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RESEARCH ARTICLE

TA-65, A Telomerase Activator Improves Cardiovascular Markers in Patients with Metabolic Syndrome

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Abstract: ***Background*:** Telomerase Activator 65 (TA-65), a compound extracted from *Astragalus membranaceus* has been used in Chinese traditional medicine for extending lifespan. Scarce information exists on the effects of TA-65 on parameters of metabolic syndrome (MetS).

Methods: We recruited 40 patients with MetS to determine the effects of TA-65 on dyslipidemias, hypertension, and oxidative stress in this at-risk population. The study was a double-blind, randomized crossover design in which patients were allocated to consume either 16 mg daily of a TA-65 supplement or a placebo for 12 weeks. Following a 3-week washout, participants were allocated to the alternate treatment for an additional 12 weeks. Anthropometric and biological markers were measured at the end of each treatment. Plasma lipids, glucose, C-reactive protein (CRP), liver enzymes, and glycosylated hemoglobin were measured using a Cobas c-111. Inflammatory cytokines were measured by Luminex technology and markers of oxidative stress by the use of spectroscopy.

***Results*:** Compared to the placebo period, HDL cholesterol (HDL-C) was higher while body mass index, waist circumference, and the LDL/HDL ratio were lower ($p < 0.05$) during TA-65 treatment. In addition, plasma tumor necrosis factor-α (TNF-α) was lower during the TA-65 period ($p< 0.05$). Positive correlations were observed in changes between the placebo and the TA-65 periods in HDL-C and CRP ($r = -0.511$, $p < 0.01$), alanine aminotransferase ($r = -0.61$, $p < 0.001$) and TNF-α ($r = -0.550$, $p < 0.001$) suggesting that the favorable changes observed in HDL were associated with decreases in inflammation.

***Conclusion*:** TA-65 improved key markers of cardiovascular disease risk, which were also associated with reductions in inflammation.

Keywords: Telomerase activator, metabolic syndrome, inflammation, oxidative stress, HDL.

1. INTRODUCTION

In 1980, telomeres, a specialized tandem DNA repeat sequence (TTAGGG) which offers protection against chromosome degradation, were discovered [1]. The DNA polymerase cannot fully replicate the 3' end of linear DNA after each cell division, which would result in the continuous loss of coding DNA without the presence of telomeres at the end of the strand. Instead, telomeres are shortened with each DNA replication while coding DNA remains intact [2]. Telomere shortening is associated with cellular death and aging. However, telomere length can be maintained or increased by the addition of telomeric DNA, a process that is guided by the enzyme telomerase [2].

TA-65 is a single chemical entity extracted from the root of *Astragalus membranaceus*. This root extract has been used safely for hundreds of years in traditional Chinese medicine [3]. Several studies have shown beneficial effects of TA-65 in increasing telomerase activity and telomere length. For example, TA-65 has been shown to stimulate the rescue of short telomeres, both *in vitro* (in mouse embryonic fibroblasts) and *in vivo*, where a decreased number of very short telomeres were observed in those mice treated with TA-65 after 3 months [4]. These results suggest that *Astragalus* root extract regulates telomerase at the transcriptional level, probably via the Mitogen-Activated Protein Kinase (MAPK) pathway [8]. A more recent study conducted in 117 healthy subjects demonstrated that taking 250 U (equivalent to 8 mg) of TA-65 increased telomere length over a 12-month period while decreases in telomere length were observed with the placebo [5]. Moreover, other studies have also shown that TA-65 increases telomerase activity and increases telomere length [6, 7]. The herbal extracts of the root of *Astragalus membranaceus* and its fractions have not shown any toxicity or genotoxicity [8, 9]. Further, doses as high as 100g/kg in mice have not shown any adverse effects [1].

The chronic over-expression of inflammatory cytokines caused by the abundance of senescent cells may result in a variety of metabolic perturbations including diabetes [10], arteriosclerosis, and cardiovascular disease [11, 12]. In a study conducted on 114 human subjects who consumed 10-50 mg of TA-65 daily for 12 months, a significant reduction of the percent of senescent cytotoxic cells was also observed [13]. TA-65 has also been shown to have beneficial effects on several chronic conditions [14] including glucose intolerance and insulin resistance [10], cancer and immunity [11, 14], neural depression [15], age-related macular degeneration [16], and cardiovascular disease [17]. For example, Yesilada *et al*. isolated triterpene saponins from the roots of several *Astragalus* species and demonstrated a decrease in TNF-α production in peripheral blood cultures [18].

Although we have some information on the effects of TA-65 in clinical studies, to our knowledge the present study is the first evaluating outcomes in individuals with metabolic syndrome (MetS). MetS is a constellation of symptoms which double the risk for heart disease and quintuple the risk for diabetes mellitus [19]. MetS are characterized by central obesity, hypertension, hyperglycemia, and dyslipidemia in combination with oxidative stress and systemic inflammation [20]. There are many proposed strategies to

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improve the biomarkers of MetS including dietary interventions [21], increased physical activity [21], or the use of bioactive components that may target specific physiological pathways associated with the symptoms [21, 22].

The purpose of this clinical intervention was to evaluate the effects of TA-65 on the biomarkers of MetS. We hypothesized that compared to placebo, TA-65 would improve glucose metabolism, reduce dyslipidemias, increase antioxidant capacity, and reduce systemic inflammation in patients with MetS.

2. METHODS

2.1. Experimental Design

We recruited 40 men and women between the ages of 32-70 years who had MetS, defined as having any 3 or more of the following 5 characteristics: blood pressure (BP) $\geq$ 130/85 mm of Hg (either number, or use of antihypertensive medications); plasma glucose $\geq$ 100 mg/dL; triglycerides (TG) $\geq$ 150 mg/dL, waist circumference (WC) $\geq$ 88 cm for women or $\geq$ 102 cm for men, and HDL cholesterol (HDL-C) < 40 mg/dL for men or < 50 mg/dL for women. Ninety-four participants were interviewed and 40 met the inclusion criteria. Subjects were allocated to consume 16 mg (2 capsules) of TA-65 (n= 20) or placebo (n = 20) for 12 weeks. After 3 weeks of washout, they were allocated to the alternate treatment. This was a double-blind randomized study; both the subjects and the investigators were blinded to the treatment. TA-Sciences prepared the capsules, which were identical, containing either the active ingredient or the placebo and they were labeled A or B. The randomization was done by the Company. All subjects started with A and then followed with B; however they were randomized, for example subject 1 started with the active ingredient, subject 2 with placebo, subjects 3 and 4 with TA-65, subjects 5 and 6 with placebo, et. The investigators were not unblinded to the intervention until all assays were fully completed.

The period between recruiting and finishing the last intervention lasted 24 months, from August 2015 to August 2017. One patient declined to continue due to stomach problems unrelated to the study and 2 more were removed due to sudden increases in plasma glucose, which were above the required criteria. Thirty-seven subjects (11 men and 26 women) completed the whole intervention (Fig. **1**).

Criteria for exclusion were: participants with a BMI $\geq$ 40 kg/m^2, current or past diagnosis of liver or renal disease, diabetes, cancer, stroke, heart disease, severe infectious or autoimmune diseases, and pregnant or lactating women. Other exclusion criteria were use of any glucose-lowering medications or supplements, use of immunosuppressants, anticoagulants, methadone, suboxone, MAO inhibitors, or lithium. Participants with fasting plasma TG $\geq$ 500 mg/dL, glucose $\geq$ 126 mg/dL, or BP $\geq$ 145/100 mm Hg were also excluded. The study was approved by the University of Connecticut Institutional Review Board under protocol H14-278. Subjects were consented prior to screening. The study was registered at Clinicaltrials.gov, protocol # NCT02531334.

2.2. Supplement Manufacturing and Processing

TA-65, a single chemical entity was purified from the root of *Astagalus membranaceus* and subsequently assayed by high-performance liquid chromatography for the content of the proprietary single-molecule TA-65. The product was encapsulated using the excipients silicone dioxide and cellulose, which has a stability of 24 months. The placebo was a vegetable capsule (hydroxypropyl methylcellulose) containing silicon dioxide, water, and cellulose.

2.3. Anthropometrics and Blood Pressure

Weight was measured to the closest 0.1 kg and height to the closest 0.5 cm on a portable stadiometer/scale to calculate BMI (kg/m^2). WC was measured at the top of the iliac crest to the nearest 0.5 cm, using a flexible measuring tape placed against the skin. BP was determined on the right arm using an Omron automated BP cuff as described by Pickering *et al*. [23]. BP and WC were measured in triplicate by the same individual to account for variability.

2.4. Dietary Records

Subjects were asked to provide 3-day dietary records during each arm of the intervention to ensure consistent dietary habits throughout the study. Dietary intake data were analyzed using Nu-

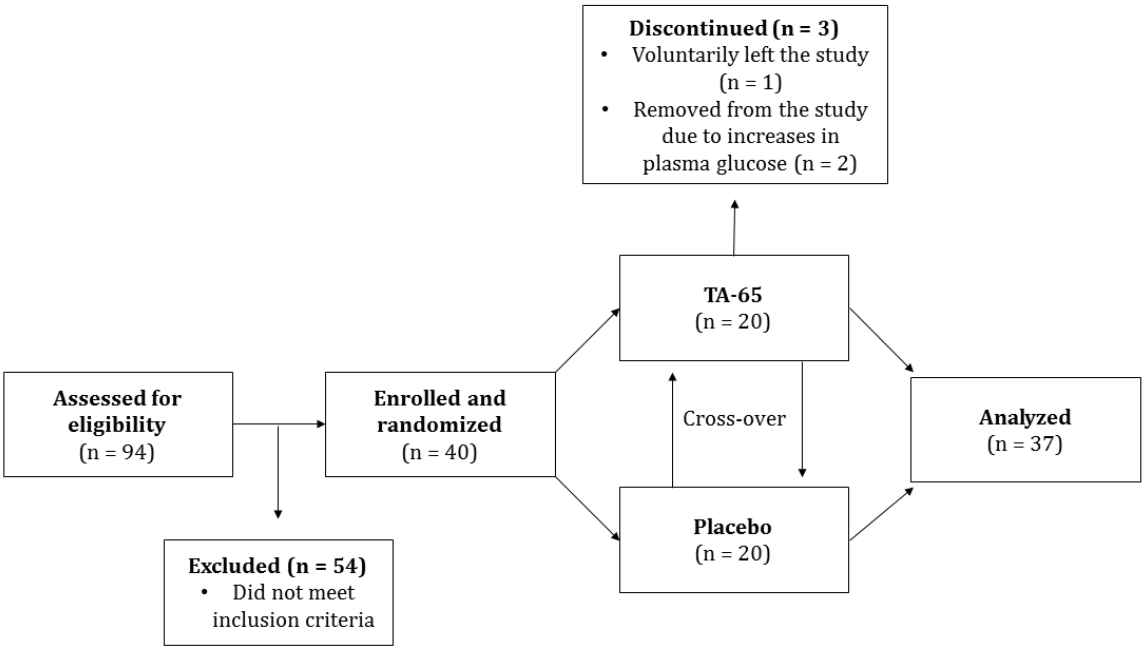

Fig. (1). Flow chart the intervention in which n = 40 individuals with metabolic syndrome were randomly assigned to TA-65 or placebo for 3 months and after a 3 week washout, they were crossed over to the alternate interventions. Nine-four subjects were screened and forty individuals participated. 1 voluntarily dropped the study for personal reasons and 2 were removed due to increases in plasma glucose (not related to the study).

trition Data System for Research software (2013) developed by the Nutrition Coordinating Center (NCC), University of Minnesota, Minneapolis, MN.

2.5. Plasma Lipids, Glucose, Glycosylated Hemoglobin, Insulin, and Biomarkers of Inflammation

Fasting plasma (40mL) was collected from the antecubital vein at baseline and the end of each intervention period, and plasma was isolated by centrifugation for analysis. Total cholesterol (TC), triglycerides (TG), glucose, HDL-C, C-reactive protein (CRP), liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and glycosylated hemoglobin (HbA1c) were determined using the Cobas c-111 Analyzer (Roche Diagnostics, Indianapolis, IN). LDL cholesterol (LDL-C) was calculated by the Friedewald equation as previously reported [24]. Insulin was measured by ELISA according to manufacturer instructions (Crystal Chem, Elk Grove Village, IL). Inflammatory cytokines TNF-α, monocyte chemoattractant protein-1 (MCP-1), interleukin (IL)-6, and IL-8 were determined by use of the LINCOplex: Multiplex Biomarker Immunoassay for Luminex Instrumentation/xMAP Technology (Luminex 200 System, Austin, TX). The technique uses fluorescently labeled microsphere beads with antibodies to each individual cytokine [25].

2.6. Antioxidants

Glutathione peroxidase (GPx), superoxide dismutase (SOD), total antioxidant capacity (TAC), catalase, and 8-isoprostanes were measured in plasma samples using commercially available kits (Cayman Chemical Company, Ann Arbor, MI). GPx activity was measured indirectly by a coupled reaction with glutathione reductase based on the recycling of oxidized glutathione to reduced glutathione [26]. SOD activity was assessed by measuring the extent of superoxide radical generation by xanthine oxidase and hypoxanthine [26]. TAC was measured by assessing the extent of oxidation of 2,2'-Azino-di-3-ethylbenzthiazoline sulfonate. Catalase activity was assessed by measuring formaldehyde production in the presence of hydrogen peroxide [27]. 8-isoprostanes were measured by ELISA to examine the competitive binding of 8-isoprostane and an 8-isoprostane-acetylcholinesterase conjugate to 8-isoprostane-specific rabbit antiserum binding sites [27]. Lastly, measurement of thiobarbituric acid reactive substances (TBARS) was assessed as a marker of lipid peroxidation in plasma samples using a commercial kit (R&D Systems, Minneapolis, MN) and absorbance was measured using a BioTek Synergy 2 Multi-Mode Microplate Reader.

2.7. Lymphocyte Telomere Length

Telomere length (base pairs) was measured in lymphocytes in whole blood at baseline and at the end or the TA-65 and placebo periods by Repeat Diagnostics Inc. in North Vancouver, BC, Canada.

2.8. Statistical Analysis

Differences in anthropometric and plasma biomarkers, inflammatory markers, and oxidative stress parameters were compared between the TA-65 and the placebo periods using Student's paired t-test. Data are presented as mean ± SD. Pearson correlations were calculated between changes between supplement and placebo on plasma HDL-C and changes in inflammatory markers. Level of significance was set at $p < 0.05$.

3. RESULTS

3.1. Initial Characteristics

The initial characteristics of the subjects are presented in Table **1**. Participants had a mean BMI of 32.3 ± 2.7 kg/m^2 placing them in the obesity category. In terms of MetS characteristics, all subjects (100%) fit the criteria for WC, 63% either had high systolic BP, high diastolic BP, or both, 70% were hyperglycemic, 48% had elevated plasma TG, and 43% had low HDL-C. Interestingly 50% of subjects had LDL cholesterol values higher than 100 mg/dL although this parameter is not a component of the MetS. Mean plasma insulin and HbA1c were within normal ranges.

Table 1. Initial characteristics of subjects (n = 40) with metabolic syndrome.

Parameter	Values
Age (years)	52.4 ± 9.5
BMI (kg/m^2)	32.3 ± 3.7
Waist Circumference (cm)	113.9 ± 13.2 for men and 105.1 ± 8.9 for women
Systolic BP (mm Hg)	126.3 ± 12.5
Diastolic BP (mm Hg)	84.1 ± 7.9
Total Cholesterol (mg/dL)	183.6 ± 33.9
LDL-C (mg/dL)	104.5 ± 30.2
Triglycerides (mg/dL)	136.0 ± 71.5
HDL-C (mg/dL)	40.1 ± 9.2 for men and 56.1 ± 19.0 for women
Glucose (mg/dL)	105.7 ± 9.9
HbA1c (%)	5.6 ± 0.5
Insulin (pmol/L)	52.4 ± 30.0

3.2. Dietary Intake

Results of the dietary intake assessment are presented in Table **2**. There were no differences in macronutrient intake, type of fatty acids, dietary fiber, added sugar, and carotenoids throughout the intervention. Overall, subjects consumed high fat, low fiber diets. There was a high degree of interindividual variation in carotenoid consumption, however, participants remained consistent between dietary periods suggesting that diet had no effect on the biomarkers that were measured.

3.3. Plasma Lipids, Glucose, Glycosylated Hemoglobin, Insulin, and Biomarkers of Inflammation

As indicated in Table **3,** subjects had lower BMI and WC after the supplement period ($p < 0.05$). In addition, HDL-C was higher ($p < 0.05$) and the LDL-C/HDL-C ratio ($p < 0.05$) ($P < 0.05$), a key marker of cardiovascular disease risk, was lower in participants following the TA-65 period. No changes were observed in blood pressure, plasma TG, or in parameters of glucose metabolism (plasma glucose, HbA1c, or insulin). In addition, there were no changes in ALT, AST, CRP, IL-6, IL-8 or MCP-1 between treatments (Table **4**). However, compared to the placebo period, TNF-α was lower following the intake of TA-65. In addition, there were strong negative correlations between the changes observed in HDL-C between the supplement and the placebo periods and changes in CRP, liver enzymes and TNF-α, suggesting a protective role of HDL-C against inflammation (Table **5**).

3.4. Antioxidants

There were no significant changes in GPx, SOD, catalase, TAC, TBARS, or 8-isoprostanes. However, we observed a lower TAC/8-isoprostanes ratio in participants during the TA-65 period compared to placebo ($p < 0.05$) (Table **6**).

Table 2. Dietary daily intake of participants with metabolic syndrome (n = 37) during the TA-65 and the placebo periods.

Dietary Component	TA-65	Placebo
Total Energy (kcal)	1713 ± 463	1754 ± 501
Fat Energy (%)	40.1 ± 6.4	38.9 ± 6.9
Carbohydrate Energy (%)	38.4 ± 8.3	40.2 ± 7.5
Protein Energy (%)	18.3 ± 4.4	17.5 ± 3.6
Cholesterol (mg)	287.2 ± 124.7	286.9 ± 145.9
SFA (g)	27.5 ± 10.6	25.9 ± 9.9
MUFA (g)	27.0 ± 10.5	27.7 ± 10.1
PUFA (g)	16.2 ± 5.9	16.9 ± 10.1
Omega-3 Fatty Acids (g)	1.85 ± 0.84	1.78 ± 1.65
Trans Fatty Acids (g)	2.47 ± 1.17	2.63 ± 1.47
Added Sugar (g)	32.9 ± 22.9	34.2 ± 29.3
Total Fiber (g)	16.3 ± 5.9	17.5 ± 7.8
Soluble Fiber (g)	5.7 ± 2.3	6.2 ± 2.3
Insoluble Fiber (g)	10.2 ± 4.6	11.7 ± 6.1
Glycemic Index	58.8 ± 5.4	59.2 ± 5.3
Glycemic Load	92.5 ± 43.1	98.8 ± 38.6
β-Carotene (μg)	2641 ± 2837	3321 ± 2575
α-Carotene (μg)	348 ± 442	564 ± 559
Cryptoxanthin (μg)	120 ± 362	142 ± 287
Lycopene (μg)	3317 ± 3073	3679 ± 3770
Lutein + Zeaxanthin (μg)	2416 ± 4393	2385 ± 2773

[1]Values are expressed as mean ± SD. There were no significant differences in dietary intake between the TA-65 and the placebo period. All p values were > 0.05.

3.5. Lymphocyte Telomere Length

Telomere length did not change significantly over time. Fig. **(2)** depicts the values for telomere length from baseline until the end of the intervention in those subjects who started with TA-65 (n =17) (panel A) and for those who started with placebo (Panel B) (n =20). Although there were no significant differences, subjects who started with TA-65 maintained telomere length even after 6 months where only a 1% decrease in telomere length was observed (Panel A). In contrast to those who started with placebo had a 2% decrease in telomere length, which was not further decreased but was maintained when they switched to TA-65 (panel B).

4. DISCUSSION

In this study, we have demonstrated that TA-65 exerts a protective effect in individuals with MetS as documented by the lower BMI, WC, LDL-C/HDL-C ratio, plasma TNF-α, and the higher HDL-C and TAC/8-isoprostanes ratio following 12-week of TA-65 treatment as compared with placebo. All these changes occurred independent of dietary intake, since diet was maintained constant through the intervention. The results also show that telomere length was sustained from initial after 3 or 6 months of taking the

Table 3. Anthropometric and plasma biomarkers of participants with metabolic syndrome (n = 37) after consuming TA-65 or placebo for 12 weeks[1].

Parameter	TA-65	Placebo	P Value
BMI (kg/m^2)	32.6 ± 3.8[a]	32.9 ± 3.9[b]	0.014
Waist Circumference (cm)	108.9 ± 10.1[a]	109.8 ± 10.8[b]	0.044
Systolic BP (mm Hg)	123.8 ± 10.5[a]	124.9 ± 13.5[a]	NS[2]
Diastolic BP (mm Hg)	83.6 ± 8.0[a]	83.8 ± 8.9[a]	NS
Total Cholesterol (mg/dL)	178.4 ± 32.8[a]	182.7 ± 40.1[a]	NS
LDL-C (mg/dL)	100.5 ± 30.1[a]	104.1 ± 36.3[a]	NS
HDL-C (mg/dL)	52.9 ± 21.5[a]	49.3 ± 17.8[b]	0.042
LDL-C/HDL-C Ratio	2.15 ± 0.90[a]	2.43 ± 1.14[b]	0.031
Triglycerides (mg/dL)	124.8 ± 67.3[a]	131.2 ± 62.7[a]	NS
Glucose (mg/dL)	104.5 ± 13.3[a]	103.6 ± 11.7[a]	NS
Insulin (pmol/L)	58.3 ± 37.7[a]	57.9 ± 43.4[a]	NS
HbA1c (%)	5.54 ± 0.45[a]	5.54 ± 0.48[a]	NS

[1] Values are expressed as mean ± SD.
[2] NS= Non-significant

Table 4. Inflammatory biomarkers in participants with metabolic syndrome (n = 37) after consuming TA-65 or placebo for 12 weeks[1].

Parameter	TA-65	Placebo	P Value
ALT (U/L)	31.2 ± 11.1	34.5 ± 18.7	NS[2]
AST (U/L)	26.2 ± 7.1	28.9 ± 21.8	NS
CRP (mg/dL)	0.39 ± 0.41	0.41 ± 0.44	NS
TNF-α (pg/mL)	5.5 ± 2.4	6.4 ± 3.1	0.040
IL-6 (pg/mL)	5.42 ± 1.13	5.63 ± 0.91	NS
IL-8 (pg/mL)	6.9 ± 0.8	7.4 ± 1.4	NS
MCP-1 (pg/mL)	112.0 ± 31.4	112.9 ± 29.5	NS

[1] Values are expressed as mean ± SD
[2] NS=Non-significant

Table 5. Correlations between changes in HDL and biomarkers of inflammation between the placebo and the TA-65 periods.

	Correlation	P value
ALT	-0.610	0.0001
AST	-0.445	0.001
CRP	-0.511	0.001
TNF-α	-0.550	0.0001

Table 6. Measurements of antioxidant capacity in subjects with metabolic syndrome (n = 37) after consuming TA-65 or placebo for 12 weeks[1].

Parameter	TA-65	Placebo	P Value
TAC (mM Trolox equivalents)	2.1 ±1.7	1.7 ± 1.6	NS[2]
8-isoprostanes (pg/mL)	57.4 ± 29.4	65.8 ± 34.0	NS
TBARS (μM)	0.151 ± 0.025	0151 ± 0.026	NS
Catalase (nmol/min/mL)	16.0 ± 11.1 0.16	17.2 ± 7.2	NS
SOD (U/mL)	2.2 ± 0.8	2.1 ± 1.1	NS
GPx (nmol/min/mL	159.7 ± 39.6	155.7 ± 42.6	NS
TAC/8-isoprostanes (pg/mL)	0.049 ± 0.052	0.032 ± 0.027	0.049

[1] Values are expressed as mean ± SD.

[2] NS=Non-significant

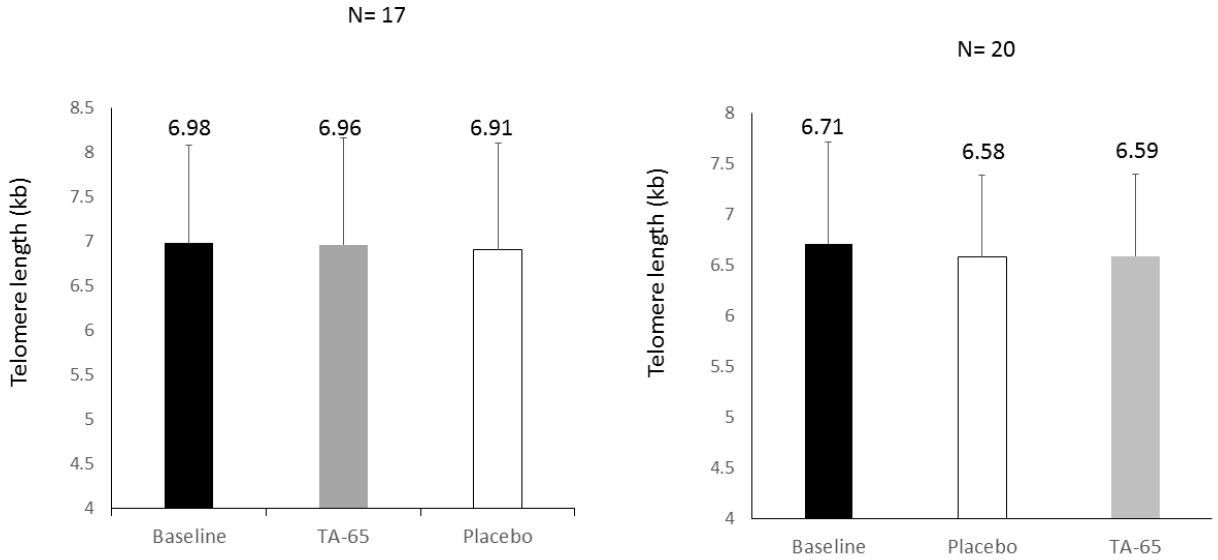

Fig. (2). Comparisons of Telomere length for those subjects who started the intervention with TA-65 and then were switched to placebo (n = 17) (panel A) and for those subjects who started the intervention with placebo and then switched to TA-65 (n =20). The dark values on top of the bars represent the mean telomere length for that specific time.

supplement indicating an extended effect of TA-65 in maintaining telomere length Leukocyte telomere length has been identified as a biomarker of aging. The most characterized function of TA-65 is its ability to decrease the shortening of telomeres during DNA transcription [13, 14, 28]. It is this function that associates TA-65 with increases in life span as has been shown in cell studies, animal studies and clinical interventions [11, 29]. Boccardi *et al.* [30] on the other hand, reported that a healthy diet as exemplified by the Mediterranean diet promoted health-span by maintaining rather than increasing telomere length suggesting that both maintenance and increases of telomere length are important determinants of aging. Other studies have also shown that the main functions of telomerase activity are slowing telomere attrition by preserving the proliferative potential of stem cells [31]. It is also well established that cell senescence is related to the production of inflammatory mediators [32], reduction of the body's intrinsic antioxidant protections [33], increases in dysregulation of the insulin receptor leading to insulin resistance [34], and dyslipidemias [35]. Thus, we designed this study to evaluate the effectiveness of TA-65 in alleviating these conditions in individuals with MetS.

Central obesity is the most common feature of MetS and is associated with increased release of free fatty acids into circulation, which targets specific organs leading to dyslipidemia, insulin resistance, and inflammation [36]. It was interesting to note in this study that participants had both lower BMI and WC during the TA-65 period, which was small but clinically significant. At this point, it is uncertain why subjects had lower BMI and WC following TA-65 intake. However, participants reported a non-significant decrease in total calories and in carbohydrate intake, where high intake of both is highly associated with increased WC [37]. Therefore, we speculate that TA-65 may have affected the behavior of our participants and that they followed a healthier eating pattern during the TA-65 period, which resulted in the positive effects on WC. A study by Daubenmier *et al.* [38] reported that being enrolled in a mindfulness intervention pilot study affected telomerase activity in a positive manner and they found a positive correlation between restrained eating and telomerase activity.

Clinical studies have reported that intake of TA-65 results in improvement of plasma lipids [10, 39]. In the current study, although no differences in TC or TG were observed between TA-65

and placebo, HDL-C was higher at the end of TA-65 and, consequently, there was a concomitant decrease in the LDL-C/HDL-C ratio, a very well- known biomarker of cardiovascular disease risk [40]. Other studies have reported lower hepatic lipid accumulation in aged mice treated with TA-65 compared to placebo [10], which suggests the effectiveness of TA-65 in decreasing triggers of inflammation.

Another key findings in the present study were the lower levels of plasma TNF-α after TA-65 treatment, which are in agreement with the observed decreases in this cytokine following incubation of cells with triterpenes isolated from several *Astragalus* species [18]. As discussed before, aging is associated with increases in inflammatory cytokines including TNF-α, IL-6, and others, which have also shown disorders in mesenchymal stem cells [41]. Telomere shortening is related to inflammation and the associated chronic diseases including cardiovascular diseases, diabetes, osteoporosis, and cancer [42]. The lowering of TNF-α was an important finding because it correlates with decreased inflammation. It has been demonstrated that TNF-α induces insulin resistance via the p38 MAPK pathway [43]. Thus the decreases of this inflammatory cytokine during the TA-65 period appear to be important in this population with MetS.

The catalytic subunit of telomerase, telomerase reverse transcriptase (TERT), has also been found to act as a regulator of mitochondrial-derived reactive oxygen species (ROS) [44]. Decreases in ROS have been observed when TERT is activated pharmacologically [45] while deletion of TERT in cell cultures and animal models has been shown to increase mitochondrial ROS [46]. The current study documents a role of TA-65 in protecting against oxidative stress. Although no significant changes were observed in the protective enzymes for oxidation in this study, there was a trend for TAC values to be higher and for the 8-isoprostanes, an important marker of oxidative stress, to be lower during the TA-65 period, which resulted in a significant decrease in TAC/8-isoprostanes ratio. These results demonstrate an improvement in the body's total antioxidant capacity versus oxidative biomarkers by TA-65 intervention.

CONCLUSION

In conclusion, 12-week TA-65 supplementation exerted some protective effects against dyslipidemia, inflammation, and oxidative stress, all of which are metabolic abnormalities associated with MetS. Because MetS is a precursor to the development of type-2 diabetes or heart disease, dietary strategies for reversal of MetS biomarkers is a preventative treatment for this population. Therefore, TA-65 supplementation, in combination with lifestyle changes aimed at an appropriate diet and exercise, appears to be a good alternative for improving symptoms of MetS and reducing future health complications in this at-risk population.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Review Board (IRB) of the University of Connecticut and informed consent was obtained from all subjects prior to the initiation of the study.

HUMAN AND ANIMAL RIGHTS

Human rights were protected by the University of Connecticut under protocol IRB H14-278.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The study was supported by a grant from TA Sciences, Inc. awarded to MLF. All the other authors do not have a conflict of interest.

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The authors wish to thank the late Dr. Jeffrey Anderson for his medical advice for our subjects and for screening all medications for inclusion/exclusion criteria. MLF designed the study, analyzed all data, and wrote the final version of this manuscript; MST recruited patients, assessed inclusion/exclusion criteria, performed blood draws and contributed to the analysis of diet records, plasma lipids and the parameters of glucose metabolism; BSL recruited patients, performed blood draws and measured plasma lipids and inflammatory cytokines and contributed to data analysis and interpretation; DMD and AM contributed significantly to patient recruitment, blood draws, standardization of techniques, and data analysis; MM performed all assays related to oxidative stress; OKC provided advice on the experimental design and interpreted all data related to oxidative stress measurements; AGN, HA and IMV helped in subject interviewing, blood draws, and measurement of liver enzymes and glycosylated hemoglobin.

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