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Potential Effects of Resveratrol on Obesity-Related Nephropathy in Iraqi Obese Women

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Abstract

Obesity-related nephropathy is a considerable causing factor of end-stage renal disease. Obesity is described as a condition of chronic oxidative stress and chronic systemic inflammation. Increased inflammation in adipose tissue and kidneys enhances the development of kidney damage in obesity. Resveratrol is a polyphenolic compound noted to exert worthy effects on various diseases such as cardiovascular diseases, atherosclerosis, diabetes mellitus, and nephropathy. The healthful effects of resveratrol are thought to be attributed to its antioxidant properties. In this interventional prospective randomized controlled trial, female patients diagnosed with obesity according to the WHO criteria and were randomly allocated to either control or resveratrol group. Resveratrol supplement showed a significant reduction in weight, body mass index (BMI) and waist circumference (WC). Hormonal determinants of glycemic status showed a significant reduction in betatrophin and C-peptide levels. There was a significant reduction in the levels of serum and urinary creatinine, microalbuminuria (MAU), collagen IV (COL.IV) and alpha glutathione-S-transferase (alpha GST), whereas estimated glomerular filtration rate (eGFR) is significantly elevated. Liver enzymes including serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) are significantly reduced. Serum levels of total cholesterol (TC), triglycerides (TGs) and very low density lipoprotein (VLDL-c) are significantly reduced, while the change was not significant in the serum level of low density lipoprotein (LDL-c) compared with control group, high density lipoprotein (HDL-c) is significantly elevated. There was a significant elevation in serum levels of adiponectin and superoxide dismutase 1 (SOD1) and a significant reduction in serum levels of resistin and interleukin-6 (IL-6). From the above results, one can conclude that oral supplementation of resveratrol can improve nephropathy associated with obesity.

Keywords : obesity-related nephropathy, resveratrol

INTRODUCTION

Obesity is a global health problem in which excess body fat has accumulated to the extent that it may have a hazardous effect on the health[(1)]. People are generally considered obese when their body mass index (BMI), a value obtained by dividing a person's weight by the square of the person's height, is over 30 Kg/m^2 with the range of 25-30 Kg/m^2 defined as overweight[(2)]. There is a strong relationship between obesity and a variety of diseases, including hypertension, diabetes mellitus, hyperlipidemia, osteoarthritis, cancer, and nephropathy[(3)]. It is recognized that abdominal obesity (android obesity or central obesity) is associated with increased risk of cardiovascular disease (CVD) and type 2 diabetes, whereas gynoid obesity (lower body obesity characterized by fat located around the hips and buttocks) is rarely correlated with metabolic complications[(4)]. Both increased food intake and the lack of physical activity are believed to explain most cases of obesity. In addition, other factors including genetics, medical conditions, lack of sleep and use of drugs, all can predispose to obesity[(5)]. Dietary changes and exercise represent the first step in the management of obesity, Low calorie and fibers rich food such as fruits, vegetables are good food to have every day. In addition to dietary changes, moderate intensive activity of 150 to 250 minutes every week is helpful to lose weight[(6)]. Obesity is considered as a potent risk factor for the initiation and development of kidney disease. Higher BMI is associated with the presence and development of proteinuria, reduction of estimated glomerular filtration rate (GFR), and finally end stage renal disease (ESRD)[(7)]. Obesity leads to a complex metabolic abnormalities that have a deleterious effect on the kidneys, such as hypertension, diabetes mellitus, and hyperlipidemia, which can mediate renal injury[(8)]. Obesity itself can result in renal injury through direct effects including inflammation and oxidative stress[(9)]. Adipose tissue is considered as an active endocrine tissue that could affect the kidneys directly, via the production of an adipokines including leptin, resistin, and IL-6, which has inflammatory properties[(10,11)]. Adiponectin is an adipocyte-secreted hormone that has anti-inflammatory action. It is highly presented in human serum, but its level decreases in obese humans, especially in individuals with visceral obesity[(12)]. An analysis of oxidative markers in obese individuals suggests that oxidative damage is correlated with high BMI and the percentage of body fat. Reactive oxygen species (ROS) stimulate redox-sensitive transcription factors, particularly nuclear factor-κB (NF-κB), promoting the release of proinflammatory cytokines and the expression of adhesion molecules and growth factors, like IL-6 and TNF-α, which can enhance the progression of renal damage in obesity[(13)].

Resveratrol (3,4,5-trihydroxy-trans-stilbene) is a natural non - flavonoid polyphenolic compound found in Grapes, red wine, *Polygonum cupsidatum* roots, peanuts, and berries of *Vaccinum* species, that has many healthful effects including cardioprotective, neuroprotective, antitumor and nephroprotective properties[(14)]. The basic structure of resveratrol consists of two phenolic rings linked to each other by a double styrene bond, and this double bond is responsible for the isometric cis-and trans-forms of resveratrol[(15)]. The major metabolites of resveratrol are the glucuronide- and sulfate-conjugates, where the glucuronide conjugates are documented to be the major metabolites in the rodents, while sulfates are primarily found in humans[(16)]. The main resveratrol target is the sirtuin class of nicotinamide adenine dinucleotide (NAD)-dependent deacetylases. There are seven sirtuins have been exhibited in mammals, of which SIRT-1 is thought to be responsible for the beneficial effects of resveratrol. The pathways that are regulated by sirtuins include fat metabolism, gluconeogenesis and glycolysis in the liver and cell survival[(17)]. Resveratrol treatment improved albuminuria and lowered the increased levels of renal oxidative stress and inflammation in the kidneys through the scavenging of ROS. Furthermore, resveratrol regulates the activity and expression of

antioxidant enzymes including catalase (CAT) and superoxide dismutase (SOD) either by transcriptional regulation via nuclear factor E2-related factor 2 (Nrf2), activator protein-1 (AP1), forkhead box protein O (FOXO), or through enzymatic modifications[18].

PATIENTS AND METHODS

This interventional prospective randomized controlled trial was carried out on 50 female patients diagnosed with obesity according to the WHO criteria, with BMI ≥ 30 kg/m^2, age range of 15-58 years old, and waist circumference of > 80 cm, under supervision of professional endocrinologists, from October2016 to August 2017. The protocol was reviewed and approved by the Scientific and Ethics Committee in the College of Pharmacy/ University of Al-Mustansiriayah, and Obesity Research and Therapy Unit in Alkindi College of Medicine/ University of Baghdad. Patient's oral consent was taken and all participants were advised to take a low carbohydrate and fat dietary regimen and achieving 60 minutes of aerobic exercise per day during their treatment duration. Certain exclusion criteria were followed to avoid interference with the study design and include: any cause of nephropathy rather than obesity, drugs that may cause kidney damage, like NSAIDs and aminoglycosides, urinary tract infections (UTIs), Presence of heart or hepatic failure, uncontrolled thyroid function, pregnancy and lactation, conditions that may interfere with adipokine levels (rather than obesity) like rheumatoid arthritis, those on vitamins or dietary supplements, those with unstable glycemic control and lipid profiles, patients with a history of resveratrol allergy, patients on medications that may interfere with resveratrol absorption, patients on drug therapy that may increase body weight, like oral contraceptives.

Female patients were randomly allocated to either control group (taking orlistat, metformin and fluoxetine) or resveratrol group (taking orlistat, metformin, fluoxetine plus resveratrol). From 50 female patients, only 46 completed this study, the other 4 were excluded (3 from control group and 1 from resveratrol group) due to poor compliance, violation of the study protocol, or other reasons.

At baseline and for all patients, a specially designed questionnaire was filled, recording their medical history and pretreatment characteristics. The demographic and baseline characteristics were evenly distributed for both groups, as summarized in table 1. Parameters of the anthropometry, hormonal determinants of glycemic status, kidney and liver function, lipid profiles, in addition to the inflammatory and oxidative stress markers, were evaluated at baseline (pre-treatment) and after 8 weeks (post-treatment) for both groups. Adverse effects (if any) recorded at the end of study.

Ten milliliters of venous blood samples were drawn by vein puncture from all participants as a baseline sample and then after 8 weeks as endline sample. Serum samples were stored frozen at –20^{o}C till analysis was done. Samples of urine were drawn from patients to measure urine creatinine, microalbuminuria, collagen IV (COL.IV) and alpha glutathione-S-transferase (alpha GST). The BMI describes relative weight to height according to the following equation: BMI= weight/ height (kg/m²).

The SGOT, SGPT, TC, TGs, HDL-C, LDL-C were measured by standard enzymatic techniques. Estimated glomerular filtration rate (eGFR) was calculated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) online calculator from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) website using serum creatinine levels[19]. The levels of betatrophin, C-peptide, Col. IV, α-GST, adiponectin, resistin, IL-6 and SOD1 were measured by enzyme-linked immunosorbent assay (ELISA) technique according to their manufacture (Elabscience company).

Statistical analysis

The results were presented as mean ± SEM or percentage of difference. All of the statistical analyses were achieved via the statistical package SPSS version 22.0 (SPSS, Inc.). Two sample t-test was applied to compare the means of the baseline characteristics between the two groups and then data were analyzed by using the analysis of covariance (ANCOVA) for this clinical trial. The significance level for all tests was taken as *P*-value less than 0.05.

RESULTS

After adjustment of baseline means for control and resveratrol groups according to the analysis of covariance, there was a significant reduction (*P*-value <0.05) in anthropometric parameters (weight, body mass index and waist circumference) in resveratrol group compared with control group (table 2), levels of betatrophin and C-peptide (table 3), serum and urinary creatinine, microalbuminuria, COL.IV and α-GST, while eGFR is elevated significantly in resveratrol group compared with those on control (*P*-value <0.05). (table 4). The levels of SGOT and SGPT are decreased significantly in resveratrol group (table 5), in addition to serum total cholesterol, TGs and VLDL-c (*P*-value <0.05), while the reduction in LDL-c was not significant in resveratrol group compared with control group (*P*-value> 0.05), HDL-c is elevated significantly (*P*-value <0.05) (table 6). The levels of adiponectin and SOD1 are significantly elevated, whereas the levels of resistin and IL-6 are significantly reduced in resveratrol group compared with control group (*P*-value <0.05) (table 7).

Table 1: Baseline characteristics for control and resveratrol groups

Baseline characteristics	Control group (n=22)	Resveratrol group (n=24)	*P*-value
Age (years)	37.14±5.557	37.38±6.697	0.897
Weight(kg)	107.05±10.417	107.83±13.031	0.823
Height (cm)	158.73±5.633	158.71±6.531	0.992
BMI (kg/m2)	42.6455±3.402	42.8246±3.655	0.865
Waist circumference(cm)	121.5±8.099	121.04±12.791	0.886
eGFR (ml/min)	73.509±7.2	73.817±8.06	0.893
Duration of obesity	10.134±2.132	10.375±3.2	0.897
Lipid lowering agent history (statins)	3(13.64%)	2(8.33%)	0.667

Data were expressed as mean ± standard error of mean (SEM) or percentage %, BMI=body mass index, eGFR= estimated glomerular filtration rate, N = no. of patients, *P*- value > 0.05 considered not significant difference.

Table 2: Effect of resveratrol supplement on anthropometric parameters.

Parameter	Group	Adjusted baseline mean	Adjusted endline mean±SEM	Outcome mean±SEM	*P*-value	% of difference
wt (kg)	Control N= 22	107.46	104.394±0.665	−3.066±0.665	0.021	↓2.85%
	Resveratrol N= 24		96.306±0.637	–11.154±0.637		↓10.37%
BMI (kg/m^2)	Control N= 22	42.73	41.392±0.282	−1.338±0.282	0.001	↓3.13%
	Resveratrol N= 24		38.383±0.270	–4.347±0.270		↓10.17%
W.C (cm)	Control N= 22	121.26	117.846±0.734	−3.414±0.734	0.001	↓2.81%
	Resveratrol N= 24		113.433±0.703	–7.827±0.703		↓6.45%

Data expressed by mean ±SEM and percentage of difference
P<0.05 was considered a significant difference between treatment groups at endline
N= number of patients, SEM = standard error of mean, wt = weight, BMI = body mass index,
W.C =waist circumference.

Table 3: Effect of resveratrol supplement on hormonal determinants of glycemic status

Parameter	Group	Adjusted baseline mean	Adjusted endline mean±SEM	Outcome mean±SEM	*P*-value	% of difference
Betatrophin (pg/ml)	Control N= 22	43701	41783.530±559.797	–1917.47±559.797	0.001	↓4.38%
	Resveratrol N= 24		35717.735±535.965	–7983.27±535.965		↓18.27%
C-peptide (ng/ml)	Control N= 22	3.306	3.134±0.050	–0.17±0.050	0.001	↓5.20%
	Resveratrol N= 24		2.814±0.048	–0.49±0.048		↓14.88%

Data expressed by mean ±SEM and percentage of difference
P<0.05 was considered a significant difference between treatment groups at endline
N= number of patients, SEM= standard error of mean.

Table 4: Effect of resveratrol supplement on renal function.

Parameter	Group	Adjusted baseline mean	Adjusted endline mean±SEM	Outcome mean±SEM	*P*-value	% of difference
Serum creatinine (mg/dl)	Control N= 22	0.920	0.876±0.007	–0.044±0.007	0.001	↓4.78%
	Resveratrol N= 24		0.806±0.007	–0.114±0.007		↓12.39%
Urinary creatinine (mg/dl)	Control N= 22	158.70	121.000±3.510	–37.7±3.510	0.001	↓23.75%
	Resveratrol N= 24		88.209±3.361	–70.49±3.361		↓44.41%
eGFR (ml/min)	Control N= 22	73.67	77.707±0.961	4.037±0.961	0.001	↑5.48%
	Resveratrol N= 24		85.956±0.920	12.286±0.920		↑16.68%
MAU (mg/g Cr)	Control N= 22	62.30	50.176±2.537	–12.124±2.537	0.001	↓19.46%
	Resveratrol N= 24		19.314±2.429	–42.986±2.429		↓69.00%
COL. IV (µg/g Cr)	Control N= 22	8.151	6.632±0.243	–1.52±0.243	0.012	↓18.64%
	Resveratrol N= 24		2.359±0.232	–5.79±0.232		↓71.06%
Alpha GST (ng/mg Cr)	Control N= 22	13.411	11.349±0.404	–2.06±0.404	0.001	↓15.38%
	Resveratrol N= 24		4.788±0.386	–8.62±0.386		↓64.30%

Data expressed by mean ±SEM and percentage of difference
P<0.05 was considered a significant difference between treatment groups at endline
N= number of patients, SEM= standard error of mean, eGFR= estimated glomerular filtration rate, MAU= microalbuminuria, COL. IV= collagen IV, Alpha GST= alpha glutathione-s-transferase.

Table 5: Effect of resveratrol supplement on liver function.

Parameter	Group	Adjusted baseline mean	Adjusted endline mean±SEM	Outcome mean±SEM	*P*-value	% of difference
SGOT (mg/dl)	Control N= 22	30.52	28.444±0.763	–2.076±0.763	0.001	↓6.802%
	Resveratrol N= 24		21.802±0.731	–8.718±0.731		↓28.56%
SGPT (mg/dl)	Control N= 22	29.09	27.180±0.783	–1.91±0.783	0.001	↓6.565%
	Resveratrol N= 30		17.335±0.750	–11.755±0.750		↓40.409%

Data expressed by mean ±SEM and percentage of difference
P<0.05 was considered a significant difference between treatment groups at endline
N= number of patients, SEM = standard error of mean, SGOT = serum glutamic oxaloacetic transaminase, SGPT = serum glutamic pyruvic transaminase.

Table 6: Effect of resveratrol supplement on lipid profile levels.

Parameter	Group	Adjusted baseline mean	Adjusted endline mean±SEM	Outcome mean±SEM	*P*-value	% of difference
Total cholesterol (mg/dl)	Control N= 22	198.72	191.038±2.170	–7.68±2.170	0.001	↓3.86%
	Resveratrol N= 24		169.216±2.077	–29.5±2.077		↓14.84%
triglyceride (mg/dl)	Control N= 22	172.413	165.784±3.997	–6.63±3.997	0.001	↓3.84%
	Resveratrol N= 24		125.381±3.827	–47.03±3.827		↓27.28%
HDL-c (mg/dl)	Control N= 22	42.033	42.145±1.802	0.11±1.802	0.004	↑0.26%
	Resveratrol N= 24		50.047±1.726	8.014±1.726		↑19.07%
LDL-c (mg/dl)	Control N= 22	115.483	107.613±3.523	–7.87±3.523	0.115	↓6.81%
	Resveratrol N= 24		99.772±3.373	–15.711±3.373		↓13.60%
VLDL-c (mg/dl)	Control N= 22	37.133	31.724±1.004	–5.41±1.004	0.001	↓14.57%
	Resveratrol N= 24		24.124±0.962	–13.01±0.962		↓35.03%

Data expressed by mean ±SEM and percentage of difference
P<0.05 was considered a significant difference between treatment groups at endline
N= number of patients, SEM= standard error of mean, HDL-c= high density lipoprotein cholesterol, LDL-c= low density lipoprotein cholesterol, VLDL-c= very low density lipoprotein cholesterol.

Table 7: Effect of resveratrol supplement on inflammatory and oxidative stress markers

Parameter	Group	Adjusted baseline mean	Adjusted endline mean±SE	Outcome mean±SEM	*P*-value	% of difference
Adiponectin (ng/ml)	Control N= 22	17.237	24.492±0.731	7.255±0.731	0.001	↑42.09%
	Resveratrol N= 24		37.483±0.700	20.246±0.700		↑117.46%
Resistin (ng/ml)	Control N= 22	24.175	20.491±0.324	–3.68±0.324	0.001	↓15.24%
	Resveratrol N= 24		12.616±0.310	–11.559±0.310		↓47.81%
IL-6 (pg/dl)	Control N= 22	40.11	35.719±0.664	–4.39±0.664	0.001	↓10.95%
	Resveratrol N= 24		25.549±0.636	–14.56±0.636		↓36.30%
SOD-1 (pg/ml)	Control N= 22	3111.1	3285.949±64.110	174.849±64.110	0.001	↑5.62%
	Resveratrol N= 24		4499.151±61.381	1388.05±61.381		↑44.62%

Data expressed by mean ±SEM and percentage of difference
P<0.05 was considered a significant difference between treatment groups at endline
N= number of patients, SEM= standard error of mean, IL-6 = interleukin-6, SOD-1 = superoxide dismutase-1.

DISCUSSION

The present study indicated that the patients on resveratrol supplement in a dose of 1000 mg twice a day for 8 weeks showed a significant reduction (p<0.05) in weight, BMI, and waist circumference (10.37%, 10.17% and 6.45%, respectively) compared with those on control for the same period of treatment (2.85%, 3.13% and 2.81%, respectively) and this agree with Mendez del Villar *et al*. study that showed a significant reduction in weight, BMI and waist circumference after using resveratrol at a dose of 500mg for 90 days[20]. Poulsen M. M. *et al*. showed that treatment with resveratrol supplementation had no effect on energy expenditure, adipose tissue content and metabolic events[21]. Mechanisms contributing to anti-obesity effects of resveratrol are inhibition of adipogenesis and lipogenesis. The inhibition of adipogenesis and lipogenesis was partially mediated by suppression of insulin signaling and activation of AMP-activated protein kinase (AMPK) α1[22].

Obesity has been observed to play a main role in developing of diabetes and insulin resistance. The main causing factor of insulin insensitivity is the release of NEFAs, increased NEFAs release is noticed in obesity and in type 2 diabetes, and is related with insulin resistance in both conditions[23]. Betatrophin, also known as angiopoietin-like protein 8 (ANGPTL 8), or lipasin, is a hormone found in liver and adipose tissue and is a potent regulator of lipid metabolism and glucose homeostasis. Melton *et al*. showed that betatrophin induced dramatic β-cell proliferation in an insulin-resistant mouse model. This exciting finding suggested that β-cell regeneration is a potential alternative treatment for diabetes[24]. The largest report on betatrophin levels in non-diabetic individuals, reported a positive association between betatrophin and BMI, waist/hip ratio, glycated hemoglobin (HbA1c), plasma levels of insulin and triglyceride (TG) levels[25]. C-peptide is released in equal amounts to insulin and hence can be used to assess secretion of endogenous insulin. Obesity is correlated with insulin resistance, high level of C-peptide and chronic inflammation[26]. The present study indicated that the patients on resveratrol supplement showed a significant reduction (p<0.05) in betatrophin and C-peptide level (↓18.27% and ↓14.88%, respectively) compared with those on control (↓4.38% and ↓5.20%, respectively) after 8 weeks of treatment and this consist with Jinmi Lee *et al.* who found that AMP-activated protein kinase can suppresses the expression of ANGPTL8 in HepG2 cells[27]. Chen *et al.* reported that resveratrol in a dose of 300mg/day for 3 months has no effect on C-peptide in patients with non-alcoholic fatty liver disease[28]. Guo K. *et al*. found that serum levels of betatrophin and C-peptide are decreased significantly in obese individuals after surgery for weight reduction[29]. Resveratrol decreases betatrophin level through activation of AMPK that leads to inhibition of liver X receptor/sterol regulatory element-binding protein 1 (LXR/SREBP-1) signaling. Furthermore, the effect of AMPK on betatrophin expression is affected by activation of PPAR α which results in reduced expression of betatrophin through increased mitochondrial fatty acid oxidation in liver[30]. Resveratrol can lower insulin resistance and C-peptide in obese individuals through its anti-inflammatory action via the inhibition of the nuclear factor-κB (NF-κB) pathway[31].

Obesity-related glomerulopathy (ORG) has been noted in the obesity without obvious diabetes and pre-existing renal diseases, characterized by proteinuria and progressive renal dysfunction. Microalbuminuria (MAU) is considered as an early marker of renal damage[32]. A dramatic decrease in urinary albumin excretion and glomerular hyperfiltration has been shown in obese individuals with a great reduction in body mass index[33]. The present study showed a significant difference (p<0.05) in the levels of serum and urinary creatinine, eGFR, MAU, COL. IV and alpha GST (↓12.39%, ↓44.41%, ↑16.68%, ↓69.00%, ↓71.0 and ↓64.30%, respectively) among patients on resveratrol supplement compared with those on control (↓4.78%, ↓23.75%, ↑5.48%, ↓19.46%, ↓18.64% and ↓15.38%, respectively) after 8 weeks of treatment, and this agree with the study of Chen KH. *et al*. who used resveratrol treatment in streptozotocin (STZ) induced diabetes in rats. They found that resveratrol ameliorated renal dysfunction or diabetic nephropathy by lowering urinary levels of creatinine, microalbuminuria and proteinuria. In diabetic glomeruli also, levels of fibronectin and type IV collagen in the renal cortex were decreased by resveratrol[34]. Resveratrol treatment improved albuminuria and lowered the increased levels of renal oxidative stress and inflammation in the kidneys through the scavenging of ROS. Furthermore, resveratrol regulates the activity and expression of antioxidant enzymes including catalase (CAT) and superoxide dismutase (SOD) [35].

Non-alcoholic fatty liver disease (NAFLD) is highly correlated with obesity, with a documented rate of up to 80% in obese subjects. A bright liver at ultrasound and increased levels of hepatic enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma- glutamyltransferase (GGT), are common features in patients with NAFLD, and their occurrence increases progressively with increasing BMI[36]. In the present study, there is a significant reduction (p<0.05) in the levels of SGOT and SGPT (↓28.56% and ↓40.409%, respectively) among patients on resveratrol supplement compared with those on control (↓6.802% and ↓6.565%, respectively) after 8 weeks of treatment, and this was agree with the study of Chen S. *et. al*. who used resveratrol treatment in a dose of 300 mg twice daily for 3 months on patients with NAFLD[37], and disagree with Chachay *et. al.* study who found an increase in liver enzymes with using resveratrol[38]. Resveratrol might decrease deposition of fat through inhibiting sterol regulatory element binding protein-1c (SREBP-1c) expression by SIRT1-FOXO1 pathway[39].

The present study showed a significant decrease (p<0.05) in the levels of serum total cholesterol, TGs and VLDL-c (↓14.84%, ↓27.28% and ↓35.03%, respectively) in patients taking resveratrol supplements compared with those on control (↓3.86%, ↓3.84% and ↓14.57%, respectively) after 8 weeks of treatment. Meanwhile, serum LDL-c levels decreased not significantly (↓13.60%) in resveratrol group compared with control (↓6.81%). Serum HDL-c levels showed a significant increase (p<0.05) in patients taking resveratrol supplements (↑19.07%) compared with those on control (↑0.26%) after the same period of treatment. Militaru C. *et. al*. study showed that resveratrol in a dose of 20mg/day for 2 months, significantly decrease serum levels of TC, TGs and LDL-c. In addition, the serum level of HDL-c is significantly increased in patients with stable angina pectoris[40]. Jun Yoshino J. *et. al.* found that using of resveratrol in a dose of 75mg/day for 12 weeks does not improve lipid profile in non-obese, post-menopausal women[41]. The major hypothesized mechanism by which resveratrol lowers cholesterol is the down-regulation of the hepatic 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase enzyme, a main enzyme in the biosynthesis of cholesterol. Another suggested mechanism is through elevated expression of cholesterol 7α-hydroxylase (CYP7A1) in the liver that results in higher bile acid synthesis and secretion, thereby reducing the plasma levels of total and LDL cholesterol[42].

Adipose tissue has been described as an active endocrine organ which acts as the body's major energy store. Increased adiposity and adipocyte dysfunction lead to dysregulation of the adipose tissue-derived secretory factors, referred to as adipokines, which can result in developing of many metabolic diseases through altered lipid and glucose homeostasis. In addition, to increased oxidative stress and inflammatory responses[43]. Obesity is associated with decreased activity of antioxidant enzymes like catalase and SOD1, in addition the concentration of adiponectin that has anti-inflammatory actions is also decreased, while inflammatory markers such as resistin and IL-6 are increased[44]. In the present study, there is a significant increase (p<0.05) in the serum level of adiponectin and SOD1 (↑117.46% and ↑44.62%, respectively) in patients taking resveratrol supplements compared with those on control (↑42.09% and ↑5.62%, respectively) after 8 weeks of treatment. Meanwhile, Serum resistin and IL-6 levels showed a significant decrease (p<0.05) in patients taking resveratrol supplements (↓47.81% and ↓36.30%, respectively) compared with those on control (↓15.24% and ↓10.95%, respectively) after the same period of treatment. Tome-Carneiro J. *et. al.* found that using of resveratrol supplement in a dose of 16mg/day for one year in patients with coronary artery disease, significantly increase serum

level of Adiponectin[45]. Witte *et. al.* showed that resveratrol in a dose of 200mg/day for 26 weeks in overweight subjects, significantly decrease IL-6 level[46]. Meanwhile, Bhatt *et. al.* found that treatment with resveratrol in a dose of 250mg/day for 6 months in patients with type 2 diabetes mellitus significantly increase the level of SOD1[47]. Resveratrol enhances adiponectin multimerization and up-regulation by activating SIRT1. One study has observed that resveratrol increases the expression levels of disulfide bond-A oxidoreductase-like Protein (DsbA-L), a protein that promotes multimerization and stability of adiponectin in cells[48]. Reduction in the expression of resistin after treatment with resveratrol might be secondary to resveratrol-induced PPARγ repression, where resistin gene-expression is under the control of PPARγ. Activation of SIRT1 in white adipocytes have been associated with the repression of PPARγ[49]. Resveratrol up-regulates expression of nuclear factor-E2-related factor-2 (Nrf2), a transcription factor that regulates several genes responsible for detoxification of reactive oxygen species. In fact, Nrf2 regulates the expression of genes encoding antioxidant and detoxifying proteins, such as SOD, glutathione synthetase (GSS) and NAD(P)H-quinone oxido-reductase[50].

One of the limitations of this study is difficulty of obtaining patients with obesity and nephropathy, in addition to misdiagnosed or undiagnosed cases. Another limitation is unselection of the patients with hypertension and diabetes mellitus as inclusion criteria for this study. Age of patients and non-including of men represents one of the limitations of this study.

From this study, many recommendations can be suggested for future work, including further study with large-scale sample and long-term duration. The study of resveratrol effect on other inflammatory markers, like tumor necrosis factor alpha (TNF-α) and C-reactive protein (CRP). The study can be re-evaluated by using different doses and other dosage forms of resveratrol. Future clinical studies needed to determine the effect of resveratrol on hypertension, hyperuricemia, and diabetes mellitus associated with obesity.

CONCLUSION

From above results, one can conclude that oral supplementation of resveratrol can result in improvement of anthropometric parameters, hormonal determinants of glycemic status, renal function, liver function, lipid profiles, and inflammatory and oxidative stress markers.

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REFERENCES

1. World Health Organization. Obesity: Preventing and managing the global epidemic report on a WHO consultation. WHO Technical Report Series 894. ***Geneva*** : WHO; 2000.
2. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. ***Jama***. 2012 Feb 1;307(5):491-7.
3. Segula D. Complications of obesity in adults: a short review of the literature. Malawi Medical Journal. 2014;26(1):20-4.
4. Wiklund P, Toss F, Weinehall L, Hallmans G, Franks PW, Nordstrom A, Nordstrom P. Abdominal and gynoid fat mass are associated with cardiovascular risk factors in men and women. ***The Journal of Clinical Endocrinology & Metabolism***. 2008 Nov 1;93(11):4360-6.
5. Peebles R. Adolescent obesity: etiology, office evaluation, and treatment. Adolesc Med. 2008;19(3):380-405.
6. Racette SB, Deusinger SS, Deusinger RH. Obesity: overview of prevalence, etiology, and treatment. Physical therapy. 2003 Mar 1;83(3):276-88.
7. Kovesdy CP, Furth SL, Zoccali C, World Kidney Day Steering Committee. Obesity and kidney disease: hidden consequences of the epidemic. Nephron. 2017;135(4):243-51.
8. Eknoyan G. Obesity and chronic kidney disease. Nefrologia. 2011 May;31(4):397-403.
9. Tang J, Yan H, Zhuang S. Inflammation and oxidative stress in obesity-related glomerulopathy. International journal of nephrology. 2012;2012.
10. Wolf G, Ziyadeh FN. Leptin and renal fibrosis. InObesity and the Kidney 2006 (Vol. 151, pp. 175-183). Karger Publishers.
11. Ellington AA, Malik AR, Klee GG, Turner ST, Rule AD, Mosley TH, Kullo IJ. Association of plasma resistin with glomerular filtration rate and albuminuria in hypertensive adults. Hypertension. 2007 Oct 1;50(4):708-14.
12. Tesauro M, Mascali A, Franzese O, Cipriani S, Cardillo C, Di Daniele N. Chronic kidney disease, obesity, and hypertension: the role of leptin and adiponectin. ***International journal of hypertension***. 2012 Dec 23;2012.
13. Elmarakby AA, Sullivan JC. Relationship between oxidative stress and inflammatory cytokines in diabetic nephropathy. ***Cardiovascular therapeutics***. 2012 Feb 1;30(1):49-59.
14. Catalgol B, Batirel S, Taga Y, Ozer NK. Resveratrol: French paradox revisited. Frontiers in pharmacology. 2012 Jul 17;3:141.
15. Gambini J, Inglés M, Olaso G, Lopez-Grueso R, Bonet-Costa V, Gimeno-Mallench L, Mas-Bargues C, Abdelaziz KM, Gomez-Cabrera MC, Vina J, Borras C. Properties of resveratrol: in vitro and in vivo studies about metabolism, bioavailability, and biological effects in animal models and humans. Oxidative medicine and cellular longevity. 2015 Jun 28;2015.
16. Walle T, Hsieh F, DeLegge MH, Oatis JE, Walle UK. High absorption but very low bioavailability of oral resveratrol in humans. Drug metabolism and disposition. 2004 Dec 1;32(12):1377-82.
17. Markus MA, Morris BJ. Resveratrol in prevention and treatment of common clinical conditions of aging. Clinical interventions in aging. 2008 Jun;3(2):331.
18. Kitada M, Kume S, Imaizumi N, Koya D. Resveratrol improves oxidative stress and protects against diabetic nephropathy through normalization of Mn-SOD dysfunction in AMPK/SIRT1-independent pathway. ***Diabetes***. 2011 Feb 1;60(2):634-43.
19. Calculate eGFR using the CKD-EPI formula. [Cited in 2015 Nov.].Availablefrom:https://www.qxmd.com/calculate/calculator_251/egfr-using-ckd-epi.
20. Méndez-del Villar M, González-Ortiz M, Martínez-Abundis E, Pérez-Rubio KG, Lizárraga-Valdez R. Effect of resveratrol administration on metabolic syndrome, insulin sensitivity, and insulin secretion. ***Metabolic syndrome and related disorders***. 2014 Dec 1;12(10):497-501.
21. Poulsen MM, Vestergaard PF, Clasen BF, Radko Y, Christensen LP, Stødkilde-Jørgensen H, Møller N, Jessen N, Pedersen SB, Jørgensen JO. High-dose resveratrol supplementation in obese men. ***Diabetes***. 2013 Apr 1;62(4):1186-95.
22. Li S, Bouzar C, Cottet-Rousselle C, Zagotta I, Lamarche F, Wabitsch M, Tokarska-Schlattner M, Fischer-Posovszky P, Schlattner U, Rousseau D. Resveratrol inhibits lipogenesis of 3T3-L1 and SGBS cells by inhibition of insulin signaling and mitochondrial mass increase. Biochimica et Biophysica Acta (BBA)-Bioenergetics. 2016 Jun 30;1857(6):643-52.
23. Jelic K, Luzio SD, Dunseath G, Colding-Jorgsensen M, Owens DR. A Cross-Sectional Analysis of NEFA Levels Following a Standard Mixed Meal in a Population of Persons with Newly Diagnosed Type 2 Diabetes Mellitus Across a Spectrum of Glycemic Control. ***Diabetes***. 2007 Jun 2;56.
24. Yi P, Park JS, Melton DA. Betatrophin: a hormone that controls pancreatic β cell proliferation. ***Cell***. 2013 May 9;153(4):747.
25. Espes D, Martinell M, Liljebäck H, Carlsson PO. Betatrophin in diabetes mellitus: the epidemiological evidence in humans. Current diabetes reports. 2015 Dec 1;15(12):104.
26. Pickens CA, Matsuo KH, Fenton JI. Relationship between body mass index, c-peptide, and delta-5-desaturase enzyme activity estimates in adult males. PloS one. 2016 Mar 29;11(3):e0149305.
27. Lee J, Hong SW, Park SE, Rhee EJ, Park CY, Oh KW, Park SW, Lee WY. AMP-activated protein kinase suppresses the expression of LXR/SREBP-1 signaling-induced ANGPTL8 in HepG2 cells. ***Molecular and cellular endocrinology***. 2015 Oct 15;414:148-55.

28. Chen S, Zhao X, Ran L, Wan J, Wang X, Qin Y, Shu F, Gao Y, Yuan L, Zhang Q, Mi M. Resveratrol improves insulin resistance, glucose and lipid metabolism in patients with non-alcoholic fatty liver disease: a randomized controlled trial. Digestive and Liver Disease. 2015 Mar 31;47(3):226-32.
29. Guo K, Yu H, Lu J, Bao Y, Chen H, Jia W. Decreased serum betatrophin levels correlate with improved fasting plasma glucose and insulin secretion capacity after Roux-en-Y gastric bypass in obese Chinese patients with type 2 diabetes: a 1-year follow-up. Surgery for Obesity and Related Diseases. 2016 Aug 31;12(7):1343-8.
30. Zhang T, Yamamoto N, Ashida H. Chalcones suppress fatty acid-induced lipid accumulation through a LKB1/AMPK signaling pathway in HepG2 cells. ***Food & function***. 2014;5(6):1134-41.
31. Lawrence T. The nuclear factor NF-κB pathway in inflammation. Cold Spring Harbor perspectives in biology. 2009 Dec 1;1(6):a001651.
32. V Mathew A, Okada S, Sharma K. Obesity related kidney disease. ***Current diabetes reviews***. 2011 Jan 1;7(1):41-9.
33. Agrawal V, Krause KR, Chengelis DL, Zalesin KC, Rocher LL, McCullough PA. Relation between degree of weight loss after bariatric surgery and reduction in albuminuria and C-reactive protein. Surgery for Obesity and Related Diseases. 2009 Feb 28;5(1):20-6.
34. Chen KH, Hung CC, Hsu HH, Jing YH, Yang CW, Chen JK. Resveratrol ameliorates early diabetic nephropathy associated with suppression of augmented TGF-β/smad and ERK1/2 signaling in streptozotocin-induced diabetic rats. ***Chemico-biological interactions***. 2011 Mar 15;190(1):45-53.
35. Kitada M, Kume S, Imaizumi N, Koya D. Resveratrol improves oxidative stress and protects against diabetic nephropathy through normalization of Mn-SOD dysfunction in AMPK/SIRT1-independent pathway. ***Diabetes***. 2011 Feb 1;60(2):634-43.
36. Marchesini G, Moscatiello S, Di Domizio S, Forlani G. Obesity-associated liver disease. ***The Journal of Clinical Endocrinology & Metabolism***. 2008 Nov 1;93(11_supplement_1):s74-80.
37. Chen S, Zhao X, Ran L, Wan J, Wang X, Qin Y, Shu F, Gao Y, Yuan L, Zhang Q, Mi M. Resveratrol improves insulin resistance, glucose and lipid metabolism in patients with non-alcoholic fatty liver disease: a randomized controlled trial. Digestive and Liver Disease. 2015 Mar 31;47(3):226-32.
38. Chachay VS, Macdonald GA, Martin JH, Whitehead JP, O'Moore–Sullivan TM, Lee P, Franklin M, Klein K, Taylor PJ, Ferguson M, Coombes JS. Resveratrol does not benefit patients with nonalcoholic fatty liver disease. ***Clinical Gastroenterology and Hepatology***. 2014 Dec 31;12(12):2092-103.
39. Ponugoti B, Kim DH, Xiao Z, Smith Z, Miao J, Zang M, Wu SY, Chiang CM, Veenstra TD, Kemper JK. SIRT1 deacetylates and inhibits SREBP-1C activity in regulation of hepatic lipid metabolism. ***Journal of Biological Chemistry***. 2010 Oct 29;285(44):33959-70.
40. Militaru C, Donoiu I, Craciun A, Scorei ID, Bulearca AM, Scorei RI. Oral resveratrol and calcium fructoborate supplementation in subjects with stable angina pectoris: effects on lipid profiles, inflammation markers, and quality of life. ***Nutrition***. 2013 Jan 31;29(1):178-83.
41. Yoshino J, Conte C, Fontana L, Mittendorfer B, Imai SI, Schechtman KB, Gu C, Kunz I, Fanelli FR, Patterson BW, Klein S. Resveratrol supplementation does not improve metabolic function in nonobese women with normal glucose tolerance. ***Cell metabolism***. 2012 Nov 7;16(5):658-64.
42. Chen Q, Wang E, Ma L, Zhai P. Dietary resveratrol increases the expression of hepatic 7α-hydroxylase and ameliorates hypercholesterolemia in high-fat fed C57BL/6J mice. Lipids in health and disease. 2012 May 20;11(1):56.
43. Hauner H. Secretory factors from human adipose tissue and their functional role. Proceedings of the Nutrition Society. 2005 May;64(2):163-9.
44. Fernández-Sánchez A, Madrigal-Santillán E, Bautista M, Esquivel-Soto J, Morales-González Á, Esquivel-Chirino C, Durante-Montiel I, Sánchez-Rivera G, Valadez-Vega C, Morales-González JA. Inflammation, oxidative stress, and obesity. International journal of molecular sciences. 2011 May 13;12(5):3117-32.
45. Tomé-Carneiro, J., Gonzálvez, M., Larrosa, M., Yáñez-Gascón, M.J., García-Almagro, F.J., Ruiz-Ros, J.A., Tomás-Barberán, F.A., García-Conesa, M.T. and Espín, J.C., 2013. Grape resveratrol increases serum adiponectin and downregulates inflammatory genes in peripheral blood mononuclear cells: a triple-blind, placebo-controlled, one-year clinical trial in patients with stable coronary artery disease. Cardiovascular Drugs and Therapy, 27(1), pp.37-48.
46. Witte AV, Kerti L, Margulies DS, Flöel A. Effects of resveratrol on memory performance, hippocampal functional connectivity, and glucose metabolism in healthy older adults. ***Journal of Neuroscience***. 2014 Jun 4;34(23):7862-70.
47. Kumar BJ, Joghee NM. Resveratrol supplementation in patients with type 2 diabetes mellitus: a prospective, open label, randomized controlled trial. Int. Res. J. Pharm. 2013 Aug;4(8):246-9.
48. Liu M, Zhou L, Xu A, Lam KS, Wetzel MD, Xiang R, Zhang J, Xin X, Dong LQ, Liu F. A disulfide-bond A oxidoreductase-like protein (DsbA-L) regulates adiponectin multimerization. Proceedings of the National Academy of Sciences. 2008 Nov 25;105(47):18302-7.
49. Mercader J, Palou A, Bonet ML. Resveratrol enhances fatty acid oxidation capacity and reduces resistin and Retinol-Binding Protein 4 expression in white adipocytes. ***The Journal of nutritional biochemistry***. 2011 Sep 30;22(9):828-34.
50. Scapagnini G, Sonya V, Nader AG, Calogero C, Zella D, Fabio G. Modulation of Nrf2/ARE pathway by food polyphenols: a nutritional neuroprotective strategy for cognitive and neurodegenerative disorders. ***Molecular neurobiology***. 2011 Oct 1;44(2):192-201.