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Modified resveratrol Longevinex improves endothelial function in adults with metabolic syndrome receiving standard treatment

Keisuke Fujitaka[a], Hajime Otani[a,*], Fusakazu Jo[a], Hiromi Jo[a], Emiko Nomura[a], Masayoshi Iwasaki[a], Mitsushige Nishikawa[a], Toshiji Iwasaka[a], Dipak K. Das[b]

[a]*Second Department of Internal Medicine, Kansai Medical University, Moriguchi 570-850, Japan*
[b]*Cardiovascular Research Center, University of Connecticut School of Medicine, Farmington, CT, USA*

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Abstract

Resveratrol is known to improve endothelial function in animals, but little is known about its effect on human subjects. Metabolic syndrome (MetS) is a cluster of cardiovascular risk factors underlying endothelial dysfunction. We hypothesized that the modified resveratrol, Longevinex, improves endothelial function in patients with MetS. Thirty-four patients who had been treated for MetS and lifestyle-related disease were randomly assigned to group A, in which Longevinex was administered for 3 months and then discontinued for 3 months, whereas in the time-matched group B, Longevinex was administered between 3 and 6 months. These 2 groups of patients received similar drugs at baseline for diabetes mellitus, dyslipidemia, or hypertension. Flow-mediated dilatation significantly increased during the administration of Longevinex but decreased to baseline 3 months after the discontinuation of Longevinex in the group A patients. Conversely, in the group B patients, flow-mediated dilatation remained unchanged for the first 3 months without Longevinex but was significantly increased 3 months after the treatment with Longevinex. Longevinex did not significantly affect blood pressure, insulin resistance, the lipid profile or inflammatory markers during 6-month follow-up. These results demonstrate that Longevinex specifically improves endothelial function in subjects with MetS who were receiving standard therapy for lifestyle-related disease.

Keywords: Resveratrol; Metabolic syndrome; Lifestyle-related disease; Flow-mediated dilatation; Human

Abbreviations: ApoE, apolipoprotein E; BMI, body mass index; eNOS, endothelial nitric oxide synthase; FMD, flow-mediated dilatation; HbA1c, glycosylated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitive C-reactive protein; IL-6, interleukin 6; LDL, low-density lipoprotein; MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus; TGs, triglycerides.

1. Introduction

Metabolic syndrome (MetS) is characterized by the accumulation of visceral fat associated with the clustering of metabolic and pathophysiologic cardiovascular risk factors including impaired glucose tolerance or type 2 diabetes mellitus (T2DM), dyslipidemia, and hypertension [1]. The prevalence of MetS is rapidly increasing worldwide, not only in industrialized countries but also in developing countries associated with a lifestyle change. Metabolic syndrome is exerting a strong impact on the global incidence of life-threatening cardiovascular diseases such as stroke and myocardial infarction [2,3].

Therapeutic approaches to MetS are essentially composed of lifestyle modifications in conjunction with drug treatment for the MetS-associated complications. Lifestyle modification has been shown to slow or even prevent T2DM

* Corresponding author. Tel.: +81 6 6992 1001; fax: +81 6 6992 3954.
E-mail address: otanih@takii.kmu.ac.jp (H. Otani).

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development. For example, energy restriction and regular exercise greatly reduce waist circumference and body mass index (BMI), lower blood pressure, and improve the lipid profile. Nevertheless, effective treatment for cardiovascular risk factors in MetS often requires pharmacologic intervention in T2DM, dyslipidemia, or hypertension. However, because the currently available pharmacologic tools are frequently not sufficiently effective [4], additional treatments are required to prevent the development of cardiovascular disease in MetS.

Epidemiologic studies suggest that the consumption of wine, particularly red wine, reduces the incidence of both mortality and morbidity from coronary heart disease [5]. The cardioprotective effect of red wine has been attributed to resveratrol, which is present mainly in grape skin. Resveratrol modulates vascular cell function, inhibits low-density lipoprotein (LDL) oxidation, and suppresses platelet aggregation [6]. Various reports support the unifying hypothesis that the reduction of cardiovascular risk factors by resveratrol is mediated by endothelial nitric oxide synthase (eNOS) and its effect on the improvement of endothelial cell function [7-9]. Animal studies suggest that an adequate supplementation of resveratrol might help to prevent the occurrence of atherogenic cardiovascular disease in MetS.

The phenolic compounds that include resveratrol possess a low bioavailability and rapid clearance from the plasma [10]. Longevinex is a modified form of resveratrol that is microencapsulated in plant starches and dextrins to enhance absorption and prevent photoisomerization from trans to cis resveratrol, thereby increasing the plasma half-life.

The beneficial effect of Longevinex may also be attributed to its contents of vitamin D_3, quercetin, and rice bran phytate. Vitamin D is essential to muscle, bone, brain, immune, and cardiovascular health. It inhibits progressive vascular calcification with advancing age [11]. Although Longevinex contains vitamin D_3 at a dose 1200 IU, which is 3 times more than the recommended daily allowance, it is still well within the safe upper limit established by the National Academy of Sciences and corresponds with the dosage recently found to be beneficial in a human clinical trial [12]. Quercetin is a polyphenol like resveratrol and is abundant in fruits, vegetables, and tea. Quercetin attenuates atherosclerosis in apolipoprotein E knockout mice by inhibiting vascular oxidative stress and inflammation, and this effect may be mediated by an improvement of endothelial function [13]. Rice bran phytate is an iron and copper chelator and anticalcifying agent. A recent study suggests that rice bran phytate reduces the risk of high-fat diet–induced hyperglycemia via regulation of hepatic glucose-regulating enzymes [14]. Thus, the combined administration of resveratrol with vitamin D_3, quercetin, and rice bran phytate may potentiate the beneficial effect of resveratrol on endothelial function. Therefore, it is anticipated that Longevinex exerts enhanced biologic effects compared with unmodified resveratrol. Importantly, a recent study determined that, in contrast to resveratrol, which exhibited a J-shaped or inverted U-shaped dose-response curve in protecting the heart against ischemia/reperfusion injury, Longevinex did not display any such hormetic activity [15].

Based on the reported beneficial effects of resveratrol on endothelial function in animal studies and the potentially enhanced biologic effects of Longevinex, the objective of the present study was to test the hypothesis that it improves endothelial function in patients with MetS. We therefore investigated whether this modified resveratrol formula improves endothelial function and ameliorates lifestyle-related diseases, for example, the hypertension, insulin resistance, and dyslipidemia associated with MetS.

2. Methods and materials

2.1. Subjects and treatment

Thirty-four patients diagnosed with MetS and lifestyle-related disease and receiving standard treatment, including medication in addition to nutrition and exercise counseling for at least 3 months, were enrolled in the present study. Metabolic syndrome was diagnosed using the criteria of the Japan Society for the Study of Obesity [16]. Abdominal obesity with waist circumference 85 cm or greater for males and 90 cm or greater for females was an absolute requirement for diagnosis of MetS. Besides abdominal obesity, 2 or more of the following criteria are required: serum triglycerides (TGs) 150 mg/dL or greater, serum high-density lipoprotein cholesterol (HDL-C) less than 40 mg/dL, systolic blood pressure 130 mm Hg or greater and/or diastolic blood pressure 85 mm Hg or greater, and fasting blood glucose 110 mg/dL or greater. Those patients who met these criteria were randomly assigned to group A (n = 17), in which Longevinex was administered for 3 months and then discontinued for 3 months, whereas in the time-matched group B (n = 17), Longevinex was administered between 3 and 6 months. These patients had already been receiving standard treatments for T2DM, dyslipidemia, or hypertension in addition to diet and exercise for at least 3 months, and these medications were continued during a 6-month follow-up period without any change. The patients received 1 capsule of Longevinex containing 100 mg trans resveratrol daily after dinner. Longevinex was a gift from Resveratrol Partners (Los Angeles, Calif., USA). This study was conducted according to the principles expressed in the Declaration of Helsinki 1975 as revised in 1983. Written informed consent was obtained from each subject after full explanation of the purpose, nature, and risk of all of the procedures. The protocol was approved by the ethical review committee at Kansai Medical University, Moriguchi, Japan, and all studies were carried out in Kansai Medical University.

2.2. Measurements in subjects

Systolic and diastolic blood pressure readings were taken twice in our outpatient clinic with an automatic electronic

sphygmomanometer (HEM-907; Omron, Tokyo, Japan) in the sitting position after resting for at least 5 minutes. Height, weight, BMI, waist circumference, glycosylated hemoglobin A1c (HbA1c), fasting blood glucose, serum TGs, serum HDL-C, serum LDL-cholesterol, serum insulin, serum interleukin 6 (IL-6), and high-sensitive C-reactive protein (hsCRP) levels were measured in the morning after an overnight fast without any discontinuation of medication. True waist circumference was measured midway between the 10th rib and the iliac crest with the subjects in the standing position and recorded at the end of a gentle expiration. Blood glucose was measured with a glucose oxidase method using GA-1152 (Arkrey, Kyoto, Japan). Hemoglobin A1c was measured using a high-performance liquid chromatography method using HLC-723G8 (Tosoh, Tokyo, Japan). Plasma lipids were assayed by routine-automated laboratory methods using COLESTEST (Shimizu Medical, Tokyo, Japan).

Serum insulin concentration was measured by electrochemiluminescence immunoassay using a commercially available kit MODULAR ANALYTICS E170 (Roche Diagnostics GmbH, Mannheim, Germany). The homeostasis model assessment of insulin resistance (HOMA-IR), an insulin resistance index, was calculated as described previously [17]. Interleukin 6 was measured by an enzymatic chemiluminescent immunoassay (CLEIA Fujitsubo; Fujirebio Corp, Tokyo, Japan). Serum hsCRP was measured with an ultrahigh sensitivity latex turbidimetric immunoassay method using CRP Latex X2 (Denka Seiken, Tokyo, Japan).

Endothelial function was assessed using flow-mediated dilatation (FMD) as described previously [18]. After overnight fasting, patients were required to lie at rest for at least 15 minutes, and FMD was assessed at the right arm with the patient in a supine position in a quiet, temperature-controlled room (22°C-25°C). Using high-resolution ultrasound with a 10-MHz linear array transducer, the longitudinal image of the right brachial artery was recorded at baseline and then continuously from 30 seconds before 2 minutes or more after cuff deflation after suprasystolic compression (50 mm Hg above the systolic blood pressure) of the right forearm for 5 minutes. The diastolic diameter of the brachial artery was determined semiautomatically using an instrument equipped with software for monitoring the brachial artery diameter (UNEX, Nagoya, Japan). In brief, continuous recording of 2-dimensional grayscale images and B-mode waves of the brachial artery in the longitudinal plane was performed with a stereotactic probe-holding device. A segment with near (media-adventitia) and far (intima-inner lumen) interfaces was manually determined. These border interfaces were identified automatically using the B-mode waves, and the diastolic diameter of the brachial artery per beat was synchronized with the electrocardiographic R wave and tracked automatically. Flow-mediated dilatation was calculated as the percentage change in diameter from the baseline to the peak value after cuff release: %FMD = (vessel diameter reactive hyperemia − vessel diameter at rest) × 100/vessel diameter at rest.

2.3. Statistical analyses

For nonparametric data, differences between the groups at baseline and changes from baseline between the groups were analyzed using the Mann-Whitney *U* test. Differences in FMD at 3- and 6-month follow-up between the groups were analyzed by 2-way repeated-measures analysis of variance. All data are expressed as the mean ± SD. $P < .05$ was interpreted as statistically significant.

3. Results

The baseline clinical characteristics are shown in Table 1. Body weight, BMI, and waist circumference did not significantly differ between the groups. The average systolic and diastolic blood pressures were maintained within the optimum target range in most of patients in both groups using angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor blockers, diuretics, and calcium channel blockers. Fasting blood glucose, fasting serum insulin, HbA1c, and HOMA-IR were controlled below the level of diagnostic criteria for T2DM in both groups using sulfonyl urea, pioglitazone, biguanide, and α-glucosidase inhibitors. Lipid profiles (TGs, HDL-C, and LDL-cholesterol) were kept within the reference range using statins and fibrate. In terms of inflammatory markers, the average IL-6 level was slightly increased from the reference range (<3.0 pg/mL) in group B, whereas hsCRP was maintained within the reference range (<0.2 mg/dL) in both groups.

Table 1
Baseline clinical characteristics

Parameters	Group A	Group B	*P*
Age (y)	63 ± 9	62 ± 14	.9083
Sex (M/F)	12/5	13/4	>.999
Current smoker, n (%)	5 (29.4)	3 (17.6)	.6880
BW (kg)	69 ± 12	76 ± 8	.1315
BMI (kg/m^2)	26.1 ± 4.5	27.9 ± 3.8	.2954
WC (cm)	94 ± 8	97 ± 7	.2978
SBP (mm Hg)	131 ± 15	129 ± 14	.7286
DBP (mm Hg)	74 ± 12	73 ± 6	.6584
FBS (mg/dL)	110 ± 18	110 ± 18	.9669
FSI (μg/mL)	15.2 ± 17.1	12.4 ± 7.4	.6475
HbA1c (%)	5.4 ± 0.4	5.6 ± 0.4	.3782
HOMA-IR	4.1 ± 4.9	3.3 ± 1.8	.7151
TGs (mg/dL)	148 ± 81	153 ± 53	.8556
HDL-C (mg/dL)	51 ± 14	49 ± 15	.8039
LDL-cho (mg/dL)	112 ± 23	117 ± 27	.5565
IL-6 (pg/mL)	2.9 ± 3.9	3.8 ± 4.1	.5960
hsCRP (mg/dL)	0.147 ± 0.195	0.159 ± 0.173	.4879

Group A, Longevinex was administered for 3 months and then discontinued for 3 months; group B, Longevinex was administered between 3 and 6 months. BW indicates body weight; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood glucose; FSI, fasting serum insulin; triglycerides; LDL-cho, low-density lipoprotein cholesterol. Data are expressed as means ± SD.

Table 2
Changes in physical and metabolic parameters in group A

Parameters	Baseline	3 months	6 months
BW (kg)	76 ± 8	75 ± 7	75 ± 7
BMI (kg/m^2)	27.9 ± 3.8	27.6 ± 3.6	27.7 ± 3.7
WC (cm)	97 ± 6	96 ± 6	97 ± 7
SBP (mm Hg)	129 ± 14	127 ± 14	135 ± 15
DBP (mm Hg)	73 ± 6	76 ± 10	80 ± 15
FBS (mg/dL)	110 ± 18	112 ± 17	113 ± 24
FSI (μg/mL)	12.4 ± 7.4	13.5 ± 7.0	15.0 ± 15.5
HbA1c (%)	5.6 ± 0.4	5.5 ± 0.4	5.4 ± 0.5
HOMA-IR	3.3 ± 1.8	3.7 ± 1.9	4.3 ± 4.9
TGs (mg/dL)	153 ± 53	162 ± 83	173 ± 92
HDL-C (mg/dL)	49 ± 15	48 ± 14	54 ± 16
LDL-cho (mg/dL)	117 ± 27	113 ± 27	112 ± 36
IL-6 (pg/mL)	3.8 ± 4.1	3.7 ± 3.4	3.8 ± 2.2
hsCRP (mg/dL)	0.159 ± 0.173	0.175 ± 0.199	0.178 ± 0.193

Group A, Longevinex was administered for 3 months and then discontinued for 3 months. BW indicates body weight; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood glucose; FSI, fasting serum insulin; LDL-cho, low-density lipoprotein cholesterol. Data are expressed as means ± SD.

The changes in the physical and metabolic parameters during the 6-month follow-up period in groups A and B are shown in Tables 2 and 3, respectively. There was no significant change in the physical and metabolic parameters 3 months after the administration of Longevinex or 3 months after the discontinuation of Longevinex in group A. These parameters also did not change for the first 3 months without Longevinex or 3 months after administration of Longevinex in group B.

A striking effect of Longevinex was observed on FMD (Fig. 1). Longevinex treatment for 3 months increased the FMD from 4.4% ± 2.4% to 10.0% ± 3.4% in group A. However, the FMD returned to baseline 3 months after the discontinuation of Longevinex. The FMD did not change for the first 3 months without Longevinex in group B, but Longevinex did significantly increase the FMD 3 months after the administration of Longevinex in this group.

Table 3
Changes in physical and metabolic parameters in group B

Parameters	Baseline	3 month	6 month
BW (kg)	69 ± 12	69 ± 13	69 ± 12
BMI (kg/m^2)	26.1 ± 4.5	26.1 ± 4.5	26.1 ± 4.6
WC (cm)	94 ± 8	94 ± 8	92 ± 8
SBP (mm Hg)	131 ± 15	129 ± 13	133 ± 8
DBP (mm Hg)	74 ± 12	73 ± 14	76 ± 15
FBS (mg/dL)	110 ± 18	112 ± 17	113 ± 24
FSI (μg/mL)	15.2 ± 17.1	17.1 ± 16.0	10.9 ± 10.6
HbA1c (%)	5.4 ± 0.4	5.5 ± 0.5	5.6 ± 0.6
HOMA-IR	4.1 ± 4.9	4.9 ± 5.1	3.0 ± 3.1
TGs (mg/dL)	148 ± 81	169 ± 94	147 ± 92
HDL-C (mg/dL)	51 ± 14	47 ± 13	55 ± 12
LDL-cho (mg/dL)	112 ± 23	114 ± 26	124 ± 31
IL-6 (pg/mL)	2.9 ± 3.9	6.9 ± 15.6	3.3 ± 4.9
hsCRP (mg/dL)	0.147 ± 0.195	0.114 ± 0.194	0.088 ± 0.101

Group B, Longevinex was administered between 3 and 6 months. BW indicates body weight; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood glucose; FSI, fasting serum insulin; LDL-cho, low-density lipoprotein cholesterol. Data are expressed as means ± SD.

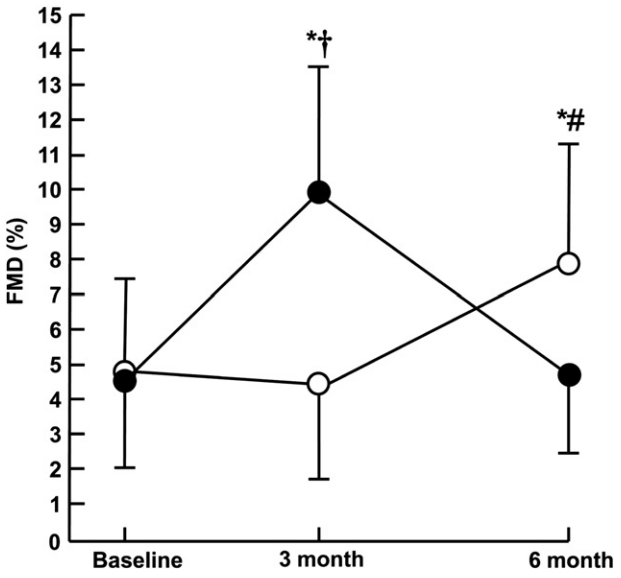

Fig. 1. Flow-mediated dilatation, or FMD, was measured as described in the text. The closed circles indicate the group A patients (n = 17) who received Longevinex for the first 3 months, whereas the open circles indicate group B patients (n = 17) who received Longevinex for the last 3 months. Each symbol represents the means ± SD. *$P < .01$ compared with baseline, $^{\dagger}P < .01$ compared with group B, $^{\#}P < .01$ compared with group A.

4. Discussion

The present study investigated the effect of a modified resveratrol formula, Longevinex, on the metabolic profile, inflammatory response, and endothelial function in patients with MetS. The most striking effect of Longevinex treatment in these patients was the increase in FMD, an established measure of endothelial function [18]. Thus, the present study supports the hypothesis that resveratrol improves endothelial function in human subjects, as has been previously demonstrated in a wide variety of animal models [7-9]. Although we evaluated FMD after chronic administration of Longevinex, resveratrol has been shown to improve endothelial function within 24 hours in obese individuals with mildly elevated blood pressure [19]. A salient finding of the present study is that the improvement of endothelial function was observed in patients whose disease conditions were already being managed by standard therapy for lifestyle-related disease.

Longevinex significantly improved FMD in patients who had already been receiving angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor blockers or statins, which are known to improve endothelial function, suggests that Longevinex may have either an additive or synergistic effect on endothelial function. Therefore, the present study suggests that Longevinex improves endothelial function in

patients with MetS through mechanism(s) distinct from the standard pharmacologic tools used for treatment of lifestyle-related disease.

The mechanism underlying the improvement of endothelial function by resveratrol has been extensively investigated in various animal models. Resveratrol is an activator of SIRT1. A role for SIRT1 in protecting against the development of atherosclerosis has recently been proposed [20]. The restoration of SIRT1 increases eNOS expression by the deacetylation of both lysine 496 and 506, indicating that SIRT1 directly regulates eNOS [21]. When apolipoprotein E (ApoE) knockout mice overexpressing endothelial cell-specific SIRT1 were fed a high-fat diet, these mice displayed blunted atherosclerosis due to enhanced eNOS expression and endothelium-dependent relaxation of the aorta, indicating a beneficial effect of SIRT1 as well as eNOS on atherogenesis. However, recent studies have called into question whether resveratrol directly activates SIRT1, raising the possibility that resveratrol acts on a target upstream of SIRT1 [22]. Resveratrol has been shown to activate the antioxidant transcription factor Nrf2 and protect endothelial cells from hyperglycemia and high-fat diet–induced apoptosis presumably through a reduction of mitochondria-derived reactive oxygen species [23].

It remains to be determined whether Nrf2 contributes to the resveratrol-induced upregulation of SIRT1 in endothelial cells and the resulting improvement of endothelial function.

Despite the apparent improvement in endothelial function, Longevinex did not ameliorate lifestyle-related diseases in our patients with MetS. It has been hypothesized that improvement of endothelial function might reverse insulin resistance and inflammatory response by inhibiting oxidative stress [24,25]. However, Longevinex had no significant effect on HOMA-IR or the inflammation markers, IL-6 and hsCRP. Because many, if not all, of the drugs coadministered with Longevinex in the present study ameliorate insulin resistance and the inflammatory response by inhibiting oxidative stress, these results suggest that the antioxidant effect had already been effectively realized by the conventional medical treatment. Indeed, the HOMA-IR and inflammatory markers already reached almost within the reference range at baseline.

The sample size in the present study may have been too small to unmask the potential anti-inflammatory effect of Longevinex. It is also possible that the duration of the Longevinex treatment was not sufficient to allow further amelioration of the lifestyle-related disease. Therefore, it is suggested that the beneficial effects of Longevinex on atherosclerosis and cardiovascular events need to be more comprehensively investigated in larger-sized clinical trials with longer follow-up periods.

In conclusion, Longevinex specifically improves endothelial function in subjects with MetS already been receiving standard therapy for lifestyle-related disease. Further studies are warranted to address whether long-term administration of Longevinex represents a novel antiatherosclerotic strategy by improving endothelial function in patients with MetS.

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