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ORIGINAL RESEARCH

Recovery Of Bone And Muscle Mass In Patients With Chronic Kidney Disease And Iron Overload On Hemodialysis And Taking Combined Supplementation With Curcumin And Resveratrol

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Introduction: Malnutrition is common in haemodialysis patients and closely related to morbidity and mortality. We evaluated the effect of twelve weeks of supplementation with resveratrol and curcumin on recovery of bone and muscle mass and protein oxidation, lipid peroxidation on patients with chronic kidney disease and iron overload undergoing hemodialysis, we performed a randomized, double-blind, placebo-controlled trial.

Methods: We included a total of 40 patients, were randomly assigned to two groups, 20 to the group with antioxidant supplementation (Resveratrol + Curcumin) (Group A), treated with a daily oral dose of 500 mg of Resveratrol and 500 mg of Curcumin, and 20 to the control group treated with placebo (Group B).

Results: Significant differences were found in the body composition of the patients between both groups. There was a significant difference in Body Mass Index (BMI) values ($p = 0.002$), fat percentage ($p = 0.007$), muscle mass ($p = 0.01$) bone mass ($p = 0.01$), as well as in the score of the subjective global evaluation ($p = 0.03$). Also differences were found between the basal and final serum levels of Triglycerides (TG) ($p = 0.01$), VLDL ($p = 0.003$). A significant decrease in the levels of serum ferritin (2003.69 ± 518.73 vs 1795.65 ± 519.00 ng/mL; $p = 0.04$). Nor were significant differences observed between the baseline and the final Thiobarbituric Acid Reactive Substances (TBARS) values (70.45 ± 69.21 vs 50.19 ± 32.62, $p = 0.24$). The same results was obtained for carbonyl values (2.67 ± 0.75 vs 2.50 ± 0.85; $p = 0.50$).

Discussion: The present study is the first assay on patients with chronic kidney disease and iron overload that demonstrates the beneficial effects of combined supplementation with Curcumin and Resveratrol on muscle and bone mass. There was a significant decrease in circulating levels of ferritin, to finding that remarkably novel.

Keywords: curcumin, resveratrol, chronic kidney disease, recovery of bone and muscle mass

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Introduction

Mechanisms Of Muscle Wasting In Chronic Kidney Disease

Muscle wasting is especially relevant in patients with chronic kidney disease (CKD) because it is progressive, and increases morbidity and the risk of death[1]. CKD induced activation of catabolism is the most important cause of muscle wasting tan decreased protein synthesis.

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The molecular pathways underlying muscle atrophy are complicated. Studies in humans and rodents have identified the ubiquitin proteasome system (UPS) as the main pathway for the degradation of skeletal muscle proteins.[1] Nuclear factor KB (NFKB) is activated in a redox-sensitive manner during muscle contraction due to increased oxidant production. Increased NFKB signaling decreases insulin action and promotes muscle wasting.[2–4]

Loss Of Bone Mass And Mineral Density In Chronic Kidney Disease Patients

CKD has also been associated with low grade inflammation, and is a major cause of both local and systemic bone loss due to excessive bone resorption and impaired bone formation. This imbalance in bone remodeling is at least in part mediated by the activation of osteoclasts and the impairment of osteoblast function by cytokines. In subjects with osteopenia, this balance is affected by excessive bone resorption or inadequate bone formation during bone remodeling, resulting in low bone density.[5,6]

Iron overload is a common complication in patients with CKD in hemodialysis; it results from the transfusions of red cells that these patients receive to treat symptomatic anemia, as well as from the administration of enteral and/or parenteral iron supplements. In a male mice model of iron overload, the administration of iron dextran increased the level of Reactive Oxygen Species (ROS) and the phosphorylation of p66 in bone, and caused trabecular and cortical thinning, while bone loss was largely prevented by treatment with the antioxidant N-acetyl-L-cysteine (NAC).[7] Recently, Eniko Balogh, et al concluded that iron and ferritin specifically inhibit osteogenic commitment and differentiation of human bone marrow both in vitro and in vivo.[8]

Some authors Durbin SM et al and Shakibaei M et al have demonstrated that Resveratrol supplementation can promote osteogenesis differentiation of mesenchymal stem cells by mediating the modulation of Sirt-1/Runx2; it can also increase osteocalcin and alkaline phosphatase (ALP) levels in plasma and mitigate the loss of femur strength in hindlimb-suspended old male rats.[9,10]

Effects Of Curcumin On Muscle Mass And Bone Density

Curcumin is a polyphenolic compound derived from the Indian spice curcumin longa; it has been studied for over 3 decades, and has been reported to have potential benefits for oxidative stress, cancer, diabetes and inflammatory disease.[11,12] Approximately 65% of the orally administered curcumin is rapidly cleared from the body, mainly in the feces.

Kazim S, et al[2] suggest that curcumin has the potential to help prevent muscle damage by downregulating the NFKB, and upregulating the nuclear factor (erythroid-derived 2) like 2. They also noted that curcumin activates Sirtuin inhibitors (SIRT1) and potentially enhances mitochondrial biogenesis and fatty acid oxidation in adipocytes and myotubes.

Some of the molecular targets of curcumin are involved in bone remodeling. Curcumin stimulates apoptosis in mature rabbit osteoclasts, having an inhibitory effect on two factors Activator protein 1 (AP-1) and NFKB involved in osteoclast survival.

Bharti et al demonstrated that curcumin suppresses Receptor Activator for Nuclear Factor K B Ligand (RANKL) signaling and osteoclastogenesis by interfering with the NFKB pathway.[13] Hie et al reported the inhibitory effects of curcumin on osteoclastic activity in insulin-dependent diabetes mellitus using rats with streptozotocin-induced diabetes.[14] In RAW 264.7 cells, curcumin also inhibited osteoclastogenesis through the inhibition of NF-KB.[15]

In ovariectomized female rats (OVX), oral administration of curcumin (10mg kg-1 per day for 4 weeks) decreased total serum cholesterol levels and improved some bone histomorphometric parameters, including the endosteal osteoid width in tibia affected by estrogen deficiency.[16]

In a study by Riva A et al on 57 healthy subjects with low bone density, an oral formulation based on turmeric phytosome (Meriva®) induced a significant increase (+ 7.1% and + 4.8% at week 24) in the bone density of the small fingers and the upper jaw, respectively, compared with the initial values.[17]

Effects Of Resveratrol On Muscle Mass And Bone Density

Resveratrol has been shown to have many beneficial biological effects, including inhibition of NFKB activity and activation of AMP-activated protein kinase (AMPK). Resveratrol has been reported to stimulate histone deacetylase activity (SIRT1), and this effect is possibly one of the main mechanisms of action of this drug.[18] Sharma et al reported that treatment with resveratrol (5 mg or 10 mg/kg

orally) for 2 weeks improved urinary protein excretion, renal dysfunction and renal oxidative stress in streptozotocin-induced diabetic rats.[19] Kim et al showed that SIRT1 activation by resveratrol reduces cisplatin induced acetylation of p53, apoptosis, and cytotoxicity in the proximal tubular cells of mice.[20] Other studies have shown that resveratrol attenuates renal injury caused by several drugs, including glycerol, gentamicin and cyclosporine, by reducing oxidative stress.[21–25]

Evidence indicates that Resveratrol prevented an increase in Muscle RING-finger protein-1 (MuRF1) expression and attenuated muscle atrophy in an in vivo model of CDK. Li Jing Sun et al found that phosphorylation of NFKB was also inhibited at the same time.[26]

To determine the effect of twelve weeks of supplementation with resveratrol and curcumin on patients with chronic kidney disease and iron overload undergoing hemodialysis, we performed a randomized, double-blind, placebo-controlled trial.

Materials And Methods

General Characteristics Of Patients

The study was designed as a randomized, double blind, placebo-controlled trial with follow up at 6 and 12 weeks. The study complies with the Helsinki declaration and was approved by the Institutional Ethical Committee of the Mexican Institute of Social Security (IMSS R-2015-785-109). All the patients were invited to participate and the consent was informed and signed their written informed consent. We included a total of 40 patients with nephropathy undergoing renal replacement therapy with hemodialysis at the High Specialty Medical Unit No. 1 Bajio, Institute Mexican Social Security. The patients were randomly assigned to two groups, 20 to the group with antioxidant supplementation (Resveratrol + Curcumin) (Group A), treated with a daily oral dose of 500 mg of Resveratrol and 500 mg of Curcumin, and 20 to the control group treated with placebo (Group B) over a period of 12 weeks. The patients were matched according to their age and gender.

Statistical Analysis

The data were analyzed using Student's *t*-test. Repeated measurements were performed during the follow-up to determine the differences between the groups.

Results

Anthropometric And Clinical Characteristics Of Patients On Hemodialysis

An analysis of the etiology of chronic kidney disease in patients on hemodialysis showed that 40% of the patients included in this study had an etiology of arterial hypertension, 25% had Diabetes mellitus type II and 35% had other etiologies, including renal hypoplasia and chronic glomerulonephritis (Table 1). The etiology of kidney disease was distributed homogeneously between both groups.

No significant differences of gender and age were found between the groups (Table 2). It can thus be inferred that both groups of patients were homogeneous in terms of the aforementioned variables, and therefore the differences found in the other measured parameters were not attributed to them.

Effect On The Biochemical And Clinical Markers Of The Group Treated With Resveratrol And Curcumin

At the end of the study, we compared biochemical markers to evaluate the effect of Resveratrol and Curcumin supplements. Significant differences were found between the

Table 1 Baseline Clinical And Anthropometric Characteristics Of Patients On Hemodialysis

Variable	Group A	Group B	Value Of p
	n=20	n=20	
Females	6/20	8/20	0.80
Males	14/20	12/20	0.85
Age (years)	38.52 ± 11.14	35.40 ± 12	0.39
Time on HD (years)	4.8 ± 2.4	5 ± 2.0	0.77
DM2 (n)	5/20	7/20	0.79
HAS (n)	8/20	6/20	0.80
OTHER (n)	7/20	7/20	0.99
BMI (kg/m^2)	21.41 ± 3.96	23 ± 2.0	0.11
WEIGHT (kg)	65.16 ± 14.62	68 ± 9.5	0.47
% Fat	24.29 ± 11.61	26 ± 10.3	0.62
MUSCLE MASS (kg)	46.01 ± 8.85	44.6 ± 6.82	0.57
BONE MASS (kg)	2.46 ± 0.44	2.46 ± 0.25	0.86
WAIST (cm)	90.80 ± 14.37	97 ± 13.8	0.17
Subjective global evaluation	11.10 ± 1.86	11.1 ± 0.99	0.99

Notes: Group A, with supplementation; Group B, control group. The data were analyzed using Student's *t*-test.

Abbreviations: HD, Hemodialysis; DM, Diabetes Mellitus type II; HAS, Hypertension.

Table 2 Baseline Biochemical Markers Of Patients On Hemodialysis

Variable	Group A (n = 20)	Group B (n = 20)	Value Of *p*
	Mean ± SD	Mean ± SD	
Glucose (mg/dl)	97.47 ± 46.49	108.1 ± 49.5	0.48
Creatinine (mg/dl)	9.94 ± 2.96	10 ± 1.88	0.93
Urea (mg/dl)	115.13 ± 38.41	120.9 ± 34.7	0.62
Uric Acid (mg/dl)	5.95 ± 1.4	7 ± 2.0	0.06
Cholesterol (mg/dl)	148.05 ± 43.91	138.2 ± 24.9	0.38
Triglycerides (mg/dl)	151.10 ± 94.44	175 ± 90.0	0.41
VLDL (mg/dl)	30.53 ± 16.35	35 ± 12	0.33
Hemoglobin (mg/dl)	12.55 ± 1.38	11.9 ± 1.4	0.14
Hematocrit (%)	38.43 ± 5.55	35.3 ± 4.8	0.06

Notes: Group A (Treatment); Group B (Placebo). The data were analyzed using Student's *t*-test.

basal and final serum levels of Triglycerides (TG) (p = 0.01) and VLDL (p = 0.003), whereas no significant differences were found in glucose and uric acid levels (Table 3).

Effect Of Treatment With Resveratrol And Curcumin On Clinical And Anthropometric Parameters

Significant differences were found in the body composition of the patients between both groups. There was a significant difference in BMI values (p = 0.002), fat percentage (p = 0.007), muscle mass (p = 0.01) bone mass (p = 0.01), as well as in the score of the subjective global evaluation (p = 0.03) (Table 4).

Oxidative Stress And Iron Overload

Iron Overload

A significant decrease in the levels of serum ferritin (−15.45%; 2003.69 ± 518.73 vs 1795.65 ± 519.00 ng/mL; p = 0.04) was observed in the patients treated with Curcumin and Resveratrol, while the control group showed no significant change (Table 5).

Lipids And Oxidized Proteins In The Serum Of Patients On Hemodialysis

Serum TBARS levels were quantified to determine the oxidative damage to lipids. To determine the oxidative damage to oxidized proteins, serum carbonyls were quantified. These measurements showed that the markers of oxidative stress had no significant changes. Nor were significant differences observed between the baseline and the final TBARS values (70.45 ± 69.21 vs 50.19 ± 32.62, p = 0.24). The same results was obtained for carbonyl values (2.67 ± 0.75 vs 2.50 ± 0.85; p = 0.50).

Discussion

The findings of this study showed that supplementation with resveratrol and curcumin induced an increase in muscle mass and bone mass in hemodialysis patients. Several studies conducted in recent years reported possible health benefits of Resveratrol and Turmeric in cardiovascular and renal disease patients. Resveratrol is a powerful antioxidant agent that can act as a ROS scavenger.[27] Moreover, Resveratrol can have several protective effects against age related disorders, including kidney diseases,

Table 3 Effect On The Biochemical Markers Of The Group Treated With Resveratrol And Curcumin Supplementation (Group A) And Control (Group B)

Variable	Group A Basal (n 20)	Group A Final Week 12 (n 20)	Value Of *p*	Group B Basal (n 20)	Group B Final Week 12 (n 20)	Value Of *p*	Value Of *p***
Glucose (mg/dl)	97.47 ± 46.49	92 ± 38.23	0.43	97.5±46.6	96.8±32.12	0.95	0.66
Triglycerides (mg/dl)	151.10 ± 94.44	93.30 ± 23.20	*0.01	152.9±93.34	149.67±90.53	0.91	0.01
Cholesterol (mg/dl)	148.05 ± 43.91	119.60 ± 25.86	0.46	149.87±37.41	159.23±36.51	0.42	0.003
VLDL (mg/dl)	30.53 ± 16.35	18.70 ± 4.83	*0.003	38.20±12.82	30.98±14.82	0.10	0.001
Uric Acid (mg/dl)	5.95 ± 1.4	5.17 ± 1.71	0.12	5.89 ±1.2	6.0±1.3	0.78	0.09

Notes: The data were analyzed using Student's *t*-test. An *Indicates statistically significant differences intragroup. **Indicates statistically significant differences intergroup.
Abbreviation: VLDL, very low- density lipoprotein.

Table 4 Clinical And Anthropometric Characteristics Of The Group Treated With Resveratrol And Curcumin

Variable	Basal (n 20)	Final Week 12 (n 20)	Value Of *p*
BMI	20.41 ± 3.96	24.62 ± 4.28	***0.002**
% Fat	24.29 ± 11.61	15.44 ± 7.8	***0.007**
Muscle (kg)	46.01 ± 8.85	53.51 ± 9.81	***0.01**
Bone (kg)	2.46 ± 0.44	2.85 ± 0.48	***0.01**
% Water	55.90 ± 10.10	60.17 ± 8.6	
Visceral Fat	6.72 ± 5.07	6.2 ± 3.9	**0.71**
SGE	11.10 ± 1.86	10.00 ± 1.24	*** 0.03**

Notes: The data were analyzed using Student's *t*-test. An * Indicates statistically significant differences.
Abbreviations: BMI, body mass index (weight [kg]/height [m2]); SGE, subjective global evaluation.

Table 5 Effect On The Ferritin Levels Of The Group Treated With Resveratrol And Curcumin Supplementation (Group A) And Control (Group B)

Variable	Group A Basal (n 20)	Group A Final Week 12 (n 20)	Value Of p*	Group B Basal (n 20)	Group B Final Week 12 (n 20)	Value Of p*	Value Of p**
Ferritin ng/mL	2003.69± 518.73	1795.65± 519.00	0.67	2078± 580.45	2008± 500.63	0.19	0.04

Notes: Group A (Treatment) and Group B (Placebo). The data represent the mean ± DE. A Student's *t*-test was performed. An *Indicates statistically significant differences intragroup. **Indicates statistically significant differences intergroup.

through the activation of NAD dependent deacetylase and Sirtuin 1 (SIRT1).[28] SIRT1 deacetylates several substrates and is an important regulator of a wide variety of cellular processes, including stress responses, cell survival, mitochondrial biogenesis and metabolism, occur in response to cellular energy levels and the redox state.[28] Regarding Turmeric, a study by Shain et al (2016) in Wistar rats treated with 100 mg/Kg/day and exercise for 6 weeks showed that Turmeric helps prevent muscle wasting by regulating NFKB and Nuclear factor erythroid (Nrf2).[2]

Furthermore, by deacetylating target proteins SIRT1 can regulate multiple cellular functions, including apoptosis, mitochondrial biogenesis, inflammation, glucose/lipid metabolism, autophagy and cellular stress adaptations.[7] An excess of ROS plays a role in a variety of diseases, as well as in the aging process, which involves numerous cellular response pathways.[29,30]

Patients with chronic kidney disease maintain inflammation and oxidative stress processes during renal replacement therapy with hemodialysis, which is why this disease is used as a model of premature aging.[31] Oxidative stress is induced by an imbalance between ROS production and antioxidant defenses; therefore, exogenous antioxidants or the modulation of antioxidant enzymes can be expected to reduce oxidative stress. In this study we observed high levels of oxidative stress and high levels of lipid and protein peroxidation in patients with chronic kidney disease in hemodialysis; these metabolic conditions contribute to the accelerated loss of muscle and bone mass.

Muscle atrophy is a common complication of CKD and is associated with increased morbidity and mortality. The processes that lead to the loss of muscle mass are also present in various catabolic conditions. Understanding the pathogenesis of CKD and induced muscle loss could lead to the use of therapeutic interventions to prevent muscle wasting, and potentially other catabolic conditions, in CKD patients.[32]

Skeletal muscle atrophy is a common complication there is a decrease in protein synthesis in skeletal muscle, while protein degradation increases due to an increase in the activity and expression of the ubiquitin-proteasome proteolytic pathway. This pathway does not respond to simple nutritional intervention. It is belived that certain agents, including glucocorticoids, cytokines, the proteolysis inducing factor (PIF) and oxidative stress are responsible for the induction of the ubiquitin-proteasome pathway in skeletal muscle under catabolic conditions. Insulin suppresses the activation of this pathway, and so the loss of insulin action in diabetes leads to muscle wasting. It is thought that cytokines, PIF and ROS induce proteasome expression by the activation of NFKB.[30]

Targets for therapeutic intervention include antagonists of the inducers of proteasome expression, intracellular signaling pathways that lead to the activation of NFKB,

and enzymes that induce ubiquitin conjugation to the substrate protein (myosin) and to proteasome.[33] Anti-cytokine and anti-PIF antibodies are effective in attenuating muscle protein degradation in certain animal experimental models, while glucocorticoid receptor antagonists are effective in the treatment of sepsis. Agents that inhibit the activation of NFKB, such as resveratrol, thalidomide, ibuprofen, eicosapentaenoic acid and beta-hydroxy-beta-methylbutyrate are effective in preserving skeletal muscle mass in cachexia.[30] These results suggest that the ubiquitin-proteasome pathway is an appropriate therapeutic target to prevent muscle wasting.[34]

Patients with chronic kidney disease (CKD) have an increased risk of mortality and morbidity that is associated with loss of body fat and lean mass.[35] A study using an in vivo model of chronic kidney disease showed that Resveratrol prevents MURF1 from increasing and attenuates muscular atrophy. Li Jing Sun et al found that phosphorylation of NFKB is also inhibited at the same time.[26]

Dong Tao W et al (2014) showed that Resveratrol prevents muscle atrophy induced by TNFα by regulating Akt/mTOR/Foxo1 signaling in C2C12 myotubes. There are also reports that treatment with Resveratrol prevents degradation induced by the Proteolysis Factor (PIF).[28] Previous studies have also shown that Resveratrol can directly eliminate ROS. Moreover, resveratrol has been reported to stimulate the activity of histone deacetylase SIRT1, which is probably one of the main mechanisms of action of this drug.[18,26]

In the present study, anthropometric parameters were evaluated at the beginning of the treatment to determine its effect on the percentage of muscle mass and bone mass. Both variables showed a significant increase after 12 weeks of supplementation (Muscle, 46.01 ± 8.85 kg versus 53.51 ± 9.81 kg, p= 0.01; Bone 2.46 ± 0.44 kg versus 2.85 ± 0.48 kg, p= 0.01), leading to a consequent increase in the BMI, which in turn had significant effect on the subjective global evaluation. The effect on the subjective global evaluation had an influence on the nutritional risk of renal patients, which has been mentioned as an important survival factor.

Several studies have analyzed the effect of supplementation on bone mass percentage; a randomized controlled trial with placebo showed that Resveratrol increases bone mineral density and bone alkaline phosphatase in obese men. That study aimed to evaluate the effects of Resveratrol treatment on the bones of men with metabolic syndrome.[36] The patients received an oral treatment consisting of 1000 mg of Resveratrol (RSV, high), 150 mg of Resveratrol (RSV, low) or placebo daily for 16 weeks. Bone alkaline phosphatase (BAP) increased in a dose-dependent manner when the patients were treated with Resveratrol (R = 0.471, P <0.001), which resulted in a significantly greater increase in BAP in the RSV (high) group compared to the group receiving placebo (week 4, 16.4 ± 4.2%, P <0.001; week 8, 16.5 ± 4.1%, P <0.001; week 16, 15.2 ± 3.7%, P <0.001). The trabecular volumetric bone mineral density of the lumbar spine (LS vBMD-trab) also increased, showing a direct dose-dependent relationship with RSV (R = 0.26, P = 0.03), with a significant increase of 2.6 ± 1.3% in the RSV (high) group compared with the placebo group (P=0.04), our study with the combined supplementation of turmeric and resveratrol, an increase in bone mass was observed.

It has been experimentally shown in murine models that Resveratrol (RSV) has anti-inflammatory properties, and studies with rodents suggest it has protective effects for bones.[37] An assay done on mice with iron overload and osteoporosis showed that Resveratrol protects against the destructive effects of iron on bones, and that there was a significant recovery of bone density and trabecular space. Other authors have described beneficial effects of Resveratrol such as promoting osteogenic differentiation by modulating Sirt1/Runx2 mediated by mesenchymal progenitor cells, increasing plasma levels of osteocalcin and alkaline phosphatase, and reducing the loss of diameter in the femur neck of male rats.[37]

Similarly, the study analyzed the effect of a combination of Turmeric 500mg/day + Resveratrol at 500 mg/day on the percentage of bone mass of CKD patients on hemodialysis. Amira Zaky et al, have demonstrated that the synergistic and therapeutic effects of resveratrol–curcumin combination, also show that both compounds exert beneficial effect either cooperatively or through differential molecular mechanisms in counteracting aluminum-induced neuroinflammation.[38]

In our study, the patients had high levels of ferritin, which produces a high level of inflammation and we were able to observe that at the end of the treatment the ferritin levels decreased significantly. There was a significant decrease in circulating levels of ferritin, a finding that is remarkably similar to what was reported in a murine model by Lu Zhao (2015). Tarantino G, et al, recently observed that transferrin levels are a predictor of adequate hemodialysis, a limitation of their study not having evaluated the transferrin levels.[39] It is possible that the accumulated iron increases the bone response through the

mentioned pathways. However, the relevant molecular mechanisms of Resveratrol, the regulation of FOXOS in bone, and osteoblast damage induced by iron overload remain unclear.

Conclusions

The present study is the first assay on patients with chronic kidney disease and iron overload that demonstrates the beneficial effects of combined supplementation with Curcumin and Resveratrol on muscle and bone mass. The subjective global evaluation had an influence on the nutritional risk of renal patients, as an important survival factor. Ferritin levels were monitored, showing a significant decrease in serum levels.

Abbreviations

ALP, Alkaline Phosphatas; AMPK, AMP-activated protein kinase; AP-1, Activator protein; BAP, Bone alkaline phosphatase; BMI, Body Mass Index; CKD, Chronic Kidney Disease; FOXO, Forkhead box O; LS vBMD-trab, Trabecular Volumetric Bone Mineral Density of the Lumbar Spine; MuRF1, Muscle RING-finger protein-1; NAC, Antioxidant N-acetyl-L-Cysteine; NAD, Nicotine Adenine Dinucleotide; NF-KB, Nuclear factor -kB; PIF1, Proteolysis Inducing Factor; RANKL, Receptor Activator for Nuclear Factor κ B Ligand; ROS, Reactive Oxygen Species; RSV, Resveratrol; SGE, Subjective global evaluation; SIRT1, Sirtuin inhibitors; TBARS, Thiobarbituric Acid Reactive Substances; UPS, Ubiquitin Proteasome System.

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Disclosure

The authors report no conflicts of interest in this work.

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