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Toenail selenium levels and prevalence of dyslipidaemia among Korean adults

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Abstract

Multiple studies have elucidated the antioxidant properties of Se, which are now well known among the nutrition and biomedical science communities. Recently, considerable interest has been focused on the possible association between Se exposure and risk of metabolic disease, such as lipid dysregulation; however, there is limited epidemiological data on this topic. The present study aimed to investigate associations between toenail Se levels and dyslipidaemia or individual lipid levels, and to examine the effect of dietary supplement use on these associations. We analysed baseline data from a cohort in the Yeungnam area, including 232 men and 269 women. Information on demographic, dietary and lifestyle characteristics was obtained through a self-reported questionnaire. Se levels in toenail specimens were measured using neutron activation analysis. Fasting blood lipid levels were measured during medical examinations. After adjusting for multiple confounding variables, we observed no association between toenail Se levels and dyslipidaemia or individual lipid profiles. However, the association was modified by dietary supplement use. Among the supplement users, higher toenail Se levels were associated with a higher prevalence of lipid dysregulation, whereas non-users exhibited a lower prevalence of lipid dysregulation. Associations between toenail Se levels, lipid levels and dyslipidaemia may be influenced by taking dietary supplements. Future large-scale, prospective cohort studies should be conducted to further evaluate the association between Se levels in the body and metabolic health effects in light of increasing rates of dietary supplement use.

Key words: Toenail analysis: Selenium: Dyslipidaemia: Epidemiological effect modifiers: Dietary supplements: Asian adults

Se is an essential mineral in the human body, and acts as an important component of antioxidant enzymes, such as glutathione peroxidase[1,2]. Enzymes containing Se are referred to as selenoproteins; to date, at least thirty mammalian selenoproteins have been identified, of which approximately twenty-five are present in humans[3].

Previous studies have reported that cereal[2,4–6], meat[1,2,6,7], fish and other seafood[2,6,8,9] and some fruit and vegetables[2,6] are major dietary sources of Se. However, the Se content of crops is greatly dependent on the soil in which they are grown[1,10,11]. In countries with low soil-Se levels, the overall dietary Se levels obtained from consumption of crops grown in the soil may be minimal. Se deficiency may decrease antioxidant activity and cause serious health problems. One example is the Keshan disease[2,12], which was first found in Keshan County of Heilongjiang province, Northeast China, where the soil Se content is extremely low[12,13]. Se supplementation may be an option to increase Se levels in populations residing in regions with low soil-Se levels; however, the dosage, reference range for intake and safety issues for Se supplementation have not been completely established[1].

Experimental studies have shown that the antioxidant effects of Se are involved in the prevention of lipid oxidation, thereby preventing the development of dyslipidaemia and progression from dyslipidaemia to CVD or cancer[14–16]. However, epidemiological studies are limited and have mostly been conducted in Europe and the USA[17–19]. In addition, the reference range for Se, which is based on a biomarker of long-term exposure to Se, remains unclear[20]. Moreover, the health effects of Se may vary depending on the genetic variants of selenoproteins[21,22], dietary sources of Se (e.g. foods or dietary supplements)[23] or the presence of effect-modifiers[24,25].

A recent epidemiological study of residents in the Yeungnam area in South Korea examining the association between toenail Hg levels and dyslipidaemia found that toenail Se status is an effect-modifier of this association[24]. However, it is unclear whether Se levels in the body directly contribute to dyslipidaemia in this population; investigation of this association might be even more relevant given the high consumption of fish rich in Se by residents in the Yeungnam area. It is also necessary to determine the optimal Se reference range for the prevention of chronic diseases, particularly lipid dysregulation.

Abbreviations: SELEN, Trace Element Study of Korean Adults in Yeungnam Area; TC, total cholesterol.

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The present study aimed to determine the association between toenail Se levels and dyslipidaemia, and to identify potential effect-modifiers of this association among Korean adults.

Methods

Study population

This study was conducted using baseline data from the Trace Element Study of Korean Adults in Yeungnam Area (SELEN) cohort study involving adults aged ≥35 years in the Yeungnam area of South Korea. Baseline participant data, including demographic, lifestyle and dietary information, were collected using a self-report questionnaire developed by SELEN investigators. The complete data on demographic, lifestyle, dietary and health information and toenail Se levels for 501 SELEN study participants were assessed for the final analysis.

Informed consent was obtained from all participants. The present study was approved by the institutional review board (IRB) at Yeungnam University Medical Center in compliance with the ethical standards for research, and was conducted with consideration of the safety and rights of the participants (IRB no. YUH-12-0468-O94).

Measurements

Participants were categorised into two groups on the basis of their education levels: high school graduates or below, and university graduates or above. On the basis of the alcohol consumption status, participants were categorised as drinkers or non-drinkers. Similarly, on the basis of the monthly household income, participants were categorised into quintiles. In terms of smoking status, patients were categorised as current smokers, former smokers and non-smokers. Physical activity frequency (per week) and hours (per day) were examined, and metabolic equivalent tasks (MET-h/week) were calculated in accordance with physical activity intensity[26].

Information on participants' anthropometric measurements and blood lipid levels was collected from health examinations conducted by the Korea National Health Insurance Service (KNHIS). All Korean workers and their dependants are legally required to have biennial health examinations through the KNHIS. We asked participants to undergo a health examination at least 6 months after completing the baseline questionnaire and toenail sample collection, and send a copy of their health examination results to the SELEN researchers. According to the KNHIS guidelines, weight, height and waist circumference (WC) measurements, as well as blood samples, were collected by trained nurses in the relevant medical institution where the medical examination was conducted[27]. We calculated the BMI of each participant, using the weight and height values recorded as part of the medical examination and by dividing the weight in kilograms by the square of height in metres. At the health examination, participants provided laboratory specimens after fasting for at least 12 h. Serum lipid levels, including TAG, total cholesterol (TC), LDL-cholesterol and HDL-cholesterol levels were measured in clinical laboratories by staff with certified qualifications in accordance with strict management protocols of the KNHIS. Atherogenic index of plasma (AIP) was calculated according to the formula log(TAG/HDL-cholesterol)[28]. The criteria for dyslipidaemia and related health conditions used in the present study were in accordance with the National Cholesterol Education Program Adult Treatment Panel III criteria[29]. Dyslipidaemia was confirmed if one or more of the following four criteria were met: (1) hypercholesterolaemia, defined as serum TC level ≥6·22 mmol/l or taking lipid-lowering drugs; (2) hyper-LDL-cholesterolaemia, defined as serum LDL-cholesterol level ≥4·14 mmol/l or taking lipid-lowering drugs; (3) hypertriacylglycerolaemia, defined as serum TAG level ≥2·26 mmol/l; and (4) hypo-HDL-cholesterolaemia, defined as serum HDL-cholesterol level ≤1·04 mmol/l for men and serum HDL-cholesterol level ≤1·30 mmol/l for women.

Dietary information was obtained through a validated 146-item semiquantitative FFQ, specifically developed for the SELEN participants[30]. In particular, for this study, we focused on a subset of questions designed to obtain information on the use of dietary supplements. Specifically, the participants were asked to report whether they currently used any dietary supplements. If this response was affirmative, participants were then asked to report the following: type of dietary supplement(s) taken (e.g. multivitamins and minerals), the brand name, dosage per day and duration of dietary supplement use. For this study, dietary supplement use was defined as consumption of at least one type of dietary supplement per day.

Although blood Se level has been used as a major biomarker in many studies, it represents only short-term Se exposure[31]. Se is stored in multiple locations, including blood, hair and nails. Among these storage sites, toenails are more likely to represent long-term exposure to Se than other storage sites[31–33]. We provided participants the sample-collection protocol for collecting nail specimens for trace-element analysis. Participants were asked to remove nail polish, and clean and dry their toes before cutting toenails. They were also asked to uniformly cut toenails from all ten toes, seal them in an envelope and send them to the SELEN researchers via postal mail. After the collection of toenail samples was completed, researchers conducted visual inspection of the participants' nail clippings to detect whether the samples were contaminated by nail polish or nail colour containing garden balsam. They also measured the sample weights to confirm that the nail specimens met the minimum analysable weight requirement. The toenail clippings were then sent to the University of Missouri Research Reactor Center in Missouri, USA, to quantify toenail Se levels using neutron activation analysis. Details on the validity of the analytical methods and measurement tools used in this study have been described previously[31,34–36]. In brief, each sample (8–90 mg) was cleaned ultrasonically with dilute nitric acid and deionised water before analysis, placed in a precleaned, high-density polyethylene vial (0·4 ml) and subjected to neutron irradiation at a thermal neutron flux of $6{\cdot}5 \times 10^{13}$ n/cm^2 per s. During this irradiation, Se^{77m} is produced, which decays by isomeric transition with a half-life of 17·36 s, producing a gamma ray with energy of 161·9 keV that is quantified by high-resolution gamma-ray spectroscopy. The spectrometer consists of a high-purity germanium detector, power supply, spectroscopy amplifier, analog-to-digital convertor and loss-free

counting module provided by ORTEC operating on a Canberra Genie gamma-ray spectroscopy network (Canberra). Toenail Se concentrations were determined by standard comparison using a certified Se standard solution (High-Purity Standards) and traceable to the US National Institutes of Standards and Technology (NIST SRM 3149; Gaithersburg, MD). All analytical procedures were performed by trained laboratory staff blinded to person-identifiable information, demographic descriptors and nutritional metrics. For approximately 40 % of the subjects, there was adequate sample to prepare and analyse in duplicate. In those cases, the mean percent CV (CV) for all duplicate pairs was 2·14 % and the range was 0·09 % to 8·47 %. For each analysis, batch replicates of a biological standard reference material, issued by the US NIST (NIST SRM 1577, Bovine Liver; NIST), having a certified Se concentration, were analysed by the same methodology as described for the toenail samples. The average Se concentration measured in these replicates (1·136 (SD 0·016) μg/g, CV: 1·44 %) was in good agreement with the certified Se concentration (1·1 (SD 0·1) μg/g).

Statistical analysis

We conducted a sample size calculation using G*Power software(version 3.1.9.2; University of Kiel) with an α-error probability of 0·05, power (1-β error probability) of 0·95 and effect size (OR) of 1·24[37]. On the basis of the result of this calculation, the total sample size needed was at least 375. Assuming that 30 % of the data collected would be missing in information owing to participant attrition and/or measurement errors, we determined the necessary total sample size to be approximately 500 participants. To compare various demographic, lifestyle, dietary and health factors with Se levels, the cohort was divided into tertiles according to toenail Se levels. Categorical variables were compared using the χ^2 test, and mean values were compared with continuous variables using ANOVA and the Tukey's *post hoc* test. Potential confounding variables were selected based on previous studies and preliminary analysis. OR and 95 % CI were obtained using multivariable logistic regression to analyse the prevalence of dyslipidaemia and individual lipid profiles, according to tertiles of toenail Se levels. To control the effect of potential confounders, the following models were tested: model 1 = adjusted for age and sex; model 2 = model 1 plus adjusted for education level, household income, smoking status, BMI and total energy intake; and model 3 = model 2 plus further adjusted for MET, alcohol intake, fat intake, toenail Hg level and family history of chronic diseases (hypertension, diabetes, CVD and cancer). Multivariable adjusted mean serum lipid levels, including TC, HDL-cholesterol, LDL-cholesterol and TAG, were calculated using general linear regression analysis. Potential effect-modifiers, including various demographic, lifestyle, dietary and health-related variables, were examined using multiplicative terms in logistic regression. As the use of dietary supplements was an effect-modifier of the association between toenail Se levels and dyslipidaemia, we further examined the association of Se with dyslipidaemia and individual lipid profiles stratified by the use of dietary supplements. The *P* value for trend in tertiles of Se levels in linear regression was evaluated using the median value of the category as a continuous variable. All analyses in the present study were performed using SAS (version 9.3; SAS Institute), and $P < 0·05$ was considered statistically significant.

Results

In total, 501 participants were divided into groups according to tertiles of toenail Se levels, and their general characteristics were compared (Table 1). The mean values of toenail Se levels were 0·60 μg/g in the 1st tertile, 0·69 μg/g in the 2nd tertile and 0·79 μg/g in the 3rd tertile. The average age of the study participants was approximately 44 years. We observed higher toenail Se levels among younger participants than in those from older participants ($P = 0·002$). Seventy-nine percent of all participants consumed alcohol, and the proportion of drinkers was higher among those with higher levels of toenail Se ($P = 0·02$). No significant differences in the multivariate-adjusted mean serum lipid levels were observed among the tertiles.

General characteristics of participants were compared in accordance with the use or non-use of dietary supplements, and are shown in Table 2. Dietary supplement users were more likely to be female ($P = 0·008$), non-smokers ($P < 0·001$), college graduates or above ($P = 0·004$) and have a family history of hypertension ($P = 0·03$) or diabetes ($P = 0·03$). Furthermore, those with a higher household income were more likely to use dietary supplements ($P = 0·008$). After adjusting for multiple demographic and lifestyle variables, no significant differences were observed in serum TC, LDL-cholesterol, HDL-cholesterol and AIP between dietary supplement users and non-users.

The OR of dyslipidaemia and lipid abnormalities according to tertiles of toenail Se are shown in Table 3. In minimally and fully adjusted models, toenail Se levels were not associated with the prevalence of dyslipidaemia, hypercholesterolaemia, hypo-HDL-cholesterolaemia, hyper-LDL-cholesterolaemia and hypertriacylglycerolaemia.

However, we observed that the associations between toenail Se level and dyslipidaemia or individual lipid profiles were modified by the use or non-use of dietary supplements (Table 4). Among dietary supplement users, the prevalence of hypercholesterolaemia was 3·56 times higher in participants in the 3rd tertile of toenail Se levels than in those from the 1st tertile (OR 3·56; 95 % CI 1·12, 11·26); the prevalence of hypertriacylglycerolaemia was 2·68 times higher in participants in the 3rd tertile than in those from the 1st tertile (OR 2·68; 95 % CI 1·09, 6·64); and the prevalence of dyslipidaemia was 2·72 times higher in participants in the 3rd tertile than in the those in the 1st tertile (OR 2·72; 95 % CI 1·41, 5·26). Conversely, for non-users of dietary supplements, these associations were reversed, showing an OR of 0·21 (95 % CI 0·07, 0·59) for hypertriacylglycerolaemia and an OR of 0·40 (95 % CI 0·17, 0·91) for dyslipidaemia.

Discussion

The present study examined the associations between toenail Se levels and prevalence of dyslipidaemia and individual lipid profiles using baseline data from the SELEN cohort study. We found that these associations were modified by dietary

Table 1. Demographic and lifestyle characteristics of the study participants according to the tertiles (T) of toenail selenium levels (Numbers and percentages; mean values with their standard errors)

	Tertile of toenail Se (μg/g)						
	T1 (*n* 167) (0·48–0·66)		T2 (*n* 167) (0·66–0·71)		T3 (*n* 167) (0·71–1·10)		
Characteristics	*n*	%	*n*	%	*n*	%	*P**
Sex							0·7
Men	78	46·71	81	48·50	73	43·71	
Women	89	53·29	86	51·50	94	56·29	
BMI							0·4
Underweight	5	3·01	5	2·99	3	1·80	
Normal	79	47·59	73	43·71	79	47·31	
Overweight	52	31·33	47	28·14	39	23·35	
Obese	30	18·07	42	25·15	46	27·54	
Smoking status							0·3
Non-smoker	104	62·28	104	62·28	119	71·26	
Former smoker	26	15·57	31	18·56	23	13·77	
Current smoker	37	22·16	32	19·16	25	14·97	
Alcohol consumption							0·02
Non-drinker	48	28·74	28	16·77	31	18·56	
Drinker	119	71·26	139	83·23	136	81·44	
Education							0·01
High school graduate or lower	69	41·32	43	25·90	50	29·94	
College graduate or higher	98	58·68	123	74·10	117	70·06	
Monthly household income (KRW)							0·5
<3 000 000	44	26·35	30	17·96	34	20·36	
3–3 990 000	36	21·56	49	29·34	37	22·16	
4–4 990 000	29	17·37	27	16·17	33	19·76	
5–5 990 000	26	15·57	22	13·17	28	16·77	
≥6 000 000	32	19·16	39	23·35	35	20·96	
Residence area							0·5
Urban	91	54·49	101	60·48	96	57·49	
Rural	76	45·51	66	39·52	71	42·51	
Family history of hypertension	53	31·90	53	31·90	55	33·10	0·9
Family history of diabetes	31	18·80	37	22·20	42	25·50	0·3
Dietary supplement use	92	55·09	91	54·49	101	60·48	0·5
	Mean	SE	Mean	SE	Mean	SE	
Age (years)	46·00[a]	0·41	44·40[b]	0·41	44·10[c]	0·41	0·002
Toenail Se (μg/g)	0·60[a]	0·003	0·69[b]	0·003	0·79[c]	0·003	<0·001
Toenail Hg (μg/g)	0·38	0·02	0·42	0·02	0·42	0·02	0·2
MET (h/week)	33·98	3·64	33·76	3·64	31·47	3·66	0·9
Total fat intake (g/d)†	39·24	0·80	39·95	0·80	41·06	0·80	0·3
Blood lipid levels‡							
TAG (mmol/l)	1·30	0·07	1·34	0·07	1·34	0·08	0·6
Total cholesterol (mmol/l)	4·64	0·22	4·90	0·24	4·68	0·24	0·9
HDL-cholesterol (mmol/l)	1·40	0·06	1·44	0·06	1·47	0·06	0·3
LDL-cholesterol (mmol/l)	2·99	0·07	2·97	0·08	2·98	0·08	0·9

KRW, Korean Republic Won; MET, metabolic equivalent tasks.
[a,b,c] Tukey's multiple comparison test was applied to determine statistical difference between the means.
* *P* values are derived from general linear regression analysis or χ^2 test.
† Adjusted for total energy intake.
‡ Adjusted for age, sex, household income, physical activity level, education level, BMI, total energy intake, alcohol consumption and smoking status.

supplement use. Among supplement users, those with higher Se levels were more likely to have prevalent dyslipidaemia and hypertriacylglycerolaemia than those with lower Se levels. However, among supplement non-users, those with higher Se levels were more likely to have lower rates of dyslipidaemia and hypertriacylglycerolaemia than those with lower Se levels.

Considering that Se content in foods varies according to the Se levels in the soil in which the crops were grown[6], Se intake and, consequently, the level of Se in the body is likely dependent on an individual's place of residence. The Nurses' Health and Health Professional studies in the USA have shown that average concentrations of toenail Se were 0·77 (SD 0·13) μg/g in men and 0·84 (SD 0·15) μg/g in women[38]. The average concentrations of toenail Se in the Netherlands Cohort Study in Europe were relatively lower at 0·55 (SD 0·13) μg/g in men and 0·57 (SD 0·15) μg/g in women[39]. The average concentrations of toenail Se in the SELEN participants were 0·68 (SD 0·08) μg/g in men and 0·70 (SD 0·09) μg/g in women, which fall in between values reported in the USA and Europe. Considering the U-shaped association between Se levels and metabolic health risks and a relatively narrow safe range of Se levels that is non-toxic[24,40], the study results of the SELEN participants may

Table 2. Demographic and lifestyle characteristics of the study participants according to the use of dietary supplements
(Numbers and percentages; mean values with their standard errors)

	Supplement use				
	No (*n* 217)		Yes (*n* 284)		
Characteristics	*n*	%	*n*	%	*P**
Sex					0·008
Men	115	53·00	117	41·20	
Women	102	47·00	167	58·80	
BMI					0·2
Underweight	8	3·69	6	1·77	
Normal	101	46·54	130	45·94	
Overweight	52	23·96	86	30·39	
Obese	56	25·81	62	21·91	
Smoking status					<0·001
Non-smoker	130	59·91	197	69·37	
Former smoker	30	13·82	50	17·61	
Current smoker	57	26·27	37	13·03	
Alcohol consumption					0·6
Non-drinker	44	20·28	63	22·18	
Drinker	173	79·72	221	77·82	
Education					0·004
High school graduate or lower	85	39·35	77	27·11	
College graduate or higher	131	60·65	207	72·89	
Monthly household income (KRW)					0·008
<3 000 000	51	23·50	57	20·07	
3–3 990 000	66	30·41	56	19·72	
4–4 990 000	39	17·97	50	17·61	
5–5 990 000	24	11·06	52	18·31	
≥6 000 000	37	17·05	69	24·30	
Residence area					0·1
Urban	115	53·00	173	60·92	
Rural	102	47·00	111	39·08	
Family history of hypertension	58	26·98	103	36·40	0·03
Family history of diabetes	38	17·59	72	25·62	0·03
	Mean	SE	Mean	SE	
Age (years)	44·10	0·30	45·30	0·41	0·01
Toenail Se (μg/g)	0·69	0·005	0·69	0·01	0·5
Toenail Hg (μg/g)	0·41	0·01	0·40	0·02	0·7
MET (h/week)	34·07	2·62	31·28	3·52	0·1
Total fat intake (g/d)†	39·59	0·57	40·99	0·78	0·5
Blood lipid levels‡					
TAG (mmol/l)	1·34	0·07	1·30	0·06	0·6
Total cholesterol (mmol/l)	4·70	0·21	4·75	0·20	0·8
HDL-cholesterol (mmol/l)	1·42	0·06	1·44	0·05	0·7
LDL-cholesterol (mmol/l)	2·96	0·07	3·00	0·07	0·6
AIP	0·63	0·06	0·61	0·05	0·8

KRW, Korean Republic Won; MET, metabolic equivalent tasks; AIP, atherogenic index of plasma.
* *P* values are derived from general linear regression analysis or χ^2 test.
† Adjusted for total energy intake.
‡ Adjusted for age, sex, household income, physical activity level, education level, BMI, total energy intake, alcohol consumption and smoking status.

Table 3. Lipid profiles according to the tertiles (T) of toenail selenium levels (Odds ratios and 95 % confidence intervals)

	Tertile of toenail Se level (μg/g)					
	T1	T2		T3		
Lipid profiles	OR	OR	95 % CI	OR	95 % CI	$P_{for\ trend}$
Hypercholesterolaemia						
Cases (*n*)	11	21		17		
Model 1*	1·00	2·16	1·00, 4·68	1·73	0·78, 3·86	0·2
Model 2†	1·00	2·03	0·92, 4·45	1·60	0·71, 3·61	0·3
Model 3‡	1·00	2·18	0·95, 5·00	1·69	0·72, 4·00	0·3
Hypo-HDL-cholesterolaemia						
Cases (*n*)	27	28		34		
Model 1	1·00	1·07	0·59, 1·94	1·31	0·74, 2·32	0·4
Model 2	1·00	1·12	0·61, 2·06	1·27	0·70, 2·28	0·4
Model 3	1·00	1·17	0·63, 2·19	1·36	0·74, 2·49	0·3
Hyper-LDL-cholesterolaemia						
Cases (*n*)	12	12		12		
Model 1	1·00	1·07	0·46, 2·49	1·10	0·47, 2·56	0·8
Model 2	1·00	1·01	0·43, 2·37	1·04	0·44, 2·44	0·9
Model 3	1·00	0·95	0·39, 2·35	0·95	0·39, 2·35	0·9
Hypertriacylglycerolaemia						
Cases (*n*)	34	36		29		
Model 1	1·00	1·10	0·64, 1·91	0·88	0·50, 1·56	0·7
Model 2	1·00	1·12	0·63, 1·98	0·84	0·47, 1·53	0·6
Model 3	1·00	1·14	0·63, 2·04	0·93	0·51, 1·70	0·8
Dyslipidaemia						
Cases (*n*)	57	65		64		
Model 1	1·00	1·29	0·82, 2·02	1·28	0·81, 2·01	0·3
Model 2	1·00	1·31	0·82, 2·10	1·26	0·79, 2·01	0·3
Model 3	1·00	1·37	0·84, 2·21	1·34	0·83, 2·18	0·2

* Model 1: adjusted for age and sex.
† Model 2: model 1 plus additionally adjusted for education level, household income, smoking status, BMI and total energy intake.
‡ Model 3: model 2 plus additionally adjusted for physical activity level, alcohol consumption, fat intake, toenail Hg level and family history of hypertension, diabetes, CVD and cancer.

provide meaningful scientific data for the formulation of dietary guidelines for safe and optimal daily intake of Se.

In this study, we observed that the direction of association between toenail Se levels and lipid dysregulation was reversed in accordance with dietary supplementation. Se is an essential trace element with antioxidant properties; adequate intakes of Se and other antioxidants decrease lipid oxidation and increase protective effects against various metabolic health conditions, such as lipid dysregulation[16,23,24,37,41–48]. However, the cumulative antioxidant levels, resulting from the prolonged and/or unnecessary intakes of dietary supplements, including fat-soluble antioxidants that are stored and not easily depleted in the body, may be high or even excessive among dietary supplement users. In addition, considering that the effects of antioxidants are synergistic, the net interactive antioxidant effect might be higher than the sum of the individual antioxidant effects[49]. Thus, it is plausible that high Se levels in dietary supplement users might contribute to high total antioxidant levels that may far exceed the upper limit of the biologically safe range for antioxidants. Furthermore, excessive levels of antioxidants in the body may inhibit normal oxidant–antioxidant defense functions that require optimal levels of free radicals for the tight regulation of metabolic pathways[38], including prevention of lipid dysregulation.

Epidemiological studies investigating the association between dietary supplementation and serum lipid levels have shown inconsistent results. In the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX) study, participants receiving long-term antioxidant supplements, including Se (100 μg/d), exhibited increased serum TAG levels compared with those receiving a placebo[50]. Similarly, a randomised study of a Chinese population showed that long-term use of supplements with vitamin C, vitamin E and Se was associated

Table 4. Lipid profiles and dyslipidaemia according to the tertiles (T) of toenail selenium levels, stratified by dietary supplement use* (Odds ratios and 95 % confidence intervals)

	Tertile of toenail Se (μg/g)					
	T1	T2		T3		
Dietary supplement uses	OR	OR	95 % CI	OR	95 % CI	$P_{for\ trend}$
Users						
Hypercholesterolaemia	1·00	1·86	0·56, 6·18	3·56	1·12, 11·26	0·03
Hyper-LDL-cholesterolaemia	1·00	1·89	0·52, 6·84	2·12	0·56, 8·02	0·3
Hypo-HDL-cholesterolaemia	1·00	1·48	0·63, 3·46	1·89	0·84, 4·25	0·1
Hypertriacylglycerolaemia	1·00	1·65	0·65, 4·19	2·68	1·09, 6·64	0·03
Dyslipidaemia	1·00	1·71	0·87, 3·34	2·72	1·41, 5·26	0·003
Non-users						
Hypercholesterolaemia	1·00	2·69	0·78, 9·33	0·56	0·12, 2·67	0·5
Hyper-LDL-cholesterolaemia	1·00	0·52	0·12, 2·25	0·70	0·16, 3·02	0·6
Hypo-HDL-cholesterolaemia	1·00	0·81	0·29, 2·24	0·73	0·25, 2·08	0·5
Hypertriacylglycerolaemia	1·00	0·72	0·31, 1·68	0·21	0·07, 0·59	0·003
Dyslipidaemia	1·00	1·01	0·48, 2·14	0·40	0·17, 0·91	0·03

* OR were adjusted for age, sex, education level, household income, residential area, smoking status, alcohol consumption, BMI, total energy intake, toenail Hg level and family history of hypertension and diabetes.

with small, but significant, increases in TC and LDL-cholesterol levels[51]. Prior two large trials, the Se and Vitamin E Cancer Prevention Trial[52] and the Nutritional Prevention of Cancer Trial[53], found that Se supplementation did not prevent type 2 diabetes. On the contrary, both the trials the latter study raised the concern that Se supplementation might increase the risk for type 2 diabetes. Furthermore, cumulative evidence has suggested that excessive intake of Se may result in hair loss, weak nails, lack of mental alertness, garlic breath odour and excessive tooth decay and discolouration[43,54]. In contrast to the aforementioned trials, observational studies conducted in Finland, China, the USA and the UK reported inconsistent results[17,19,55,56].

Dietary supplement use has been a controversial topic in a number of studies[57–60]. First, dietary supplements can affect health in various ways depending on the individual's current nutritional status. Dietary supplements may be effective if an individual has a nutrient deficiency[1,60,61]. However, if an individual's body has adequate nutrient levels before supplementation, additional use of dietary supplements may lead to toxicity and negative health effects[1,6,25,61]. Second, the complex interactions between various phytochemicals and other macromolecules present in whole foods may affect the absorption and bioavailability of various nutrients, including antioxidants[62,63]. Purified nutrients present in dietary supplements, on the other hand, may have a limited capacity to replicate these complex interactions, and, therefore, may not have the same bioavailability as nutrients from whole foods[62,63].

The present study has several limitations. The study participants were limited to residents of the Yeungnam area of South Korea; thus, we cannot generalise the results of our study to other populations. Furthermore, this study analysed the baseline data of the SELEN cohort in a cross-sectional manner. Thus, it is possible that limitations exist in the investigation of causality between the exposure and outcome. To minimise this bias, information on metabolic function biomarkers, such as WC and blood lipids, was collected at least 6 months after the completion of initial data collection on exposure variables (e.g. toenail specimen collection). Further, as toenail Se concentration reflects long-term exposure to Se of up to 1 year, the occurrence of reverse causation might have been minimised in this study. Finally, although the size of toenail specimens and the timing of specimen collection may contribute to differences in the observed toenail Se levels, we did not fully control for such factors in the present study.

In conclusion, our findings showed that, among middle-aged adults living in the Yeungnam area of South Korea, the association between toenail Se levels, serum lipid levels and dyslipidaemia was significantly modified by dietary supplementation. Higher toenail Se levels were associated with a higher prevalence of lipid dysregulation among dietary supplement users; however, among supplement non-users, higher toenail Se levels were associated with a lower prevalence of dyslipidaemia and hypertriacylglycerolaemia. Additional large-scale, prospective cohort studies should be conducted in the future to further evaluate the association between Se intake and metabolic health effects in light of increasing rates of dietary supplement use.

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J. J. conducted the analysis and wrote the manuscript. J .S. M. performed the assays. J. S. M. and K. P. reviewed the manuscript. K. P. developed the study design, supervised the analysis and contributed to the discussion. All authors read and approved the final manuscript.

None of the authors has any conflicts of interest to declare.

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