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Review

# Review of Isoflavones and Their Potential Clinical Impacts on Cardiovascular and Bone Metabolism Markers in Peritoneal Dialysis Patients

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**ABSTRACT:** Cardiovascular disease is the most important cause of mortality in patients with chronic kidney disease, including patients undergoing peritoneal dialysis. Oxidative stress, systemic and vascular inflammation, and lipid abnormalities are important causes of cardiovascular disease in these patients. Bone disorders are also a common complication in dialysis patients and can lead to bone fractures, decreased quality of life, vascular calcification, cardiovascular disease, and increased mortality. Studies in non-uremic populations have shown that soy isoflavones have beneficial effects on oxidative stress, inflammation, lipid abnormalities, and markers of bone metabolism; however, very few studies in this field have been conducted with peritoneal dialysis patients. This paper reviews the key data regarding the effects of soy isoflavones on cardiovascular disease and bone markers and discusses the role of this nutraceutical in preventing and managing the complications of peritoneal dialysis.

**Keywords:** cardiovascular diseases, chronic kidney disease, dialysis, isoflavones, mineral and bone disorder

## INTRODUCTION

Kidney failure is a common medical problem that is on the rise worldwide due to the aging population. Renal replacement therapy, including peritoneal dialysis (PD) and hemodialysis (HD), is able to increase the life expectancy of patients, although it remains far lower than that of the general population. According to previous investigations, 45% of HD patients and 65% of PD patients survive for at least three years after starting treatment (Tse et al., 2003). One of the reasons for the higher survival rates in PD patients compared to HD patients is that patients who receive PD as their initial treatment modality are generally younger than those who receive HD. These therapies extended the life span of patients with end stage renal disease, although they expose patients to complications (Tse et al., 2003). PD is a well-established and cost-effective form of renal replacement therapy that was principally introduced in the 1960s as a viable alternative treatment to HD (Gokal and Mallick, 1999). Compared to HD, PD is a home-based treatment with better outcomes and a more favorable patient experience; however, it is associated with a collection of complications unique to the modality (Briggs et al., 2019). The most frequent long-term dialysis complications include cardiovascular disease, bone disorders, and disorders related to inflammation and oxidative stress (Gejyo et al., 1986; Tse et al., 2003). Patients undergoing dialysis are more likely to experience these problems compared with the general population because, in addition to the traditional risk factors, they also have uremia-related risk factors (Longenecker et al., 2002; McCullough, 2007).

Isoflavones, also known as isoflavonoids, are a group of flavonoids that have structural similarities to the hormone estrogen (Manach et al., 2004). The isoflavones present in food include genistein, daidzein, glycitein, formononetin, and biochanin A (Zaheer and Humayoun Akhtar, 2017). Isoflavones can bind to estrogen receptors in the body and exhibit hormone-like properties, thus placing them in the group of phytoestrogens (Manach et al., 2004). Isoflavones are found almost exclusively in leguminous plants, and soybeans and soy-derived products contain significant quantities of isoflavones (Manach et al., 2004). The dietary intake of isoflavones varies greatly, and people living in Asian countries seem to have the highest dietary intakes of isoflavones. Estimates of intake

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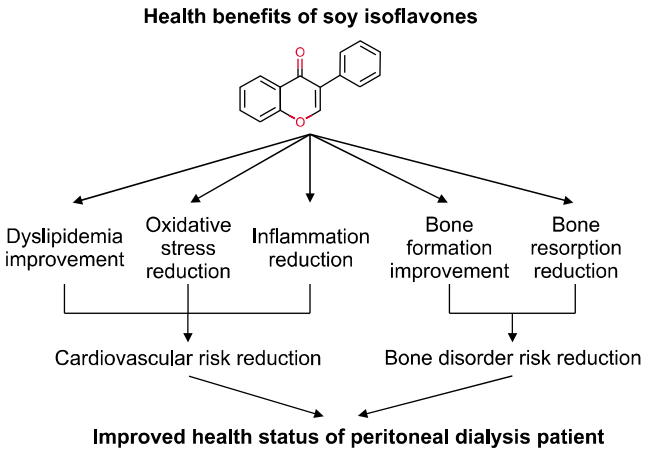


**Fig. 1.** Health benefits of soy isoflavones.

in these subjects range from 15 to 50 mg/d (Peterson et al., 2012), which is significantly lower than the doses currently used in clinical studies.

The beneficial effects of isoflavones and soy foods have been demonstrated and include reducing the risk factors of cardiovascular disease, including decreasing high blood pressure (Sathyapalan et al., 2018), high serum concentrations of total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides (Jenkins et al., 2002; Azadbakht et al., 2008), and increasing low serum concentrations of high-density lipoprotein cholesterol (HDL-C) (Teixeira et al., 2004). The improvement of bone markers following the consumption of isoflavones has also been reported (Uesugi et al., 2002; Harkness et al., 2004). The health benefits of soy isoflavones are summarized in Fig. 1.

## ISOFLAVONES AND CARDIOVASCULAR MARKERS IN PD PATIENTS

The predominant cause of death in patients with chronic kidney disease, including PD patients, is cardiovascular disease (CVD). The prevalence of CVD in PD patients is approximately 3 to 45 times that in the general population, and the mortality rate from CVD in these patients is reported to be approximately 50% (Liu and Chertow, 2015). Lipid abnormalities as well as vascular and systemic inflammation are among the most important cardiovascular risk factors in these patients. Low serum levels of HDL-C and high serum levels of LDL-C, triglycerides, and total cholesterol are some of the lipid abnormalities in these patients (Pandya et al., 2015; Prabhu et al., 2013). High serum lipoprotein(a) [Lp(a)] concentrations are also common in PD patients; in approximately half of these patients, the serum Lp(a) concentration is higher than the normal range (Tabibi et al., 2010; Yari et al., 2020a). There is no established consensus on the best strategy for lipid abnormality management in PD patients, especially high serum Lp(a) concentrations (Santos et al., 2019). High serum Lp(a) concentrations in PD patients are due to increased hepatic synthesis of Lp(a), which occurs as a result of the loss of amino acids and proteins from the peritoneal cavity. Various studies have shown that increased protein loss from the body increases hepatic synthesis of Lp(a) via unknown mechanisms (Shoji et al., 1992; Heimbürger et al., 1996). An inverse correlation was also observed between Lp(a) and serum albumin (Yang et al., 1995). High serum Lp(a) concentration is a well-known risk factor for CVD (Dahlén and Stenlund, 1997; Djurovic and Berg, 1997; Bucci et al., 2016; Santos et al., 2019), stroke, and peripheral vascular disease (Bucci et al., 2016). There are two main mechanisms for this phenomenon. Firstly, each Lp(a) molecule consists of an LDL molecule and an apoprotein(a) molecule, which are linked together by a disulfide bond. The Lp(a) lipoprotein enters the subendothelial region of the arteries and is subsequently trapped and oxidized in the glycoprotein matrix in this region. These oxidized Lp(a) lipoproteins are then removed by macrophages in the subendothelial region of the arteries by scavenger receptors, which then turn into foam cells, resulting in the formation of atheroma and atherosclerosis (Marcovina and Koschinsky, 1998). Secondly, because apoprotein(a) forms part of the Lp(a) structure and is structurally very similar to plasminogen, it can bind to fibrin in blood clots instead of plasminogen. This prevents the binding of plasminogen to fibrin and subsequently prevents the conversion of plasminogen to plasmin by tissue plasminogen activators. As a result, plasmin is not able to break down blood clots. Therefore, Lp(a) may play a role in thrombosis (Marcovina and Koschinsky, 1998; Santos et al., 2019).

At present, among the available drugs, nicotinic acid in high doses (2～4 g/d) is the most effective drug to reduce the concentration of Lp(a) (Saeedi and Frohlich, 2016). However, nicotinic acid is associated with several side effects, including flushing, rash, pruritus, nausea, vomiting, diarrhea, abdominal pain, hypotension, intolerance to glucose, hyperuricemia, increased blood transaminases and alkaline phosphatases, and acute liver failure (Malloy and Kane, 2001). Therefore, due to the fact that gastrointestinal complications and pruritus are common in dialysis patients (Bargman and Skorecki, 2015), the use of nicotinic acid in these patients, especially in high doses, can aggravate the above complications. Therefore, nicotinic acid cannot be used in high doses in dialysis patients.

It seems that soy isoflavones are effective in reducing serum Lp(a). Although studies in this area are very limited, a recent study by Yari et al. (2020a) revealed that supplementation with soy isoflavones over 8 weeks could reduce serum Lp(a) concentrations in PD patients by

10%. This reduction was significant compared to the placebo group. In agreement with this study, Tabibi et al. (2010), in a study of PD patients, showed that daily consumption of 28 g of raw textured soy flour, containing approximately 61 mg of isoflavones, could reduce serum Lp(a). Bloedon et al. (2008) also showed that daily intake of 640 mg of lignin (which also exerts phytoestrogenic effects) in the form of bread containing ground flaxseed for 10 weeks reduced the serum Lp(a) concentration of hypercholesterolemic patients by 14%. However, consumption of isoflavones does not appear to have an effect on serum Lp(a) concentrations in non-renal patients (Dent et al., 2001; Jenkins et al., 2002; Simental-Mendía et al., 2018), probably because the serum Lp(a) level in these subjects is already in the normal range. The effects of soy isoflavones in reducing serum Lp(a) concentration in PD patients are partly attributed to the phytoestrogenic activity of soy isoflavones. Various studies have shown that estrogen administration can decrease serum Lp(a) by 20% to 30% by reducing Lp(a) synthesis (Espeland et al., 1998; Kosmas et al., 2019) but had no effect on Lp(a) catabolism (Su et al., 1998). The mechanism by which soy isoflavones affect serum Lp(a) concentration may be due to the effects of phytoestrogens on the hepatic synthesis of Lp(a), similar to estrogens (Kosmas et al., 2019). This phytoestrogenic activity can also increase the HDL concentration. In confirmation of this, various studies have shown that estrogen administration can increase the expression of the apoprotein AI gene (Kashyap, 1998) and thus increase HDL synthesis and its concentration in the blood (Kashyap, 1998; Mikkola and Clarkson, 2002).

Oxidative stress is common in patients undergoing PD (Descamps-Latscha et al., 2005; Mekki et al., 2010) and causes atherosclerosis and peritoneal fibrosis, leading to failure in peritoneal ultrafiltration (Noh et al., 2006; Zwolinska et al., 2009; Mekki et al., 2010). The causes of oxidative stress in PD patients include the fact that, in these patients, excess oxidant compounds accumulate in the body due to kidney failure (Canaud et al., 1999). In addition, in these patients, water-soluble antioxidant compounds, including vitamin C, are excreted through PD (Canaud et al., 1999; Locatelli et al., 2003). Furthermore, in these patients, the bioincompatibility of PD solutions (due to high glucose concentrations, thepresence of glucose breakdown compounds, acidic pH, and high osmolality) plays an important role in stimulating peritoneal mesothelial cells, causing increased free radical production and oxidative stress (Noh et al., 2006; Mekki et al., 2010). In addition, the presence of underlying disease, such as diabetes, in PD patients can contribute to the exacerbation of oxidative stress (Canaud et al., 1999).

Previous studies have shown that isoflavones reduce oxidative stress markers, such as oxidized LDL (Siefker and DiSilvestro, 2006) and malondialdehyde (MDA) (Pusparini et al., 2013; Zhang et al., 2020). However, other studies have failed to demonstrate the effect of isoflavones on oxidative stress markers, including oxidized LDL (Imani et al., 2009; Reverri et al., 2015), 8-iso-prostaglandin F2α (Siefker and DiSilvestro, 2006), lipid peroxides (Cupisti et al., 2007; Giolo et al., 2018), total antioxidant capacity (Giolo et al., 2018), and superoxide dismutase activity (Giolo et al., 2018). Similarly, the daily consumption of 100 mg of soy isoflavones for 8 weeks did not cause a significant change in serum MDA concentration as a marker of oxidative stress in PD patients (Yari et al., 2020c).

Inflammation is a common complication in patients with chronic renal failure, including PD patients (Lai and Leung, 2010), and various studies have shown that inflammation occurs in 12% to 65% of PD patients (Cho et al., 2014). Therefore, the concentration of serum inflammatory factors such as C-reactive protein is high in these patients (Cho et al., 2014). Inflammation is high in PD patients due to the decreased excretion of inflammatory cytokines, bioincompatibility of PD solutions, the consequent stimulation of peritoneal mesothelial cells, and the induction of inflammatory cytokine synthesis due to peritonitis and the accumulation of various compounds in the uremic state, including advanced glycation end compounds (Lai and Leung, 2010; Cho et al., 2014). The complications and consequences of inflammation in PD patients include atherosclerosis, fibrosis, and sclerosis of the peritoneum as well as energy-protein wasting following peritoneal ultrafiltration failure (Lai and Leung, 2010; Cho et al., 2014).

In addition to systemic inflammation, vascular inflammation is also apparent in these patients. Increased serum concentrations of intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and E-selectin are among the biomarkers of vascular inflammation in PD patients (Bonomini et al., 1998; Papagianni et al., 2004; Wang et al., 2005). Increased serum concentrations of these factors are directly associated with increased mortality from CVD (Blankenberg et al., 2001; Tedgui, 2005). The reduction of inflammatory biomarkers, both systemic and vascular, following the consumption of soy isoflavones has been demonstrated in several studies (Azadbakht et al., 2008; Sathyapalan et al., 2011; Yari et al., 2020c). Inflammatory cytokines bind to their receptors on vascular endothelial cell membranes, causing phosphorylation of the nuclear factor kappa-B (NF-κB) inhibitor. NF-κB then moves to the nucleus and, by binding to the VCAM-1 and ICAM-1 genes, induces their expression, thereby increasing the synthesis of VCAM-1 and ICAM-1 (Chen et al., 2005; Wang et al., 2011). Studies have shown that various polyphenols, including isoflavones, can reduce the expression of vascu-

**Table 1.** Summary of the main results of clinical trials into the effects of soy isoflavones on cardiovascular and bone metabolism markers in patients with kidney disease

| References | Group | Number (duration) | Intervention | Results |
|---|---|---|---|---|
| Cupisti et al., 2007 | Renal transplant patients | 25 (5 wk) | Dietary substitution of 25 g of animal proteins with soy proteins | - Significant improvement in flow mediated dilation<br>- Significant reduction in serum cholesterol and lipid peroxides |
| Imani et al., 2009 | Peritoneal dialysis patients | 40 (8 wk) | 28 g/d textured soy flour (containing 14 g of soy protein) | - Significant reduction in plasma coagulation factor IX activity<br>- No significant changes in ox-LDL, homocysteine, fibrinogen concentrations, and the activities of coagulation factors VII and X |
| Siefker and DiSilvestro, 2006 | Hemodialysis patients | 20 (4 wk) | 25 g of soy protein (52 mg of isoflavones) | - Significant reduction in oxidized low-density lipoprotein<br>- No significant changes in plasma concentrations of 8-iso-prostaglandin F2α, TNF-α, or CRP |
| Tabibi et al., 2010 | Peritoneal dialysis patients | 40 (8 wk) | 28 g/d textured soy flour (containing 14 g of soy protein) | - Significant reduction in serum Lp(a)<br>- No significant changes in serum triglyceride, total cholesterol, HDL-C, LDL-C, apo B100, or apoAI |
| Teixeira et al., 2004 | Patients with nephropathy | 14 (8 wk) | 0.5 g/kg/d isolated soy protein | - Significant reduction in urinary albumin excretion, total-to-HDL-cholesterol ratio, LDL-to-HDL cholesterol ratio |
| Yari et al., 2020a | Peritoneal dialysis patients | 40 (8 wk) | 100 mg soy isoflavones | - Significant reduction in serum N-telopeptide and receptor activator of nuclear factor kappa-B ligand<br>- No significant changes in bone resorption markers |
| Yari et al., 2020c | Peritoneal dialysis patients | 40 (8 wk) | 100 mg soy isoflavones | - Significant reduction in vascular cell adhesion molecule 1 and intercellular adhesion molecule 1<br>- No significant changes in E-selectin and hs-CRP |
| Yari et al., 2020b | Peritoneal dialysis patients | 40 (8 wk) | 100 mg soy isoflavones | - Significant reduction in serum Lp(a)<br>- Significant increase in serum HDL<br>- No significant changes in serum triglycerides, total cholesterol, and LDL-C |
| Movahedian et al., 2021 | Peritoneal dialysis patients | 38 (8 wk) | 100 mg soy isoflavones | - Significant reduction in serum glucose and pentosidine<br>- No significant changes in serum carboxymethyl lysine, fructosamine, and systolic and diastolic blood pressures |

LDL-C, low-density lipoprotein cholesterol; TNF-α, tumor necrosis factor alpha; CRP, C-reactive protein; Lp(a), high serum lipoprotein(a); HDL-C, high-density lipoprotein cholesterol.

lar inflammatory factor genes by suppressing NF-κB activity (Yahfoufi et al., 2018). Table 1 presents a summary of the main results of clinical trials into the effects of soy isoflavones on cardiovascular markers in patients with kidney disease (Yari et al., 2020c; Movahedian et al., 2021).

## ISOFLAVONES AND BONE DISORDERS IN PD PATIENTS

Bone disorders are some of the most common complications in dialysis patients (Heaf, 2015; Moe and Sprague, 2016). These complications can increase the risk of bone fractures, decrease quality of life, induce vascular calcification and CVD, and increase mortality (Cozzolino et al., 2014; Heaf, 2015; Bover et al., 2017). N-telopeptide, a marker of bone resorption (Nakashima et al., 2005), is released from bone as a result of osteoclast activity (Wheater et al., 2013). So far, only one study has been conducted to evaluate the effects of isoflavones on bone markers in PD patients; this study reported that the administration of 100 mg of soy isoflavones could reduce the serum N telopeptide concentration by up to 30% (Yari et al., 2020a).

Receptor activator of NF-κB ligand (RANKL) is another a bone resorption agent that acts by differentiating and activating osteoclasts (Kajarabille et al., 2013). RANKL is synthesized in various cells, including osteoblasts, and acts as a ligand for the RANK, which is located on the surface of osteoclasts. RANKL induces osteoclast differentiation and activation (Kajarabille et al., 2013) and also inhibits osteoclast apoptosis (Yu et al., 2015). In a study by Yari et al. (2020a), soy isoflavones significantly reduced RANKL levels during 8 weeks of intervention. Soy isoflavones suppress the RANKL gene and reduce its synthesis in osteoblasts (Yu et al., 2015). As a result, bone resorption and release of N-telopeptide from bone and its serum concentration are reduced. This action of isoflavones is accomplished by binding to estrogen receptors in the cytosol of osteoblasts (Chen and Anderson, 2002). Isoflavones, including genistein, can reduce the stimulatory effects of parathyroid hormone (PTH) on RANKL gene expression in osteoblasts (Chen and Wong, 2006), thereby reducing RANKL synthesis and PTH-induced bone resorption.

Osteoprotegerin is made by various cells, including osteoblasts and, by binding to RANKL, prevents its binding

to RANK, thereby preventing the activation of osteoclasts and, consequently, inhibiting bone resorption (Kajarabille et al., 2013). Therefore, the serum osteoprotegerin concentration is considered a marker for the inhibition of bone resorption. Two *in vitro* studies showed that soy isoflavones increase osteoprotegerin gene expression and increase its synthesis in osteoblasts (Chen and Wong, 2006; Yu et al., 2015).

The osteocalcin serum concentration is a marker of bone formation, and the serum concentration of bone alkaline phosphatase is a marker of bone formation and bone turnover. These two markers have been examined in PD patients in only one study, the results of which presented no significant changes in osteocalcin and bone alkaline phosphatase during 8 weeks of supplementation with 100 mg of isoflavones (Yari et al., 2020a). The lack of effect of soy isoflavones on bone formation markers may be due to the short duration of the intervention because it has been shown that changes in serum concentrations of bone formation markers occur later than changes in bone resorption markers (Taku et al., 2011). However, some studies in non-uremic postmenopausal women have shown that isoflavones have no effect on the serum concentrations of osteocalcin (Roudsari et al., 2005) and bone alkaline phosphatase (Kenny et al., 2009), while other studies have shown that isoflavones increase the serum concentrations of osteocalcin (Lee et al., 2017), bone alkaline phosphatase (Lee et al., 2017), and total alkaline phosphatase (Roudsari et al., 2005). Table 1 presents a summary of the main results of clinical trials into the effects of soy isoflavones on bone metabolism markers in patients with kidney disease.

## CONCLUSION

It can be concluded that, in general, soy isoflavones can play a role in preventing the complications of PD, including CVD and bone disorders. Therefore, considering the extensive complications for dialysis patients, supplementation with soy isoflavones is a reasonable approach to reduce cardiovascular complications and bone disorders in these patients. However, further randomized clinical trials with larger sample sizes and various doses of isoflavones are needed to confirm the adjuvant effects of soy isoflavones on reducing morbidity and mortality in dialysis patients.

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## AUTHOR DISCLOSURE STATEMENT

The author declares no conflict of interest.

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