The effects of caffeic acid phenethyl ester (CAPE) treatment on rheumatologic parameters and iron metabolism in diabetic rats

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ABSTRACT

Diabetology and rheumatology have much in common, including many biochemical features. Diabetic cases suffer excessively from common musculoskeletal conditions. The present study aimed to explore the association between the caffeic acid phenethyl ester (CAPE) treatment and the standard parameters of diabetic and rheumatologic controls. Serum anti-streptolysin-O (ASO), C-reactive protein (CRP), rheumatoid factor (RF) titers and glucose (GLU), cholesterol (CHOL), triglyceride (TG), high density lipoprotein (HDL), very low density lipoprotein (VLDL), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), sodium (Na), potassium (K), chloride (Cl), calcium (Ca), phosphorus (P), uric acid (UA), iron (Fe), iron-binding capacity (IBC), total iron-binding capacity (TIBC) and superoxide dismutase (SOD) levels were measured in 22 female Wistar-Albino rats. The animals were divided into three groups: group 1: non-diabetic rats as control; group 2: streptozotocin (STZ)-induced, untreated diabetic rats; and group 3: STZ-induced, CAPE-treated diabetic rats. Levels of GLU were increased in group 2. ASO values were decreased in group 3. TG and VLDL levels were increased in group 3 compared with the group 1. Higher UA levels were detected in group 3 compared with group 2. The levels of Fe and TIBC were decreased in group 3. The results of the present study indicate the reducing effect of CAPE on the serum levels of diabetic and rheumatologic parameters in diabetic rats.

Key words: caffeic acid phenethyl ester (CAPE), diabetes, iron, rat, rheumatologic parameters

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Introduction

Caffeic acid phenethyl ester (CAPE), a flavonoid-like compound, is one of the major components of honeybee propolis. CAPE, which has no reported harmful effects on normal cells (ILHAN et al., 1999), has several biological and pharmacological properties: antioxidant (SUD'INA et al., 1993), anti-inflammatory (MICHALUART et al., 1999), anti-carcinogenic (CHEN et al., 2001), antiviral (FESEN et al., 1994), and immunomodulatory (PARK and KAHNG, 1999) activities.

In previous studies CAPE has been suggested as an agent that significantly lowers hyperglycemia and reverses some diabetic complications in rat models, with both streptozotocin (STZ)-induced diabetes type 1 (JUNG et al., 2006) and type 2 (PARK and MIN, 2006). As such, it is stated that CAPE treatment should be considered in treating hyperglycemia and liver complications in diabetic patients (CELIK et al., 2009).

Recent scientific evidence has revealed unsuspected influences between iron metabolism and diabetes. The correlation is bi-directional—iron affects glucose metabolism, and glucose metabolism impinges on various iron metabolic pathways. Oxidative stress and inflammatory factors influence these relationships, amplifying and potentiating the initiated events (FERNÁNDEZ-REAL et al., 2002).

Likewise, diabetology and rheumatology are two medical specializations that have much in common, including many immuno-chemical features. Diabetes affects the connective tissues and causes alterations in the peri-articular and the musculo-skeletal systems. The biochemical mechanisms for some of these conditions have not been understood completely (CAGLIERO, 2003).

To the best of our knowledge, there have been no experimental studies regarding the effects of caffeic acid phenethylester on rheumatologic parameters and iron metabolism in STZ-induced diabetic rats. Hence, the present study was designed to investigate the possible effects of CAPE on iron metabolism and rheumatologic parameters in diabetic rats. We evaluated anti-streptolysin-O (ASO), C-reactive protein (CRP) and rheumatoid factor (RF) titers, as well as iron (Fe), iron-binding capacity (IBC), total iron-binding capacity (TIBC) levels. This study also investigated the effects of CAPE on antioxidant defense, serum lipids, electrolytes and liver enzymes affected by diabetes.

Materials and methods

Animals and diets. Twenty-six female Wistar-Albino rats (11 weeks old and 223.5 ± 41.8 body weight) were used in the study. They were kept in an environment of controlled temperature (24-26 °C), humidity (55-60 %), and controlled photoperiod (12 h light/dark cycle) during the experiment. The animals were fed a commercial balanced diet based on corn, wheat, soybean meal, hazelnut meal, meat-bone meal, and fish meal. The chemical composition of the diet was: dried matter 88 %, crude protein 23 %, crude cellulose 7 %,

crude ash 8 %, Ca 1-2.8 %, NaCl 1 %, metabolizable energy 2.600 Kcal/kg, and vitamin A 400 IU/kg. Diet and tap water were provided *ad libitum*. The experimental procedures were approved by Mustafa Kemal University, Veterinary Faculty Ethics Committee for the use and care of laboratory animals.

Induction of diabetes, CAPE treatments, and sample collection. Animals were randomly divided into three groups (each animal placed separately in a stainless-steel cage) as follows: group 1, non-diabetic control rats (n = 6); group 2, STZ-induced, untreated diabetic rats (n = 10); and group 3, STZ-induced, CAPE-treated diabetic rats (n = 10), which were injected daily with caffeic acid phenethyl ester (CAPE). CAPE was commercially purchased (Sigma Chemical Co., St. Louis, MO, USA, C8221) and administered intraperitoneally (i.p.) at a dose of 10 μmol/mL/kg/day 3 days after STZ application, and the treatment was continued for 60 days.

STZ (Sigma Chemical Co., St. Louis, MO, USA, S0130) dissolved in sodium citrate buffer (pH 4.5) and administered i.p. at a single dose of 50 mg/kg body mass. Isotonic saline solution (an equal volume) was injected (i.p.) into the control rats. Blood glucose (B-GLU) levels were measured with an Accu-Chek Active strip test in a glucometer (Roche Diagnostic, Mannheim, Germany) in all rats after 3 days of STZ treatment. A total of 4 animals from group 2 were excluded from the study during the experimental applications. Two of them were excluded due to health deterioration and the others had B-GLU levels less than 300 mg/dL.

At the end of the experimental period, blood samples were taken from the tail vein of the anaesthetized animals (50 mg/kg ketamin hydrochloride, i.m.). All blood tubes were centrifuged at $825\times$ g at 4 °C for 10 min to obtain the serum. The serum samples were immediately stored at -25 °C until biochemical assays.

Biochemical analyses. Serum samples were used for analyses of glucose (GLU), cholesterol (CHOL), triglyceride (TG), high density lipoprotein (HDL), very low density lipoprotein (VLDL), calcium (Ca), sodium (Na), potassium (K), chloride (Cl), phosphorus (P), uric acid (UA), iron (Fe), iron-binding capacity (IBC), total iron-binding capacity (TIBC), C-reactive protein (CRP), anti-streptolysin O (ASO) and rheumatoid factor (RF), as well as gamma glutamyl transferase (GGT) and alkaline phosphatase (ALP) activities, using commercially available kits (Roche Diagnostics GmbH; Mannheim, Germany) in an auto-analyzer (Cobas Integra 800; Roche Diagnostics GmbH; Mannheim, Germany). Superoxide dismutase (SOD) activities were analyzed using commercially available kits (OxiSelect SOD Activity Assay, Cell Biolabs, STA-340, USA).

Statistical analyses. The MINITAB® 16.1 program (Minitab Inc., USA) was used for the statistical analyses and the confidence interval was determined as 95 %. One-way analysis of variance was used to compare the mean values of the results of biochemical

analyses among the animals in all study groups. Tukey's test was used for posthoc comparisons when indicated by a significant F-test for a group.

Results

The GLU level in the serum was increased in the untreated diabetic rats compared with the rats of the control and CAPE-treated diabetics groups, indicating that CAPE treatment significantly ($P<0.05$) reduced serum GLU levels, even below the control level compared with the untreated-diabetic group (Table 1).

Table 1. Serum biochemical values (mean ± standard error) in control (group 1, n = 6), diabetic (group 2, n = 10) and diabetic + caffeic acid phenethyl ester (CAPE) (group 3, n = 10) groups in rats

Biochemical parameters	Groups			P value
	1	2	3	
GLU (mg/dL)	160.83 ± 18.73[b]	373.67 ± 114.54[a]	145.60 ± 39.65[b]	< 0.05
CHOL (mg/dL)	71.33 ± 5.72	78.00 ± 14.70	63.50 ± 16.05	NS
TG (mg/dL)	82.83 ± 38.34[b]	124.83 ± 63.73[ab]	225.70 ± 131.75[a]	< 0.05
HDL (mg/dL)	40.33 ± 12.99	34.17 ± 27.04	18.00 ± 14.30	NS
VLDL (mg/dL)	17.67 ± 7.79[b]	24.83 ± 12.72[ab]	45.10 ± 26.40[a]	< 0.05
ALP (IU/L)	202.5 ± 42.2	295.2 ± 186.6	278.9 ± 106.1	NS
GGT (IU/L)	2 ± 0.632	7.167 ± 5.456	7.3 ± 8.220	NS
Na (mmol/L)	152.37 ± 4.06	148.88 ± 6.39	148.90 ± 3.20	NS
K (mmol/L)	5.3317 ± 0.6972	5.1150 ± 0.77	5.6930 ± 0.5158	NS
Cl (mmol/L)	103.16 ± 1.78	101.35 ± 5.32	104.23 ± 3.70	NS
Ca (mg/dL)	11.55 ± 0.418	11.8 ± 0.469	11.26 ± 0.860	NS
P (mg/dL)	4.3 ± 1.030	4.367 ± 1.686	4.9 ± 1.719	NS
UA (mg/dL)	1.5 ± 0.3742[ab]	1.1333 ± 0.1633[b]	1.73 ± 0.4398[a]	< 0.05
Fe (μg/dL)	259.21 ± 34.67[a]	181.42 ± 81.10[ab]	136.94 ± 77.14[b]	< 0.05
IBC (μg/dL)	409.2 ± 156.8	523.5 ± 147.1	360.1 ± 108.6	NS
TIBC (μg/dL)	643 ± 133.52[a]	705.17 ± 96.35[a]	503.90 ± 59.94[b]	< 0.05
SOD (inhibition %)	0.23333 ± 0.03445	0.22833 ± 0.04262	0.17620 ± 0.07323	NS
ASO (IU/mL)	37.50 ± 13.33[a]	23.12 ± 8.22[ab]	18.84 ± 13.68[b]	< 0.05
CRP (IU/mL)	0.01583 ± 0.01429	0.025 ± 0.03886	0.002 ± 0.00632	NS
RF (IU/mL)	8.317 ± 0.752	9.267 ± 3.757	8.710 ± 7.530	NS

Different superscripts a,b in the same row indicate significant differences among group ($P<0.05$). GLU: Glucose; CHOL: Cholesterol; TG: Triglyceride; HDL: High density lipoprotein; VLDL: Very low density lipoprotein; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; Na: Sodium; K: Potassium; Cl: Chloride; Ca: Calcium; P: Phosphorus; UA: Uric acid; Fe: Iron; IBC: Iron-binding capacity; TIBC: Total iron-binding capacity; SOD: Superoxide dismutase; ASO: Anti-streptolysin-O; CRP: C-reactive protein; RF: Rheumatoid factor; NS: not significant.

In the CAPE-treated diabetic group, the TG levels were higher than those of the control group. The TG level was increased significantly by the CAPE treatment in diabetic rats compared with the control rats (P<0.05). Similarly, the level of VLDL was increased in the group of CAPE-treated diabetic rats compared with the rats of the control group. Other lipid markers (CHOL and LDL) evaluated in the present study decreased insignificantly in the CAPE-treated diabetic rats compared to controls and untreated diabetics. On the other hand, liver enzyme (ALP and GGT) activities increased in the diabetic rats (both groups 2 and 3), compared with the control group. However these results were not statistically significant.

Higher UA levels were detected in the CAPE-treated diabetic group compared with the untreated diabetics (P<0.05). CAPE did not significantly affect the Na, K, Cl, Ca and P concentrations. However, the CAPE treatment significantly reduced the levels of Fe parameters below that of other groups. In the CAPE-treated diabetic group, Fe (P<0.05) and TIBC (P<0.05) were significantly lower. SOD activity was insignificantly decreased in the CAPE-treated diabetic rats, compared with the other groups.

Levels of rheumatologic markers (ASO, CRP and RF) were decreased in the CAPE-treated diabetic group compared to the diabetic group, but with no statistically significant difference, with the exception of ASO. CAPE treatment reduced ASO levels significantly (P<0.05) compared to the control group.

Discussion

To the best of our knowledge, the present study is the first report on the effects of CAPE on Fe metabolism and rheumatologic parameters in STZ-induced diabetic rats. Our results demonstrate lower levels of Fe parameters and rheumatologic markers in the CAPE administered diabetic group.

Fe is one of the essential elements required for a variety of molecules to maintain their normal structure and functions, and for cells to live, grow, and proliferate. The homeostasis of Fe results from tightly coordinated regulation by various proteins involved in uptake, excretion and intracellular storage/trafficking (LIU et al., 2009). In the present study, CAPE treatment significantly reduced the levels of Fe (P<0.05) and TIBC (P<0.05) below those of the non-diabetic control and untreated diabetic groups. Although there has been no such study regarding the levels of Fe parameters in CAPE-treatment, there is a report investigating the protective effect of CAPE on oxidative damage due to Fe overload in rats (CÜRE, 2007). In that study, ferritin was significantly elevated in the Fe and CAPE+Fe groups. The ferritin level is specified as a marker that reflects the amount of Fe stored, and it acts as a buffer against Fe deficiency and Fe overload. This diversity from our results may be caused by the differences between the designs (Fe overload or diabetes inductions) of the experiments. On the other hand, CÜRE (2007) reported that CAPE may be an effective treatment option for protection from Fe induced oxidative stress in heart and liver tissues.

In another study investigating the effects of CAPE on Fe-induced liver damage, it is reported that CAPE treatment prevented the increase in myeloperoxidase (MPO) activity and malondialdehyde (MDA) levels and it is suggest that CAPE may be an available agent to protect the liver from injury via inhibition of MPO activity (OKTAR et al., 2009). Considering this, it may be proposed that the decreasing effect of CAPE on Fe levels may help to support acute stress responses and a healthy antioxidant system.

Diabetes has major effects on connective tissues, which have a significant impact on both the development and outcome of diseases of cartilage, bones, ligaments, and tendons. An improved understanding of the mechanisms through which diabetes alters connective tissue metabolism should lead to better preventive and therapeutic interventions. In the present study, levels of rheumatologic markers (ASO, CRP and RF) were decreased in the CAPE-treated diabetic group. CAPE treatment reduced the levels of ASO significantly compared to the controls. However, as there has been no study to compare the present findings it was not possible to further evaluate our results. However, our results could establish a base for future clinical or experimental rheumatologic studies, and incremental progress can be made in understanding the interactions between diabetes and common musculoskeletal syndromes and the role of CAPE in the treatment.

As for biochemical findings in the present study, CAPE treatment significantly (P<0.05) reduced serum GLU levels, even below the control levels, compared with the untreated-diabetic group. Parallel to previous studies (JUNG et al., 2006; CELIK et al., 2009; ABDULJAWAD et al., 2013) we can suggest the significant potential of CAPE as an antidiabetic agent. Between the investigated lipid parameters, CHOL and HDL showed insignificant decreases in the CAPE treatment group. However, we could not find lower levels of TG, VLDL and UA, which were expected to decrease by CAPE treatment (CELIK et al., 2009; YOSHIZUMI et al., 2005). However this deviation from other studies may result from the animal types, different formulations, and application routes of CAPE treatments. Furthermore, regarding the biochemical mechanism linking increased uric acid to decreased iron, the pathway is currently unclear. Uric acid is associated with inflammation, but it also acts as a powerful endogenous antioxidant (AMES et al., 1981). This has led some to contend that increased uric acid could be protective by blocking oxidative stress. However, this theory needs to be investigated.

Increased levels of triglycerides and reduced HDL concentrations are key characteristics of dyslipidemia in diabetes (SYVÄNNE and TASKINEN, 1999). Besides, lower cholesterol and higher triglyceride levels were reported in a study when iron was associated with diabetes (SILVA et al., 2011). Here, in our study, we observed changes in the levels of these lipid metabolites, probably due to the effects of reduced insulin secretion and CAPE.

It is concluded that the measurement of biochemical parameters, Fe metabolites and rheumatologic markers may help to explain the mechanism of the therapeutic effects of CAPE. In the present study, CAPE treatment significantly reduced the levels of ASO in the CAPE-treated diabetic group. In this regard CAPE treatment (LIU et al., 2013; GUREL et al., 2004; WEI et al., 2004) might also play a potential therapeutic role in rheumatic diseases. Iron is a first-line prooxidant and it contributes to the regulation of the clinical appearances of numerous systemic diseases, including diabetes. Iron regulation of cell oxidative stress may explain, at least in part, its close association with abnormalities in insulin sensitivity (FERNÁNDEZ-REAL et al., 2002). Consequently, further studies must be conducted in order to explore the biochemical mechanisms of the reducing effect of CAPE on the serum values of Fe and rheumatologic markers, and improve the ability to predict and prevent metabolic problems.

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SAŽETAK

Dijabetologija i reumatologija imaju mnoge sličnosti, uključujući biokemijske procese. Oboljeli od dijabetesa pate od teških stanja mišićno-koštanog sustava. U ovom radu istražena je povezanost između liječenja fenetil esterom kavene kiseline i standardnih pokazatelja koji se kontroliraju pri dijabetičnim i reumatoidnim bolestima. Kod 22 Wistar-Albino štakorice mjereni su: serumski anti-streptolizin-O (ASO), C-reaktivni protein (CRP), titar reumatoidnog faktora (RF), zatim razina glukoze (GLU), kolesterola (CHOL), triglicerida (TG), lipoproteina visoke gustoće (HDL), lipoproteina vrlo niske gustoće (VLDL), alkalne fosfataze (ALP), gama-glutamil transferaze (GGT), natrija (Na), kalija (K), klorida (Cl), kalcija (Ca), fosfora (P), mokraćne kiseline (UA), željeza (Fe), kapaciteta vezanja željeza (IBC), ukupnog kapaciteta vezanja željeza (TIBC) i superoksid dismutaze (SOD). Životinje su bile podijeljene u tri skupine: 1. štakorice bez dijabetesa (kontrolna skupina), 2. neliječene štakorice s dijabetesom izazvanim streptozotocinom (STZ) i 3. štakorice sa streptozotocin (STZ) - izazvanim dijabetesom liječenim fenetil esterom kavene kiseline. Razine GLU bile su povećane u skupini 2. ASO vrijednosti bile su snižene u skupini 3. Razine TG i VLDL bile su povišene u skupini 3 u usporedbi s razinama u skupini 1. Više razine UA utvrđene su u skupini 3 u usporedbi sa skupinom 2. Razine Fe i TIBC bile su snižene u skupini 3. Rezultati pokazuju reducirajuće učinke fenetil estera kavene kiseline na razinu dijabetičnih i reumatoloških pokazatelja u serumu štakorica sa šećernom bolešću izazvanom streptozotocinom.

Ključne riječi: fenetil ester kavene kiseline, dijabetes, željezo, štakor, reumatološki pokazatelji