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Effects of Isoflavones on Paraoxonase and Adiponectin in Continuos Ambulatory Peritoneal Dialysis Patients

Sürekli Ambulatuar Periton Diyalizi Hastalarında Isoflavonların Paraoksonaz ve Adiponektin Üzerine Etkileri

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ABSTRACT Objective: The level of oxidative stress may increase improperly in chronic pathological conditions such as atherosclerosis, hypertension and uremia. Increased production of reactive oxygen radical species and/or failure of antioxidant systems contribute to the pathogenesis of chronic renal failure. The aim of this study was to investigate the effects of isoflavone, which has antioxidant properties, on oxidative-antioxidative system in patients with chronic renal failure who underwent continuous ambulatory peritoneal dialysis (CAPD). **Material and Methods:** Thirty patients who underwent CAPD were included in the study. Three patients were excluded from the study, two patients due to gastrointestinal complaints and one patient due to renal transplantation. The remaining 27 patients received 40 mg oral soy isoflavones (Isoflavin® tablets, Micro-Gen) twice daily for 10 weeks. The levels of total cholesterol, triglyceride, LDL-cholesterol, HDL-cholesterol, hs-CRP, oxidized LDL, malondialdehyde, adiponectin, paraoxonase and arylesterase were measured and analyzed statistically before and after isoflavone treatment. **Results:** There was a statistically significant decrease in serum total cholesterol, LDL-cholesterol and triglyceride levels after treatment ($p<0.001$, $p=0.005$, $p<0.001$, respectively). There was a statistically significant decrease in hs-CRP levels, which is one of the markers of inflammation, and oxidized LDL and malondialdehyde levels, which are oxidative stress markers, compared to pretreatment levels ($p<0.001$, $p<0.001$, $p=0.04$, respectively). The levels of adiponectin, paraoxonase and arylesterase, which have antioxidative properties, increased significantly after treatment compared to pre-treatment levels ($p=0.002$, $p=0.03$, $p<0.001$, respectively). **Conclusion:** The use of soy isoflavones, which have antilipogenic, antihypertensive and vascular health-enhancing properties, may provide beneficial effects on inflammatory and atherogenetic processes by obtaining positive effects on antioxidative system in patients with chronic renal failure.

Keywords: Oxidative stress; inflammation; peritoneal dialysis; isoflavone; adiponectin; paraoxonase

ÖZET Amaç: Oksidatif stres; ateroskleroz, hipertansiyon ve üremi gibi kronik patolojik durumlarda uygunsuz şekilde artabilmektedir. Kronik böbrek yetmezliği patogenezine reaktif oksijen radikal yapımının artışı ve/veya antioksidan sistemlerin yetersizliği katkıda bulunmaktadır. Bu çalışmada ayaktan periton diyalizi uygulayan kronik böbrek yetmezliği olan hastalarda antioksidan özelliği olan izoflavonun oksidatif- antioksidatif sistem üzerine olan etkilerinin incelenmesi amaçlanmıştır. **Gereç ve Yöntemler:** Çalışmaya 30 adet periton diyalizi uygulayan hasta dahil edildi. İki hasta gastrointestinal yakınma, bir hasta ise renal transplantasyon uygulanması nedeniyle çalışmadan çıkarıldı. Kalan 27 hastaya günde iki kez oral yolla 40 mg soya izoflavonları (Isoflavin® tablet, Mikro-Gen) 10 hafta süresince verildi. İzoflavon tedavi öncesi ve sonrası total kolesterol, trigliserid, LDL kolesterol, HDL kolesterol, hs-CRP, okside LDL, malondialdehid, adiponektin, paraoksonaz ve arilesteraz değerleri ölçülerek istatistiksel analizleri yapıldı. **Bulgular:** Tedavisi sonrasında serum total kolesterol, LDL kolesterol ve trigliserid düzeylerinde tedavi öncesine göre istatistiksel olarak anlamlı azalma olduğu tespit edildi (sırasıyla; $p<0,001$, $p=0,005$, $p<0,001$). İnflamasyon belirteçlerinden biri olan hs-CRP ve oksidatif stres belirteçleri olan okside LDL ve malondialdehid düzeylerinde de tedavi öncesine göre istatistiksel olarak anlamlı azalmalar olduğu (sırasıyla $p<0,001$, $p<0,001$, $p=0,04$) saptandı. Antioksidatif özellikleri olan adiponektin, paraoksonaz, arilesteraz düzeyleri ise tedavi sonrasında tedavi öncesine göre istatistiksel olarak anlamlı (sırasıyla; $p=0,002$, $p=0,03$, $p<0,001$) yüksek olarak bulundu. **Sonuç:** Antilipojenik, antihipertansif ve vasküler sağlığı geliştirici özellikleri bulunan soya izoflavonlarının kronik böbrek yetmezlikli hastalarda kullanımı ile antioksidatif sistem üzerine olumlu etkiler elde edilerek inflamatuar, aterogenetik süreç üzerine faydalı etkiler sağlanabilir.

Anahtar Kelimeler: Oksidatif stres; inflamasyon; periton diyalizi; izoflavon; adiponektin; paraoksonaz

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Chronic renal failure (CRF) is characterized by progressive and irreversible loss of nephrons due to various diseases. Oxidative stress markers have been increased in patients with chronic renal failure due to the deterioration of the balance between oxidative and antioxidative systems.[1] Oxidative stress (OS) is caused by the imbalance between the formation of free radicals and the antioxidant defense mechanism. The increase in the production of oxygen radicals along with many pathological mechanisms contribute to the pathogenesis of CRF.[2] Renal replacement therapy may be useful in ameliorating some biochemical changes in end-stage renal disease. However, partially treatable uremia, fluctuations in extracellular fluid volume, and exposure to biocompatible dialysis devices can lead to increased synthesis and release of proinflammatory cytokines, elevated levels of oxidative stress, and immune system disorders.[3]

The high incidence of cardiovascular morbidity and mortality in dialysis patients has not been adequately explained by classical cardiac risk factors such as diabetes mellitus, advanced age and hypertension. Therefore, it is possible that some other etiologies such as oxidative stress, endothelial dysfunction and hyperhomocysteinemia may contribute to the harmful effects of these conditions.[4]

It has been demonstrated that soy isoflavones from the phytoestrogen family are able to remove superoxide anions and lipid peroxide radicals by their potential antioxidant action through their conjugated ring structures and hydroxyl groups, and to stabilize oxidizing agents by forming hydrogenation or complex structures in events related to free radicals. Isoflavones exhibit hypolipidemic, antioxidant, antiproliferative, anticancerogenic and antimicrobial properties as well as estrogenic and antiestrogenic activities.[5-7] In this respect, it is thought that the use of isoflavones may have a protective effect on hypertension and hyperlipidemia in patients undergoing peritoneal dialysis and may reduce cardiovascular causes, the most important cause of death in this group.

In this study, we aimed to investigate the effects of isoflavone treatment on paraoxonase (PON1), arylesterase (ARE) and adiponectin, which have antioxidant properties, and on oxidized LDL (ox-LDL) and malondialdehyde (MDA), which are oxidative stress markers.

MATERIAL AND METHODS

Thirty patients who were followed-up in Peritoneal Dialysis Unit of Fırat University Hospital were included in the study. All patients were informed and provided written informed consent prior to the study. The study was endorsed by the hospital's Clinical Research Ethics Committee, according to the ethical guidelines dictated in the Declaration of Helsinki (number: 9, March 2007, Elazığ, Turkey). Patients with infection, malignant diseases, and signs of severe hyperparathyroidism and receiving anti-inflammatory and antioxidant treatments were not included in the study. The study was completed with 27 patients because two of the patients were excluded due to gastrointestinal complaints and one due to renal transplantation. Patients underwent standard CAPD with DIANEAL peritoneal dialysis solution (Eczacıbaşı Baxter, İstanbul) at various concentrations (1.36%, 2.27% and 3.86% glucose solutions) with 4 exchanges per day.

The patients received 40 mg oral soy isoflavones (Isoflavin® tablets, Micro-Gen) twice daily for 10 weeks. Blood samples were collected from all patients for biochemical and immunological analyzes before and after isoflavone treatment. Blood samples of 2 ml and 4 ml were collected into plain tubes and sent to the immunology laboratory for hs-CRP analysis and to the central laboratory for biochemical analysis, respectively. In addition, 2 ml of 4 ml blood sample was transferred into an EDTA tube and the remaining 2 ml into a plain tube and centrifuged at 3500 rpm for 10 minutes. The obtained serum and plasma samples were transferred into Eppendorf tubes and stored at -20° C to study the levels of ox-LDL, PON1, ARE and adiponectin.

LABORATORY ANALYSIS

Blood levels of total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride levels were determined using Olympus AU 600 autoanalyzer. Hs-CRP levels were measured nephelometrically in the immunology laboratory with Dade Behring kits.

Oxidized-LDL levels were measured by enzyme-linked immunosorbent assay (ELISA) using a commercial kit (Immunodiagnostic AG, Bensheim, Germany).

The determination of MDA, the final product of lipid peroxidation, was performed spectrophotometrically by the method determined by Satoh and Yagi.[8,9] Determination of lipid peroxidation was carried out on the basis of spectrophotometric measurement at 532 nm of pink colored complex formed by 1-hour incubation of plasma samples with 0.8% thiobarbituric acid (TBA) in a boiling water bath under a pH of 3.5 and aerobic conditions. A standard 1,1,3,3-tetraethoxypropane (TEP) was used for measurements. The absorbance of the samples was calculated according to a standard solution of 4.4 nmol. The results were expressed in nmol/ml.

Serum adiponectin levels were determined by ELISA method using a human adiponectin ELISA kit (Biovendor Laboratorní medicína a.s. CTPark Modrice, Evropská 873 664 42 Modrice, Czech Republic) in accordance with the content of the kit in EL X800 ELISA reader. In the study, a "competitive" ELISA technique was used. The standard solutions were diluted 1: 3 and the control and plasma samples were diluted 1:30 and assayed according to the content of the kit. Spectrophotometric reading was performed with a reader at a wavelength of 450 nm. The results were calculated by multiplying by the dilution factor.

Serum PON1 activity was obtained by spectrophotometric analysis of 4-nitrophenol formed as a result of enzymatic hydrolysis of paraoxone (O, O-diethyl- O-p- nitrophenyl phosphate; Sigma Co., London, UK) used as substrate. One unit of PON-1 activity was defined as 1 nmol 4-nitrophenol/L serum/min.[10]

Serum ARE activity was determined by measuring the color product of phenol produced by enzymatic hydrolysis of phenylacetate (Sigma) used as substrate, by Techcomp 8500 II UV/VIS spectrophotometer, and 1 unit of ARE activity was defined as 1 mmol of 4 phenol/L serum/min.

STATISTICAL ANALYSIS

Data obtained in this study were presented as mean ± standard deviation. SPSS 21.0 for Windows software was used to evaluate the data obtained in the groups. The Wilcoxon test, which is one of the nonparametric tests, was used to evaluate the parameters obtained before and after treatment in the groups. A p value of <0.05 was considered significant.

RESULTS

Patients were divided into two groups as pre- and post-treatment groups. Of 27 patients who underwent peritoneal dialysis, 19 were male and 8 were female. The mean duration of dialysis was 43.4±33.1 months and the mean age was 45.7±12.4 years.

Post-treatment levels of TG, total cholesterol, LDL cholesterol, hs-CRP were found to be statistically lower than pre-treatment levels (p=0.005 for LDL cholesterol, $p<0.001$ for others). Post-treatment levels of HDL cholesterol were found to be statistically higher than baseline levels before treatment ($p<0.001$) (Table 1).

Post-treatment levels of MDA and ox-LDL were found to be significantly lower than pre-treatment levels (p=0.04 and $p<0.001$, respectively) (Table 2).

Post-treatment levels of adiponectin, PON1 and ARE were significantly higher than pre-treatment levels (p=0.002, p=0.03 and $p<0.001$, respectively) (Table 3).

TABLE 1: Biochemical parameters of the patients before and after treatment.

	Before treatment	After treatment	p
Triglycerides (mg/dl)	297.0±184.1	197.2±114.3	<0.001
LDL cholesterol (mg/dl)	149.3±47.3	133.8±38.6	0.005
HDL cholesterol (mg/dl)	35.4±7.7	40.2±6.7	<0.001
Total cholesterol (mg/dl)	233.1±61.4	206.5±59.6	<0.001
hs-CRP (mg/dl)	6.7±2.8	4.7±3.0	<0.001

TABLE 2: Biochemical parameters of the patients before and after treatment.

	Before treatment	After treatment	p
Oxidized-LDL (ng/ml)	107.2±58.3	56.9±22.3	<0.001
MDA (nmol/ml)	5.68±1.68	4.78±0.84	0.04

TABLE 3: Antioxidative stress markers before and after treatment.

	Before treatment	After treatment	p
Adiponectin (µg/ml)	25.6±18.8	35.7±27.7	0.002
PON1 (U/l)	565.8±275.8	650.6±335.8	0.03
Arylesterase (U/ml)	34.3±15.5	65.9±14.4	< 0.001

DISCUSSION

Cardiovascular complications are the major causes of death in patients treated for chronic renal failure. Hyperlipidemia is an important factor in the pathogenesis of coronary artery disease (CAD). Hypertension and hyperlipidemia are the most common noninfectious complications in patients undergoing CAPD. A chronic increase in glucose absorption and protein loss from peritoneum and predisposition to obesity are important causes of hyperlipidemia. Lipid abnormalities contribute to high mortality rates in these patients.[11] Soy proteins have been found to have effects that reduce hypertension, reduce serum cholesterol levels, improve vascular health, maintain bone mineral density, and reduce menopausal symptoms.[12-14] There are few clinical studies on isoflavones in patients receiving renal replacement therapy. It has been suggested that the use of soy protein instead of animal proteins in individuals with chronic glomerular disease reduces proteinuria and protects renal functions.[15] It has been shown that the use of soy isoflavones in patients with CRF in the pre-dialysis period provides a significant decrease in serum creatinine, phosphorus and CRP levels and proteinuria.[16] Lipid-lowering effects of soy protein have been shown in hyperlipidemic hemodialysis patients.[17] Studies have shown that soy protein causes a significant decrease in serum levels of total cholesterol, LDL cholesterol and TG, and an increase in HDL cholesterol levels, albeit not statistically significant. The decrease in serum levels of total cholesterol and LDL cholesterol was found to be associated with baseline levels. The effects of soy proteins on serum lipoprotein levels are controversial. Possible mechanisms in animal and human studies include an increase in bile acid excretion, a change in the amount of cholesterol absorption, an increase in serum thyroxine levels, a decrease in cholesterol metabolism and a change in the glucagon/insulin ratio.[18] Soy isoflavones are structurally similar to estrogens and may bind to estrogen receptors, reducing serum cholesterol levels through a similar mechanism.[19] In our study, it was found that treatment with soy protein had positive effects on lipid profile in CAPD patients.

The increase in CRP levels determines the presence and severity of inflammation. It is thought that hs-CRP levels may reflect the fragility of atheromatous lesion and the tendency of plaque to rupture.[20] Soy isoflavones have been found to significantly reduce CRP levels in postmenopausal women with high CRP levels.[21] In CRF, hs-CRP is a strong predictor of both cardiovascular and other causes of mortality and is closely associated with oxidative stress, vascular calcification and endothelial dysfunction.[22] Fanti et al. showed that soy isoflavones reduce high serum levels of CRP, which is a sign of systemic inflammation in patients undergoing hemodialysis (HD).[23] In our study, there was a statistically significant decrease in hs-CRP levels after isoflavone treatment compared to pre-treatment levels ($p<0.001$). This data suggests that soy proteins, which are rich in isoflavones, may have potential benefits on inflammation and nutritional status in dialysis patients.

Chronic renal failure is a clinical condition characterized by an oxidative stress of unknown causal relationship. Plasma antioxidant activity decreases in renal failure.[24] The increase in oxidative stress was determined by increased MDA levels in red blood cell membranes. Malondialdehyde levels correlate with the degree of lipid peroxidation. In the literature, there are studies showing high levels of MDA in patients undergoing HD or CAPD.[25,26] Ozden et al. showed that plasma levels of MDA after the hemodialysis session and in CAPD patients were significantly higher than those before the hemodialysis session and in the control group.[27] Samouilidou et al. showed that plasma levels of MDA were higher be-

fore and after the HD session and in patients who underwent CAPD compared to the control group.[28] Triolo et al. found a significant decrease in MDA levels after one month of use of vitamin E-modified membrane.[29] Eiselt et al. in their study comparing various dialysis membranes, reported that MDA levels increased after a dialysis session using nonmodified membranes and that this increase was prevented by the use of vitamin E modified membrane, and by vitamin C infusion during dialysis session.[25] In our study, the use of soy protein such as Vitamin E and C, which has antioxidant properties, significantly decreased MDA levels compared to pretreatment levels (p=0.04).

During renal failure and dialysis sessions, losses in the amounts of Se, vitamin E and C contribute to oxidative damage.[30] Increased OS leads to lipid peroxidation and oxidative changes of lipoproteins. Oxidative modification of LDL cholesterol is associated with atherogenesis. Preclinical and clinical studies have shown that isoflavones have effects that inhibit oxidation of LDL cholesterol and lower lipid levels. Genistein, a soy protein derivative, effectively protects vascular cells from damage due to oxidized lipoproteins.[31] Oxidized LDL is deposited at an increased rate in the arterial wall by macrophages through scavenger receptors that cause the development of atherosclerotic lesions and the formation of foam cells.[32] On the other hand, antioxidants such as SOD, catalase, glutathione peroxidase and vitamin E, which are known to be protective against OS, have been shown to protect LDL cholesterol from oxidation and reduce the development of atherosclerotic lesions.[33] De Whalley et al. reported that dietary flavone and flavonol derivatives significantly inhibit macrophage-mediated LDL cholesterol oxidation.[34] In our study, the use of isoflavone resulted in a statistically significant decrease in ox-LDL levels (p<0.001).

Paraoxonase plays an important role in protection of HDL cholesterol against oxidation. PON1 protects serum lipoproteins against oxidation by free radical products.[35] PON1 activity decreases in CRF.[36] Göçmen et al. found increased levels of ox-LDL cholesterol and decreased levels of PON1 in patients undergoing CAPD.[37] Juretic et al. found that there was a decrease in PON1 /ARE activity as a result of long-term HD treatment and that this may be associated with increased premature atherosclerosis.[10] It was thought that decreased PON1 activity in uremic patients caused a decrease in the antioxidant capacity of HDL cholesterol and that PON1 may be associated with cardiovascular diseases in dialysis patients. It is known that PON1 activity has an important protective role against atherosclerosis by protecting the serum lipoproteins, which play an important role in atherosclerosis, against oxidation.[38] PON1 can use potent oxidant structures such as lipid peroxides and H_2O_2 as substrates in enzymatic reactions. H_2O_2 is a major type of reactive oxygen compounds formed in the arterial wall endothelium, especially during atherogenesis, and can lead to the formation of more potent oxidative products by oxidizing LDL cholesterol. Therefore, the ability of PON1 to hydrolyze H_2O_2 plays an important role, especially in the elimination of potent oxidant structures.[39] It has been shown that soy isoflavones remove superoxide oxidation anions and lipid peroxide radicals as potential antioxidants through their conjugated ring structures and hydroxyl groups and can stabilize oxidizing agents by forming hydrogenation or complex structures in events related to free radicals.[40] In our study, it was found that the levels of PON1, which has antioxidant properties, after the treatment with soy protein increased significantly (p=0.03) compared to the pre-treatment levels. These findings support that isoflavone treatment may have positive effects on PON1/ARE activity, which is known to be lower in CAPD patients.

Adiponectin, an adipose tissue-specific protein, has anti-atherogenic effects and inhibitory effects on insulin resistance. Clinical studies show that obesity, insulin resistance, coronary artery disease and dyslipidemia are associated with low adiponectin levels.[41] Plasma adiponectin levels are an inverse predictor of cardiovascular events in patients with CRF.[42] In a study of 227 HD patients, an investigation of the relationship between adiponectin levels and surveillance rate and cardiovascular events showed that elevated adiponectin levels were associated with long survival, and 70% of patients with high adiponectin levels did not experience a cardiovascu-

lar event.[43] Therefore, the inadequacy of adiponectin, which has been shown to have protective effects on atherosclerosis, emerges as a problem that needs to be solved. A study investigated the effects of a diet containing soy protein on body fat composition and plasma levels of glucose, lipid and adiponectin in obese mice. Plasma levels of cholesterol, TG, free fatty acids and glucose were decreased and adiponectin mRNA levels in adipose tissue and adiponectin levels in plasma were increased with the use of a diet containing soy protein.[44] A study concluded that the use of soy protein diet in Wistar rats increases plasma levels of adiponectin and soy protein can regulate the production of adiponectin.[45] In our study, it was determined that soy protein diet at a dose of 80 mg per day for 10 weeks significantly increased adiponectin levels.

CONCLUSION

The imbalance between oxidative and antioxidative systems in patients with CRF contributes to inflammation and cardiovascular morbidity and mortality. The use of soy isoflavones, which have antilipogenic, antihypertensive and vascular health-enhancing properties may provide beneficial effects on inflammatory and atherogenetic processes by causing positive effects on antioxidative system in patients with CRF.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Elif Kılıç Kan, Bilge Aygen;* ***Design:*** *Elif Kılıç Kan;* ***Control/Supervision:*** *Bilge Aygen;* ***Data Collection and/or Processing:*** *Elif Kılıç Kan;* ***Analysis and/or Interpretation:*** *Elif Kılıç Kan, Bilge Aygen;* ***Literature Review:*** *Elif Kılıç Kan;* ***Writing the Article:*** *Elif Kılıç Kan;* ***Critical Review:*** *Elif Kılıç Kan, Bilge Aygen, Nevin İlhan;* ***References and Fundings:*** *Nevin İlhan.*

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