curcumin has beneficial effects on several metabolic syndrome associated parameters. The aim of this study was to evaluate the effect of phospholipid complex of curcumin as an antioxidant on the activity of this enzyme in subjects with metabolic syndrome.

Materials and Method: A double-blind randomised control study was undertaken in 80 patients with metabolic syndrome. Subjects in the intervention (n = 40) were given capsules of phospholipidated curcumin (1 g/day) for a period of 6 weeks. The control subjects (n = 40) received a placebo. Fasting blood samples of each person were obtained during the start and the end of the study. Paraoxonase activity was measured using a PON1 fluorescence Paraoxonase Assay Kit and Arylesterase activity was measured by photometeric method using a UV-Visible spectrophotometer.

Results: Serum paraoxonase enzyme activity did not change significantly between the curcumin treated group and the control group before the intervention (0.54 ± 0.18 U/µl versus 0.49 ± 0.14 U/µl; P > 0.05), nor did serum arylesteras activity change significantly between two study groups (152.67 [46.60 to 916.05] U/µl versus 129.77 [55.34 to 344.78] U/µl; P > 0.05). In addition, there was no significant difference in changes at baseline and after the intervention in serum PON1 activity between the curcumin treated group and the control group (-0.03±0.19 U/µl versus -0.04±0.18 U/µl; P > 0.05), nor was there a significant change in arylesteras activity (-12.36 [-88.83 to 110.24] U/µl versus -4.58 [-61.06 to 47.07] U/µl; P > 0.05).

Conclusion: Phospholipid fortified curcumin has no significant effect on serum PON1 activity.

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Introduction

Metabolic syndrome (MetS) is characterized by a clustering of cardiovascular risk factors including: central obesity, high blood pressure, insulin resistance (or hyperglycemia) and dyslipidemia (1) which can lead to increased risk of cardiovascular disease (CVD) and diabetes (2). In recent years, the prevalence of MetS has increased (3). MetS prevalence varies widely between populations.

A systematic review and meta-analysis carried out in 2013 in Iran, has reported the prevalence of MetS to be approximately 36% based on International Diabetes Federation (IDF) criteria (4), that shows a high prevalence of MetS in Iran. The direct relationship between MetS and prevalence of CVD is well supported (5); MetS presence predicts almost 25% of all cases of CVD (6).

CVD is the major cause of disability and premature death (more than 1.17 million deaths in 2010) and also high costs of health care systems globally (7). In the past twenty years, CVD mortality has increased from 20% to 45% in Iran (8). Atherosclerosis is the underlying cause of CVD disease (9) and several features of MetS may be associated with an increased development of atherosclerotic plaques. This includes low concentrations of the protective high-density lipoprotein (HDL) (10). HDL have some anti-atherogenic properties, including antioxidant properties that may protect low-density lipoproteins (LDL) from oxidation to the pro-atherogenic Ox-LDL (11). The anti-atherogenic effects of HDL may be attributable to several HDL associated proteins such as Paraoxonase (PON1) (12).

PON1 is a calcium-dependent esterase (13), expressed predominantly in the liver and is secreted into the serum where it is associated with HDL (14). In the serum, PON1 plays an important role in HDL antioxidant and anti-inflammatory activities and leads to a reduction in the possibility of creating the oxidized form of LDL during lipid peroxidation (15) and may contribute to the protection against atherosclerosis (16). The level of PON1 enzyme activity can be measured *in vitro* by measuring its hydrolase effect on paraoxon substrate or phenyl acetate. The results of some studies indicate a reduction in PON1 activity in oxidative conditions (16). Several studies have reported reduced serum PON1 in individuals with MetS (17). Serum PON1 activity and concentration vary widely in different populations (18).

The results of several studies show additive effect of antioxidants containing polyphenol on PON1 enzyme activity (19). Curcumin (diferuloylmethane) is a natural polyphenol with a bright orange-yellow pigment which exists in dried rhizomes of turmeric and the main component of the substances extracted from *C. longa* (20). There are many medicinal properties and uses for curcumin including anti-inflammatory (21) and antioxidant activities (22) and also therapeutic effects on cancer (23) that have been proposed. Curcumin has beneficial effects on almost all components of the MetS. For example the impact of increasing insulin sensitivity, which has been investigated in different studies (24), lipid-lowering effects (25) and an increasing effect on blood HDL-C (26).

Despite the potential benefits of curcumin, its pharmacological and therapeutic effects and clinical efficacy are decreased due to its limited bioavailability (27). One way to solve this problem is the use of curcumin-phospholipid complex which leads to its kinetic improvement. It has been reported that this form has a higher absorption and is eliminated from the body at a slower rate. This complex is now commercially available (27). In the present study, we investigated the effect of enhanced absorption curcumin (curcumin-phospholipid complex) on PON1 enzyme activity in patients with MetS.

Materials and methods

A double-blinded clinical study design was approved by the Research Council of Mashhad University of Medical Sciences in cooperation with Qaem Hospital, Mashhad, Iran in 2014. Informed consent was obtained from all participants. The study has been recorded in the Iranian Registry of Clinical Trials (IRCT; registration number: IRCT2014052014521N3. This research was a sub-study from our previous work (28), in which the sample size was calculated to be 35 individuals per group (α=0.05 and β=0.02).

Subjects: The study population consisted of 80 patients, who were 18 to 65 years old meeting the IDF criteria for MetS [2005] and

had been referred to the Qaem Nutrition Clinic. Exclusion criteria included: a history of systemic diseases such as lupus, kidney disease, pregnancy or lactation, consuming lipid lowering drugs and any other medications within the last 3 to 6 months.

Anthropometric measurements

Anthropometric parameters including: height, weight, BMI, waist and hip circumference, fat percentage and blood pressure were measured according to a standard protocol at baseline following the intervention. Moreover, demographic information including: age, gender, tobacco consumption history, pharmaceutical-medical history were recorded in the provided questionnaire (Table 1).

Study design

The random allocation sequence was made by means of the computer randomization method. All participants, care providers and statistician were blinded after that the patients assigned to the intervention. Consecutively numbered wrapped envelopes were used to implement the random allocation sequence. As well, the capsules bottles were coded by a non-researcher individual and remained confidential until statistical analysis.

Participants were randomized in two groups (40 participants in each group): the first group received curcumin-phospholipid complex at a daily dosage of 1 g for 6 weeks; the placebo group received capsules containing starch, similar in appearance to the intervention group for 6 weeks. All participants received similar diets during the study period. Over the 6 weeks period of the study, each patient was visited 2 times.

Blood Collection

Blood samples were collected from the volunteers before and after the intervention period. 20 ml blood samples were collected from the volunteers in plain tubes after 12 hours of fasting. The blood samples, after being transferred to the laboratory, were centrifuged for 15 minutes rotating at 3000 rpm. Then, the serum samples were isolated from the clot and were kept at -80 °C until the time of measuring the PON1 enzyme activity.

Table 1: Clinical and biochemical features in subjects before and after intervention

Variables	(A) Before	(B) Before	P-value	(C) After	(D) After	P-value
Age (years)	40.05 ± 10.48	38.59 ± 10.28	0.53	-	-	-
Weight (kg)	82.56 ± 15.64	82.12 ± 12.68	0.89	84.06 ± 14.67	81.32 ± 11.26	0.39
BMI (kg/m^2)	30.66 ± 5.06	31.22 ± 4.67	0.61	31.03 ± 5.11	31.30 ± 4.87	0.71
WC (cm)	103.00 ± 10.24	102.49 ± 9.41	0.34	100.82 ± 11.57	99.42 ± 11.86	0.45
FAT%	34.51 ± 8.07	35.21 ± 7.86	0.69	35.19 ± 8.48	34.57 ± 9.05	0.77
FBG (mg/dl)	95.97 ± 19.97	92.82 ± 16.62	0.44	103.49 ± 15.27	100.94 ± 16.74	0.50
SBP (mmHg)	120.82 ± 10.24	120.26 ± 11.50	0.82	117.44 ± 7.32	115.50 ± 11.02	0.43
DBP (mmHg)	83.48 ± 9.17	81.70 ± 10.76	0.44	80.30 ± 5.56	77.90 ± 9.44	0.24
Total-Cholesterol (mg/dl)	241.27 ± 51.69	242.12 ± 46.83	0.93	224.28 ± 44.20	216.79 ± 38.82	0.45
Triglycerides (mg/dl)	180.22 ± 124.67	182.15 ± 110.02	0.94	163.74 ± 75.23	146.65 ± 85.25	0.29
HDL-c (mg/dl)	52.23 ± 12.91	51.91 ± 10.62	0.90	49.50 ± 7.89	48.97 ± 10.71	0.81
LDL-c (mg/dl)	152.99 ± 38.48	153.78 ± 40.40	0.92	140.32 ± 36.45	139.65 ± 29.30	0.93
Current Smoking % (n)	15.4 (6)	13.9 (5)	0.31	-	-	-

Values expressed as mean ± SD. A, curcumin-phospholipid; B, Placebo; C, curcumin-phospholipid; D, Placebo; BMI: body mass index; WC: waist circumference; FBG: fasting blood glucose; SBP: systolic blood pressure, DBP: diastolic blood pressure; HDLc: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol.

Routine biochemical analysis

Lipid profile including total cholesterol, LDL-c, HDL-c, triglycerides and blood glucose levels were measured for each individual. Serum lipid and blood glucose concentrations were determined by commercially available kits through enzymatic methods.

Measurement of Paraoxonase activity: Paraoxonase activity was measured using EnzChek Paraoxonase Assay Kit (InvitrogenTM) according to the manufacturer's instructions, using a highly sensitive homogeneous fluorometric assay (excitation/emission wavelengths 360/450 nm) for the organophosphate activity of PON-1 based on the hydrolysis of a fluorogenic organophosphate analog. Enzymatic activity was calculated by converting fluorescent signal into activity using a standard curve.

Measurement of Arylesterase activity:

Arylesterase activity was determined spectrophotometrically using phenylacetate (PA) (Sigma Co., London, UK) as the substrate, as previously described (8). Briefly, enzyme activity was determined by measuring as the initial rate of hydrolysis of PA. Production of phenol was determined spectrophotometrically for 4 minutes at 270 nm. The arylesterase assay was done using serum samples which were diluted 1:100 (in dilution buffer) for assays (pH = 8.0). The diluted serum (30 µL) was added to the assay mixture (300 µL) containing 3.26 mM substrate (phenyl acetate), 1 mM CaCl2 and contained 20 mmol/L Tris-HCl (pH=8.0). Activities were expressed in Units/ml, based on the molar extinction coefficient of 1.31 mmol/L-1cm-1 for phenol were not normally distributed were assessed using Wilcoxon and Mann-Whitney tests. Descriptive variables were expressed as mean±SD and median (quartile 1 to quartile 3) for normally and not normally distributed data, respectively.

Statistical analysis

Data obtained from clinical and demographic observations as well as measured factors were analyzed using SPSS software version 16. In all calculations, $P<0.05$ was considered significant. Qualitative data in both groups including gender were measured through Chi-square test. Data were initially examined by Kolmogorov-Smirnov test in terms of the normality of data distribution. Afterwards, normal data were analyzed through paired t-test and independent t-test, and data that

Results

Considering gender frequency in each group, there were no significant differences between them and both groups were homogeneous in terms of gender ($P>0.05$). Table 1 shows the comparison of demographic information and biochemical variables of patients in the case and control groups before and after intervention. No significant difference was found between the groups ($P>0.05$).

Results from the examination of paraoxonase and arylesterase activities of PON1 in the studied groups

Table 2 shows the comparison of mean serum paraoxonase and arylesteras activity of serum PON1 before and after the intervention in two groups of curcumin-phospholipid and placebo consumers. There was no significant difference in paraoxonase activity in the curcumin-phospholipid group before and after the intervention ($P>0.05$). Moreover, there was no significant difference in paraoxonase activity in the control group after the intervention compared to before ($P>0.05$).

Arylesterase activity of the PON1 in the curcumin-phospholipid group was slightly increased after intervention, but this change was not statistically significant ($P>0.05$). Furthermore, arylesterase activity in the control group was slightly increased, but this was not also significant ($P>0.05$).

As can be seen, no significant difference was observed between the two groups before the intervention ($P>0.05$). The results indicate a none-significant change in the level of the enzyme paraoxonase and arylesteras activity between the two groups after the intervention ($P>0.05$).

Discussion

The aim of this study was to evaluate the effect of curcumin (phospholipid-complex form) on the serum PON1 enzyme activity in

the subjects with metabolic syndrome. However, we did not find any significant changes on the PON1 paraoxonase and arylesterase activities after supplementation of phospholipid complex form of curcumin.

No previous research has been reported to evaluate the impact of curcumin and particularly curcumin-phospholipid on PON1 activity in human samples. Only an in vitro study and a limited number of studies have been conducted on animal species to examine the effect of curcumin on PON1 enzyme activity. Schrader et al. (29) investigated the effect of curcumin on the level of PON1 activity in vitro. Adding curcumin to the culture medium led to a significant increase in the enzyme activity. Among the reasons for the difference between the results of the two studies, we can refer to the different processes of the response to drugs by the cells in vitro and in vivo. Various factors can influence the effects of oral drugs in vivo. The amount of drug absorption from the intestine, its plasma concentration and the concentration of drugs that finally reaches the target cell are among the determining factors in clinical effectiveness. Metabolic conditions in the body (such as hepatic metabolization and conjugation of the drug and its excretion from the body) reduce its bioavailability and this reduction is one of the notable differences between the two environments. Also the environmental and genetic backgrounds can affect the drug's response in the human body. Due to the mentioned differences, results from the two environments cannot be compared precisely and more studies are needed in the future.

Schrader et al., (29) also designed an animal model to examine whether or not oral curcumin induces PON1 activity in vivo. The study showed that curcumin has no influence on: body weight, enzyme activity and protein expression of the enzyme in rat liver. These findings are consistent with our research results.

A brief overview of animal studies on the effect of curcumin supplements onparaoxonase and arylesterase activities of PON1, demonstrate the positive effect of curcumin on the levels of serum PON1 enzyme activity (30). The difference between results obtained from human and animal studies may be in part, due to applying more control on dietary and drug intake in the animal samples compared to the human samples. Furthermore, the difference in the dosage of curcumin can be a significant point. As previously mentioned, using several different doses higher and lower than the applied dose, could elucidate the effectiveness of supplements with more confidence.

In this study, anthropometric factors (weight, BMI and waist circumference) and biochemical parameters of patients were measured. Comparison of the average of measured factors before and after the intervention showed no significant differences between the two groups. The results obtained from some animal studies indicate the inhibitory effect of curcumin on the rate of weight gain in the supplement consuming group (31) although in some studies, this effect has not been observed (26). In some human studies, which investigated the effects of curcumin supplement on the metabolic syndrome risk factors, no significant changes were noted in body weight, serum glucose level and other anthropometric factors in the curcumin supplement consuming groups (25).

One of the limitations of this study was the use of only a single dose of the drug. Therefore, for better evaluation of the drug performance, it can be suggested to use more frequent doses of supplement to maintain the drug concentration in the blood. Moreover, to ensure the absorption of curcumin supplement, it is better to determine the plasma concentration after consumption at different time intervals. Another limitation in this study was the small sample size. Considering the slight increase observed in PON1 activity of the enzyme, it seems that the use of a larger sample size in future studies may provide better results.

It should be noted that concentration and activity of PON1 are influenced by polymorphisms which have a great diversity in different populations. Consequently, in order to better investigate the enzyme activity having the genetic information of individuals could be helpful, although this is currently under investigation as a separate project.

Table 2: Comparison of paraoxonase activity and arylesteras activity between the curcumin-phospholipid group and placebo group before and after 6 weeks intervention.

Group	Paraoxonase activity (U/µl) mean ± SD				Arylesteras activity (U/ml) Median (Q1 - Q3)			
	before intervention	after intervention	p-value	Changes	before intervention	after intervention	p-value	Changes
Curcumin-phospholipid	0.54 ± 0.18	0.50 ± 0.13	0.31*	-0.03±0.19	152.67 (46.60 - 916.05)	158.39 (38.93 to 832.06)	0.83*	-12.36 (-88.83 to 110.24)
Placebo	0.49 ± 0.14	0.44 ± 0.14	0.16*	-0.04±0.18	129.77 (55.34 - 344.78)	137.40 (45.80 - 267.18)	0.94*	-4.58 (-61.06 to 47.07)
p-value	0.14	0.03	-	0.80	0.26	0.08	-	0.82

Values expressed as mean ± SD and Median (Q1-Q3). Independent t-test and Mann-Whitney test were used for normal and not normally distributed data, respectively. *: Paired t-test was used.

Comparing the present study with other conducted studies, to the best of our knowledge, it is as the first clinical trial study which has significant clinical value. Moreover, in this study curcumin-phospholipid supplement with a higher bioavailability was used for the first time, which can be considered as the strength of this study.

We have previously shown the beneficial effects of curcumin at a dose of 1 g/day in patients with metabolic syndrome (25). In current study, we used phytosomal curcumin because its absorption is 29 folds higher compared with the simple curcuminoids (32). But, it seems that this modified curcumin dose was more than has been shown to have favorable effects in patients with metabolic syndrome. Though, it is consistent with preceding studies that suggested curcumin shows a hormetic response (33); "a biphasic dose-response with a low dose stimulation or beneficial effect and a high dose inhibitory or toxic effect" (34). Further studies are warranted to detect the hormetic effects mechanisms of this phytochemical on Paraoxonase-1 activity.

Finally, it may be important to conduct subsequent studies using different doses of the drug and a larger RCT to better evaluate the effect of the drug. Additionally, HDL as the main carrier of serum PON1 has a decisive role in the concentration and activity of the enzyme. The results obtained from several studies indicate a significant relationship and correlation between the serum HDL level and PON1 activity (35). It seems that with measuring HDL particles in the serum of individuals, we could better discuss the effectiveness of curcumin on the enzyme activity. In addition, it is not yet known whether there is a difference between oral or injectable curcumin-phospholipid on the activity of enzymes, so this issue should be considered in the future studies.

Conclusions

Phospholipid complexes of curcumin at a dose of 1 g/day had no effect on PON1 activity in individuals with metabolic syndrome in our population. Considering many factors that are involved in a clinical trial, other studies in the future with different design may be helpful to better investigate the effects of curcumin on metabolic syndrome and any related mechanisms.

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Informed consent: Informed consent was obtained from all individual participants included in the study.

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