Original Article

Availability of dietary secoisolariciresinol diglucoside on borderline blood cholesterol level in men: a randomized, parallel, controlled, double-blinded clinical trial

Kouta Ookoshi, Kento Sawane, Satoshi Fukumitsu,* and Kazuhiko Aida

Innovation Center, Central Research Laboratory, NIPPN Corporation, 5-1-3 Midorigaoka, Atsugi, Kanagawa 243-0041, Japan

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Borderline low-density lipoprotein cholesterol levels (120–139 mg/dl) increase the risk of cardiovascular disease. Therefore, the use of functional dietary nutrients is expected to control blood low-density lipoprotein cholesterol levels. This study aimed to evaluate the effect of dietary secoisolariciresinol diglucoside on blood cholesterol in healthy adults with borderline low-density lipoprotein cholesterol levels. A randomized, parallel, controlled, double-blinded clinical trial was performed for participants with borderline low-density lipoprotein cholesterol levels, for 12 weeks with secoisolariciresinol diglucoside (60 mg/day) or placebo. Lipid profile [low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio, total cholesterol, and triglycerides] and liver disease risk markers were measured at weeks 0, 4, 8, and 12. Analyzing 36 participants in each group revealed a significant interaction between treatment and time, indicating reduced low-density lipoprotein cholesterol ($p = 0.049$) and total cholesterol ($p = 0.020$) levels in secoisolariciresinol diglucoside-receiving men but not women. However, no significant differences were observed in other markers regardless of gender. The results suggest that a daily intake of 60 mg of secoisolariciresinol diglucoside lowers low-density lipoprotein cholesterol and total cholesterol levels in men with borderline low-density lipoprotein cholesterol, proposing secoisolariciresinol diglucoside potential as a functional dietary nutrient for cardiovascular disease prevention. This study was registered in the UMIN-CTR database (UMIN000046202).

***Key Words*: LDL cholesterol, secoisolariciresinol diglucoside, clinical trial, cardiovascular disease, functional dietary nutrient**

Dyslipidemia is a major risk factor for various cardiovascular diseases, and its incidence has increased globally over the past 30 years, particularly in developed countries, including Japan.[1] In dyslipidemia, hypercholesterolemia is strongly associated with increased cardiovascular disease risks.[1] The Japanese guideline "Guideline for Prevention of Arteriosclerosis Diseases" reported that an individual with hypercholesterolemia with low-density lipoprotein cholesterol (LDL-C) level >140 mg/dl has an increased risk of coronary artery disease (CAD) by two times or more.[2] These guidelines established LDL-C as the major risk factor for cardiovascular diseases and suggested the importance of providing more direct approaches toward controlling LDL-C.

In addition to that in individuals with hypercholesterolemia, increased CAD risk was noted in those with blood LDL-C levels of 120–139 mg/dl. In the "Guideline for Prevention of Arteriosclerosis Diseases", individuals with LDL-C levels of 120–139 mg/dl were categorized as "borderline" whose CAD risk was higher than that of the population with LDL-C levels <120 mg/dl.[2] This guideline also suggests the importance of individuals with LDL-C at borderline levels to control blood cholesterol levels.

The use of functional dietary nutrients is attracting attention.[3] For example, lycopene, which is a carotenoid particularly abundant in tomatoes, reduced LDL-C levels in individuals with LDL-C levels from 120 to 160 mg/dl, when compared with lycopene-free placebo control.[4] Additionally, the dietary intake of cacao polyphenols has shown beneficial effects on blood cholesterol levels in healthy men.[5] Therefore, using functional dietary nutrients is an effective strategy for managing blood cholesterol levels in healthy or borderline individuals.

Secoisolariciresinol diglucoside (SDG) is a class of plant-derived phenolic compounds that are specifically abundant in flaxseed.[6] Accumulating evidence has shown that SDG undergo microbial conversion in the gut in the order secoisolariciresinol (SECO), didemethyl-SECO, and enterolignans [enterodiol (ED) and enterolactone (EL)] and acquires or enhances their physiological activities, such as estrogen receptor-stimulating activity.[7,8] Moreover, besides estrogenic activity, enterolignans also regulate lipid metabolism, such as regulating adipogenesis-related gene expression in adipocytes,[9,10] inhibiting adipocyte differentiation,[11] reducing triglyceride (TG) uptake in hepatoma cells,[10] and upregulating LDL receptor activity in HepG2 cells.[12] Therefore, these results suggest that dietary SDG has beneficial effects on lipid metabolism through its conversion to enterolignans. Indeed, several animal studies have indicated the involvement of dietary SDG in lipid metabolism. For example, dietary intake of SDG alleviates blood cholesterol levels in high-fat diet-induced hyperlipidemic mice and rats[9,13] and high cholesterol diet-induced hypocholesterolemic rats.[14]

Furthermore, the effect of SDG on blood lipid profiles has been evaluated through human intervention studies in addition to biological and animal studies.[15,16] Notably, dietary SDG (500 mg/day) did not ameliorate blood cholesterol levels in post-menopausal women [LDL-C 146 ± 39 mg/dl (mean ± SD)][17] and patients with type 2 diabetes (LDL-C >140 mg/dl).[18] In contrast, SDG (600 mg/day) reduced blood LDL-C levels in male patients with hypercholesterolemia (LDL-C >140 mg/dl).[19] Moreover, SDG (100 mg/day) improved LDL-C and hypercholesterolemia-

*To whom correspondence should be addressed.
E-mail: sfukumitsu@nippn.co.jp

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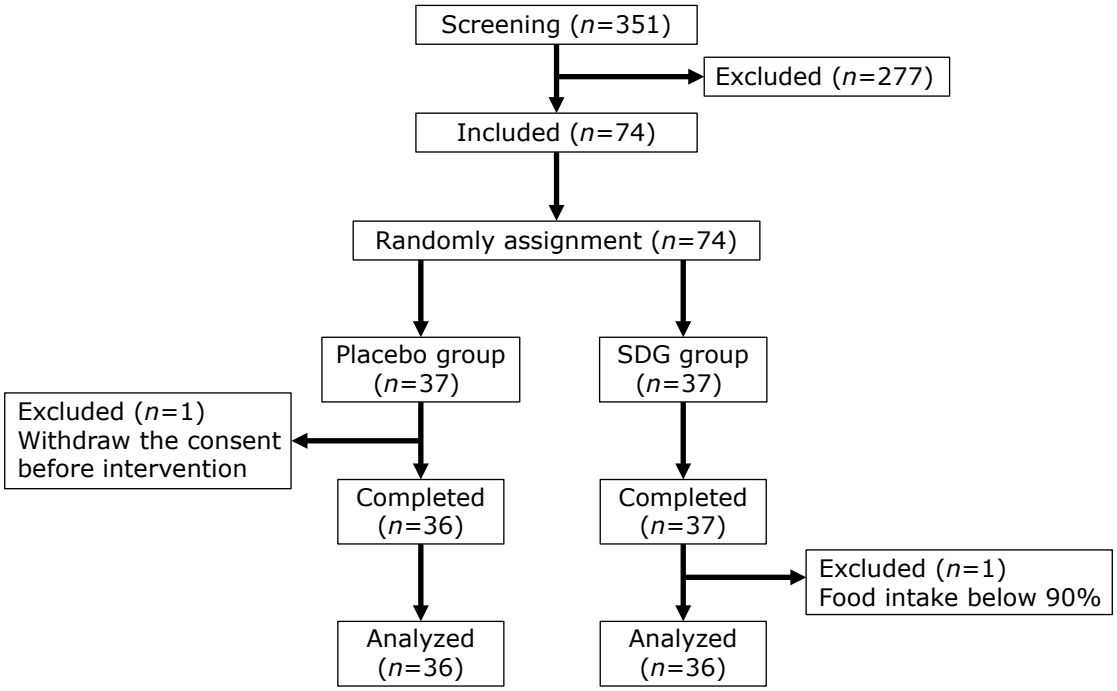

Fig. 1. Flow chart of participant selection.

derived increased hepatic disease risk factors in Japanese men with moderate hypercholesterolemia (LDL-C 120–140 mg/dl).[20] These studies indicated that the effect of SDG on blood cholesterol levels depends on participant characteristics (for example, baseline lipid profile, age, and sex) that may also affect effective quantity of SDG intake. Although SDG's effect has been examined in several individuals and in various intake quantity, its effect in borderline populations (LDL-C 120–139 mg/dl) have not been well evaluated. Additionally, the difference in efficacy between sexes has not been examined in populations with similar lipid profiles. Therefore, comprehensively demonstrating its efficacy could clarify whether SDG can contribute to blood cholesterol control in populations with borderline cholesterol levels.

This study aimed to evaluate the effect of dietary SDG (60 mg/day) on blood cholesterol control in participants with LDL-C with borderline levels and to compare effects between sexes. Participants with blood LDL-C levels from 120 to 139 mg/dl were recruited and subjected to the intervention study with a daily intake of SDG or placebo for 12 weeks. Furthermore, blood cholesterol levels were measured at 0, 4, 8, and 12 weeks, and the effect of SDG intake was assessed.

Materials and Methods

Ethics for the clinical study. The study was conducted in accordance with the Declaration of Helsinki and other nationally valid regulations and guidelines. Additionally, informed consent was obtained from all participants. The study protocol was approved by the Ethics Committee of NIPPN Corporation (Atsugi, Kanagawa, Japan, permission number: 21-02) and the Sapporo Yurinokai Hospital Clinical Trial Review Committee (Sapporo, Hokkaido, Japan, permission number: 2021-019). All experiments were conducted by the Clinical Creative Corporation (Sapporo, Hokkaido, Japan) and the Sapporo Yurinokai Hospital. The trial was registered at www.umin.ac.jp/ctr/index.htm (registration date: 27/01/2022, registration number: UMIN000046202).

Study participants. Study participants were selected from 351 candidates. Informed consent was obtained from all participants. The inclusion criteria were as follows: fasting LDL-C level 120–139 mg/dl, fasting high-density lipoprotein cholesterol (HDL-C) level >40 mg/dl, 20–65 years of age, no flaxseed allergy, concern about maintaining healthy blood vessels, no binge drinking and excessive exercise during the study period, and leading the same lifestyle (diet and exercise, among others) as before the study period, and signing the consent form. The exclusion criteria were as follows: pregnancy or planning to get pregnant, breastfeeding, participating in other clinical trials within 3 months before consent, or history of severe illness (for example, diabetes and liver, kidney, and heart diseases), flaxseed or SDG consumption, and taking medications and foods that affect lipid metabolism. We also excluded participants for whom the doctor had determined not to participate. After screening, 74 healthy Japanese individuals (40 men and 34 women, aged 20–65 years) were enrolled. Figure 1 shows the flow chart of participant screening.

Test diet. NIPPN Corporation provided the flaxseed lignan (40% SDG), and test diets were obtained from Sunsho Pharmaceutical Co. Ltd. (Fuji, Japan). The intervention group's diet contained cyclodextrin, silicon dioxide, calcium stearate, and flaxseed lignan (30 mg SDG/1 capsule). Conversely, flaxseed lignan was replaced with cyclodextrin in the placebo group. Both diets are provided as capsules and could not be distinguished on appearance or smell.

Study design. A randomized, controlled, double-blinded, parallel-group dietary intervention trial was conducted. The 74 participants were allocated into the SDG and placebo groups ($n = 20$ for men and $n = 17$ for women in both groups, respectively) at a 1:1 ratio using a stratified randomization method, with gender and LDL-C level at the screening test as allocation factors. An allocation table was sealed, and kept securely under the control of the study director to maintain blinding. For 12 weeks, participants consumed 2 capsules daily, which is equivalent to 60 mg or 0 mg SDG. The participants were encouraged to maintain their lifestyle, including dietary patterns and physical activity levels. Blood and urine samples were collected 0, 4, 8, and 12 weeks after 12-h fasting. Serum samples were collected

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Table 1. Baseline characteristics of the study population

	Total	Placebo group	SDG group
n	72	36	36
Male	38	19	19
Female	34	17	17
Age (years)	46.15 (10.02)	44.08 (10.05)	48.22 (9.70)
- Male (years)	46.13 (9.34)	47.26 (7.81)	45.00 (10.75)
- Female (years)	46.18 (10.88)	40.53 (11.26)	51.82 (7.05)
LDL-C (mg/dl)	128.96 (6.05)	129.56 (6.15)	128.36 (5.98)
HDL-C (mg/dl)	66.69 (15.08)	64.72 (13.41)	68.67 (16.54)
L/H ratio	2.04 (0.50)	2.09 (0.49)	1.99 (0.51)
TC (mg/dl)	208.38 (16.64)	206.97 (14.84)	209.78 (18.37)
TG (mg/dl)	85.90 (45.88)	88.50 (53.73)	83.31 (37.01)

Data are expressed as means (SD). SDG, secoisolariciresinol diglucoside; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; L/H, LDL-C/HDL-C; TC, total cholesterol; TG, triglyceride.

Table 2. Overview of lipid profiles of all participants at each endpoint and changes from 0 weeks

	0 week	4 weeks	8 weeks	12 weeks	Change 0 to 4 weeks	Change 0 to 8 weeks	Change 0 to 12 weeks	*p* (treatment × time)
	Placebo group SDG group	Placebo group SDG group	Placebo group SDG group	Placebo group SDG group	Placebo group SDG group	Placebo group SDG group	Placebo group SDG group	
LDL-C (mg/dl)	121.89 (15.10) 127.08 (16.66)	123.39 (15.43) 122.33 (16.76)	123.03 (17.12) 124.14 (14.33)	117.75 (17.47) 122.61 (16.73)	1.50 (12.33) –4.75 (13.36)	1.14 (15.00) –2.94 (13.52)	–4.14 (14.08) –4.47 (15.15)	0.164
HDL-C (mg/dl)	63.44 (15.27) 69.08 (16.43)	62.22 (13.86) 67.14 (16.04)	62.22 (13.64) 66.64 (16.67)	59.44 (12.83) 64.89 (15.59)	–1.22 (6.56) –1.94 (6.11)	–1.22 (6.82) –2.44 (5.74)	–4.00 (6.73) –4.19 (7.83)	0.844
L/H ratio	2.01 (0.48) 1.94 (0.54)	2.09 (0.58) 1.93 (0.55)	2.08 (0.60) 1.98 (0.56)	2.09 (0.62) 2.00 (0.59)	0.08 (0.28) –0.01 (0.21)	0.07 (0.30) 0.04 (0.21)	0.08 (0.26) 0.05 (0.20)	0.387
TC (mg/dl)	199.72 (24.50) 210.81 (21.30)	200.31 (20.84) 206.33 (20.63)	199.67 (19.02) 205.47 (19.97)	194.44 (19.25) 203.53 (20.53)	0.58 (15.05) –4.47 (16.62)	–0.06 (18.00) –5.33 (17.32)	–5.28 (18.55) –7.28 (20.46)	0.491
TG (mg/dl)	90.67 (65.49) 93.97 (38.25)	83.31 (37.94) 99.17 (55.69)	88.92 (37.92) 90.64 (39.32)	97.17 (51.14) 93.33 (46.50)	–7.36 (45.57) 5.19 (37.83)	–1.75 (39.75) –3.33 (30.99)	6.50 (46.98) –0.64 (37.96)	0.175

Data are expressed as means (SD), and *p* values indicate the interaction between treatment and time derived from a linear mixed-effects repeated-measures analysis of variance. SDG, secoisolariciresinol diglucoside; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; L/H, LDL-C/HDL-C; TC, total cholesterol; TG, triglyceride.

and stored at −80°C until use. The primary and secondary endpoints were LDL-C and HDL-C, LDL-C/HDL-C (L/H) ratio, total cholesterol (TC), and TG and hepatic disease risk markers [alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (γ-GTP)], respectively.

Measurements. All measurements were performed at 0, 4, 8, and 12 weeks. Anthropometric parameters [height, weight, and body mass index (BMI)] and vital signs [systolic blood pressure (SBP) and diastolic blood pressure (DBP)] were measured. Fasting blood lipid profiles (LDL-C, HDL-C, L/H ratio, TC, and TG) and hepatic disease risk markers (ALT, AST, and γ-GTP) were also measured.

Statistical analysis. All statistical analyses were performed using R ver. 4.0.3 software (Institute for Statistics and Mathematics, Vienna, Austria; www.r-project.org). Changes from 0 weeks to each time point (4, 8, and 12 weeks) were calculated considering the measured values. Data in tables were calculated using the CreateTableOne function in the tableone R package and presented as mean (SD), unless otherwise stated. Additionally, a linear mixed-effects repeated-measures analysis of variance (ANOVA) with adjustment for considering the baseline value as the covariate was performed using the lmer function in the lmerTest R package to evaluate the interaction between treatment (SDG and placebo) and time point on measurements.

Results

Participant characteristics. Overall, 1 participant withdrew consent before the intervention and 73 completed the study. Additionally, before analysis, we excluded one participant from the SDG group with a food intake <90% (Fig. 1). Finally, we fixed the data with 36 participants (male, $n = 19$; female, $n = 17$) in the SDG and placebo control groups each. Table 1 shows participants' baseline characteristics.

Blood lipid profiles of all participants. We measured lipid profiles (LDL-C, HDL-C, L/H ratio, TC, and TG) at 0, 4, 8, and 12 weeks and evaluated whether SDG intake effects on the profiles. No significance was observed in all lipid profiles, including LDL-C ($p = 0.164$), HDL-C ($p = 0.844$), L/H ratio ($p = 0.384$), TC ($p = 0.494$), and TG ($p = 0.175$) through the analysis of the interaction effect between treatment and time (Table 2).

Stratified analysis of blood lipid profiles of female and male participants. Next, we performed stratified analysis to analyze whether the effect of SDG on blood cholesterol levels differed by sex. In male participants ($n = 19$ for both the SDG and placebo groups), a significant interaction between treatment and time with a decreasing trend was confirmed for LDL-C ($p = 0.049$) and TC ($p = 0.020$) levels (Table 3). The interaction effect was not observed in other lipid profiles, including HDL-C level

Table 3. Overview of lipid profiles of male participants at each endpoint and changes from 0 weeks

	0 week	4 weeks	8 weeks	12 weeks	Change 0 to 4 weeks	Change 0 to 8 weeks	Change 0 to 12 weeks	*p* (treatment × time)
	Placebo group SDG group	Placebo group SDG group	Placebo group SDG group	Placebo group SDG group	Placebo group SDG group	Placebo group SDG group	Placebo group SDG group	
LDL-C (mg/dl)	120.84 (13.49) 131.26 (18.03)	120.74 (12.57) 124.89 (15.52)	127.00 (15.84) 124.68 (15.33)	122.42 (15.71) 124.74 (20.00)	−0.11 (12.36) −6.37 (16.07)	6.16 (14.70) −6.58 (13.93)	1.58 (13.55) −6.53 (17.71)	0.049
HDL-C (mg/dl)	55.00 (10.32) 64.21 (14.44)	54.11 (10.30) 61.58 (14.68)	54.05 (8.95) 60.00 (13.97)	52.42 (9.39) 58.37 (13.50)	−0.89 (5.52) −2.63 (5.81)	−0.95 (5.02) −4.21 (6.09)	−2.58 (4.74) −5.84 (9.13)	0.247
L/H ratio	2.26 (0.46) 2.14 (0.55)	2.33 (0.62) 2.13 (0.55)	2.42 (0.57) 2.19 (0.57)	2.41 (0.55) 2.23 (0.61)	0.07 (0.35) −0.01 (0.26)	0.16 (0.33) 0.05 (0.24)	0.14 (0.28) 0.09 (0.21)	0.634
TC (mg/dl)	192.53 (17.31) 211.42 (23.51)	191.63 (14.17) 205.58 (21.63)	196.68 (16.53) 199.95 (20.23)	193.47 (18.33) 200.95 (25.00)	−0.89 (14.04) −5.84 (17.91)	4.16 (15.81) −11.47 (16.86)	0.95 (16.68) −10.47 (24.67)	0.020
TG (mg/dl)	112.58 (81.15) 106.26 (45.75)	99.89 (42.37) 116.11 (64.30)	105.58 (41.45) 94.95 (41.98)	120.63 (56.17) 104.68 (52.17)	−12.68 (60.11) 9.84 (44.77)	−7.00 (51.36) −11.32 (30.11)	8.05 (61.83) −1.58 (44.90)	0.167

Data are expressed as means (SD), and *p* values indicate the interaction between treatment and time derived from a linear mixed-effects repeated-measures analysis of variance. SDG, secoisolariciresinol diglucoside; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; L/H, LDL-C/HDL-C; TC, total cholesterol; TG, triglyceride.

Table 4. Overview of lipid profiles of female participants at each endpoint and changes from 0 weeks

	0 week	4 weeks	8 weeks	12 weeks	Change 0 to 4 weeks	Change 0 to 8 weeks	Change 0 to 12 weeks	*p* (treatment × time)
	Placebo group SDG group	Placebo group SDG group	Placebo group SDG group	Placebo group SDG group	Placebo group SDG group	Placebo group SDG group	Placebo group SDG group	
LDL-C (mg/dl)	123.06 (17.06) 122.41 (14.04)	126.35 (18.04) 119.47 (18.09)	118.59 (17.86) 123.53 (13.57)	112.53 (18.30) 120.24 (12.29)	3.29 (12.42) −2.94 (9.66)	−4.47 (13.64) 1.12 (12.19)	−10.53 (12.03) −2.18 (11.76)	0.006
HDL-C (mg/dl)	72.88 (14.52) 74.53 (17.21)	71.29 (11.63) 73.35 (15.58)	71.35 (12.22) 74.06 (16.66)	67.29 (11.69) 72.18 (14.82)	−1.59 (7.72) −1.18 (6.51)	−1.53 (8.57) −0.47 (4.74)	−5.59 (8.28) −2.35 (5.80)	0.530
L/H ratio	1.73 (0.35) 1.73 (0.45)	1.83 (0.41) 1.72 (0.47)	1.71 (0.38) 1.75 (0.46)	1.74 (0.48) 1.74 (0.45)	0.10 (0.18) −0.01 (0.15)	−0.02 (0.24) 0.02 (0.18)	0.01 (0.22) 0.01 (0.19)	0.143
TC (mg/dl)	207.76 (29.07) 210.12 (19.23)	210.00 (23.12) 207.18 (20.08)	203.00 (21.49) 211.65 (18.31)	195.53 (20.75) 206.41 (14.21)	2.24 (16.38) −2.94 (15.45)	−4.76 (19.56) 1.53 (15.54)	−12.24 (18.48) −3.71 (14.33)	0.080
TG (mg/dl)	66.18 (27.65) 80.24 (21.57)	64.76 (20.90) 80.24 (37.58)	70.29 (22.69) 85.82 (36.79)	70.94 (28.04) 80.65 (36.65)	−1.41 (20.17) 0.00 (28.66)	4.12 (20.50) 5.59 (30.35)	4.76 (22.84) 0.41 (29.68)	0.903

Data are expressed as means (SD), and *p* values indicate the interaction between treatment and time derived from a linear mixed-effects repeated-measures analysis of variance. SDG, secoisolariciresinol diglucoside; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; L/H, LDL-C/HDL-C; TC, total cholesterol; TG, triglyceride.

($p = 0.247$), L/H ratio ($p = 0.634$), and TG level ($p = 0.167$) (Table 3). However, in female participants ($n = 17$ for both the SDG and placebo groups), an interaction effect between treatment and time with a decreasing trend of LDL-C levels in the placebo group was observed ($p = 0.006$) (Table 4), indicating difficulty in evaluating the effect of SDG on LDL-C levels. No significant interaction effect was observed in other lipid profiles, including HDL-C level ($p = 0.530$), L/H ratio ($p = 0.143$), and TC ($p = 0.080$), and TG ($p = 0.903$) levels (Table 4).

Hepatic disease risk markers. Since SDG's ameliorative effect on elevated hepatic disease risk markers induced by hypercholesterolemia has been reported,[20] we also evaluated whether dietary SDG affected hepatic disease risk markers (ALT, AST, and γ-GTP). Accordingly, an interaction effect was not observed for all markers among all participants (Supplemental Table 1–3*).

Discussion

Although dietary SDG intake has shown beneficial effects in regulating blood cholesterol levels in patients with hypercholesterolemia in previous studies, the effect in borderline participants (LDL-C level 120–139 mg/dl) and the difference between sexes have not been well studied. Here, we observed a beneficial effect of SDG on blood LDL-C and TC levels in male participants.

We speculated that SDG effectively controls blood LDL-C and TC levels in male participants because their reducing effect was observed in male participants in previous studies[19,20] and our results. However, the quantity of SDG intake and baseline cholesterol levels differed among studies. A study targeting Chinese male patients with hypercholesterolemia (LDL-C >140 mg/dl) reported a cholesterol-reducing effect at 600 mg/day rather than at 300 mg/day.[19] A study on Japanese male participants with moderate hypercholesterolemia reported that the LDL-C-reducing effect was observed with a daily SDG intake of 100 mg rather than 20 mg.[20] This study showed that SDG reduced LDL-C and TC levels at 60 mg/day in male participants with LDL-C levels of 120–139 mg/dl. These results indicate that SDG is particularly effective in participants with borderline or moderate cholesterol levels, whereas a higher quantity of SDG may be needed for participants with hypercholesterolemia.

In comparison to the placebo group, the SDG group did not decrease the blood cholesterol levels in female participants. This result may be due to the age imbalance among the groups. When comprehensively analyzing our results, most female study participants in the SDG group were in menopausal or postmenopausal periods (age: 51.82 ± 0.82). Accumulating evidence has shown

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that women in menopausal or postmenopausal periods have increased TC and LDL-C levels owing to decreased endogenous estrogen levels.[21] Estrogen (for example, estradiol) may affect the size and number of HDL particles and the ability of HDL particles to promote cholesterol efflux from macrophages.[22] Additionally, menopausal hormone therapy has shown positive effects on the lipid profile of postmenopausal women.[23] These studies indicate that estrogen or estrogen-like molecules may help control lipid profiles in menopausal and postmenopausal women. Here, participants inoculated with SDG that was converted in the gut to enterolignans (ED and EL) were expected to compensate for the decreased estrogen levels in the body. However, their binding activity was extremely low (approximately 3.5×10^{-7} to 2.1×10^{-6} times the half-maximal effective concentration [EC_{50}] value when compared with estradiol).[8] Therefore, we speculate that SDG intake 60 mg/day could not produce a sufficient amount of enterolignan in the body to compensate for estrogen deficiency and to alleviate the increase in estrogen deficiency-derived blood lipids. Indeed, blood cholesterol levels were not improved in healthy postmenopausal participants inoculated with SDG;[17] however, soy isoflavone, which possesses a more potent estrogenic activity than enterolignans, showed beneficial effects on blood lipid profiles.[24] Therefore, further studies should examine the effect of SDG in female participants who are not in the menopausal stage.

In addition to sex, quantity of SDG intake, and age, gut microbiome-dependent SDG conversion to enterolignan may be involved in blood lipid profiles. Indeed, gut microbiome characteristics involved in plasma enterolignan concentration and blood cholesterol profiles have been suggested in previous studies.[25,26] Moreover, individual differences in enterolignan productivity were gut microbiome composition-dependent,[27,28] suggesting that the gut microbiome-dependent conversion of SDG to enterolignans determines the therapeutic effects of SDG. Indeed, participants with an EL-producible gut microbiome with higher lignan intake have lower metabolic risk factors, including blood lipid profiles.[29] Furthermore, another study evaluating the effect of dietary SDG reported significant correlations between the blood cholesterol-lowering effect and plasma enterolignan concentrations.[19] Therefore, additional studies should clarify whether the gut microbiome composition is involved in enterolignan metabolism and the blood cholesterol-reducing effect of SDG.

This study had some limitations. First, the study population consisted entirely of Japanese participants; therefore, further studies should clarify whether similar results are observed with different participant's characteristics. Second, the circulating enterolignan concentration was not measured; therefore, the relationship between blood enterolignans and blood lipid levels could not be evaluated. Finally, because of the significant decrease in LDL-C Third, participants were not surveyed about their diets during the study period, and energy intake was not accounted for in the results. In this study, participants were randomized, and dietary patterns, including flaxseed, were controlled for during the study period to mitigate any potential impact of other diets on the evaluation. However, future trials will need to assess the effects of SDGs with adjustments for energy intake. levels in the placebo group, the effect of SDG in female participants could not be well evaluated.

The intake of SDG at 60 mg/day for 12 weeks decreased blood LDL-C and TC levels in male participants with LDL-C levels of 120–139 mg/dl. Therefore, these results suggest the benefit of SDG in controlling blood cholesterol levels in men and provide a novel strategy for preventing hypercholesterolemia, dyslipidemia, and cardiovascular diseases.

Author Contributions

KO, KS, SF, and KA were involved in study design and data interpretation. KO and KS were involved in the data analysis. KO and KS wrote the manuscript. All authors critically revised the report, commented on the drafts of the manuscript, and approved the final version.

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Abbreviations

ALT	alanine transaminase
ANOVA	analysis of variance
AST	aspartate aminotransferase
BMI	body mass index
CAD	coronary artery disease
DBP	diastolic blood pressure
ED	enterodiol
EL	enterolactone
γ-GTP	gamma-glutamyl transpeptidase
HDL-C	high-density lipoprotein cholesterol
LDL-C	low-density lipoprotein cholesterol
L/H	LDL-C/HDL-C
SBP	systolic blood pressure
SDG	secoisolariciresinol diglucoside
SECO	secoisolariciresinol
TC	total cholesterol
TG	triglyceride

Conflict of Interest

All authors were employed by NIPPN Corporation. Clinical experiments were conducted by Clinical Creative Corporation and Sapporo Yurinokai Hospital with funds provided by NIPPN Corporation. The authors have no conflicts of interest to declare.

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