Review

Effect of selenium supplementation on lipid profile levels: An updated systematic review and meta-analysis of randomized controlled clinical trials

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ABSTRACT

Aims: The aims of this meta-analysis were to assess the effects of selenium supplementation on lipid profile levels in clinical trial studies.
Methods: A systematic search of literature was carried out in PubMed, Scopus, ISI web of science, Ovid and Cochrane library up to January 19, 2019. Of 2318 relevant articles identified at the first step of search, 19 trials with 31, 21, 29 and 22 effect sizes were used for the meta-analysis assessing the effects of selenium supplementation on blood levels of HDL-C, LDL-C, TC and TG, respectively.
Results: Results of the random effect model meta-analysis showed significant effect of selenium supplementation on serum level of TC (WMD: 2.02 mg/dl; 95% CI = −3.86, −0.17; P = 0.032) while it had no significant effects on serum levels of HDL-C (WMD: 0.37 mg/dl; 95% CI = −0.66, 1.34; P = 0.45), TG (WMD: 2.43 mg/dl; 95% CI = −6.27, 1.40; P = 0.21), and LDL-C (WMD: 0.32 mg/dl; 95% CI = −2.42, 3.06; P = 0.82). Results of subgroup analysis showed that when the dosage of selenium supplementation was 200 μg/day or when the baseline level of serum TC was > 200 μg/dl, selenium supplementation could decrease significantly TG and TC concentrations, respectively.
Conclusion: Results of the current meta-analysis study showed that selenium supplementation could decrease significantly serum levels of TC and TG while it had no beneficial effects on other lipid profile levels in clinical trial studies.

1. Introduction

Selenium as an essential microelement, is found in important proteins including glutathione peroxidase (GPX), thioredoxin reductase and other seleno-proteins involved in protection against oxidative stress through their antioxidant properties (Nordberg and Arnér, 2001). Both organic (seleno-methionine and seleno-cysteine) and in-organic (selenite and selenate) forms of selenium are good dietary sources of this mineral. selenium can be found in foods including vegetables, meat, grains and dairy products (Kieliszek and Błażejak, 2016). The reference value for selenium intake was derived from saturation of seleno-protein P in one study concluding that approximately 1 μg/kg of body weight is enough for normal weight adults (Kipp et al., 2015). Selenium deficiency may result in Keshan disease, a cardiomyopathy with varying degrees of heart insufficiency that leads to congestive heart failure

(Rayman, 2008; Chen, 2012). In 1983, Solanen et al. showed for the first time an association between cardiovascular disease and serum selenium levels (Salonen et al., 1982). However, the impact of selenium on cardiovascular diseases is conflicting in epidemiological studies. While some studies have shown an inverse relationship between the serum selenium level and the risk of coronary heart disease (Flores-Mateo et al., 2006), other studies have concluded that a higher selenium concentration could increase the risk of cardiovascular disease (Xun et al., 2010). Furthermore, other conflicting findings have been published on effects of selenium supplementation on lipid profile levels in clinical trial studies. Mesdaghinia et al. in a clinical trial study showed that supplementation with 100 μg/day selenium for ten weeks could significantly increase HDL-C concentrations in pregnant women but with no significant effects on other lipid profiles (Mesdaghinia et al., 2017). In the Rayman et al. study, supplementation with 100 and

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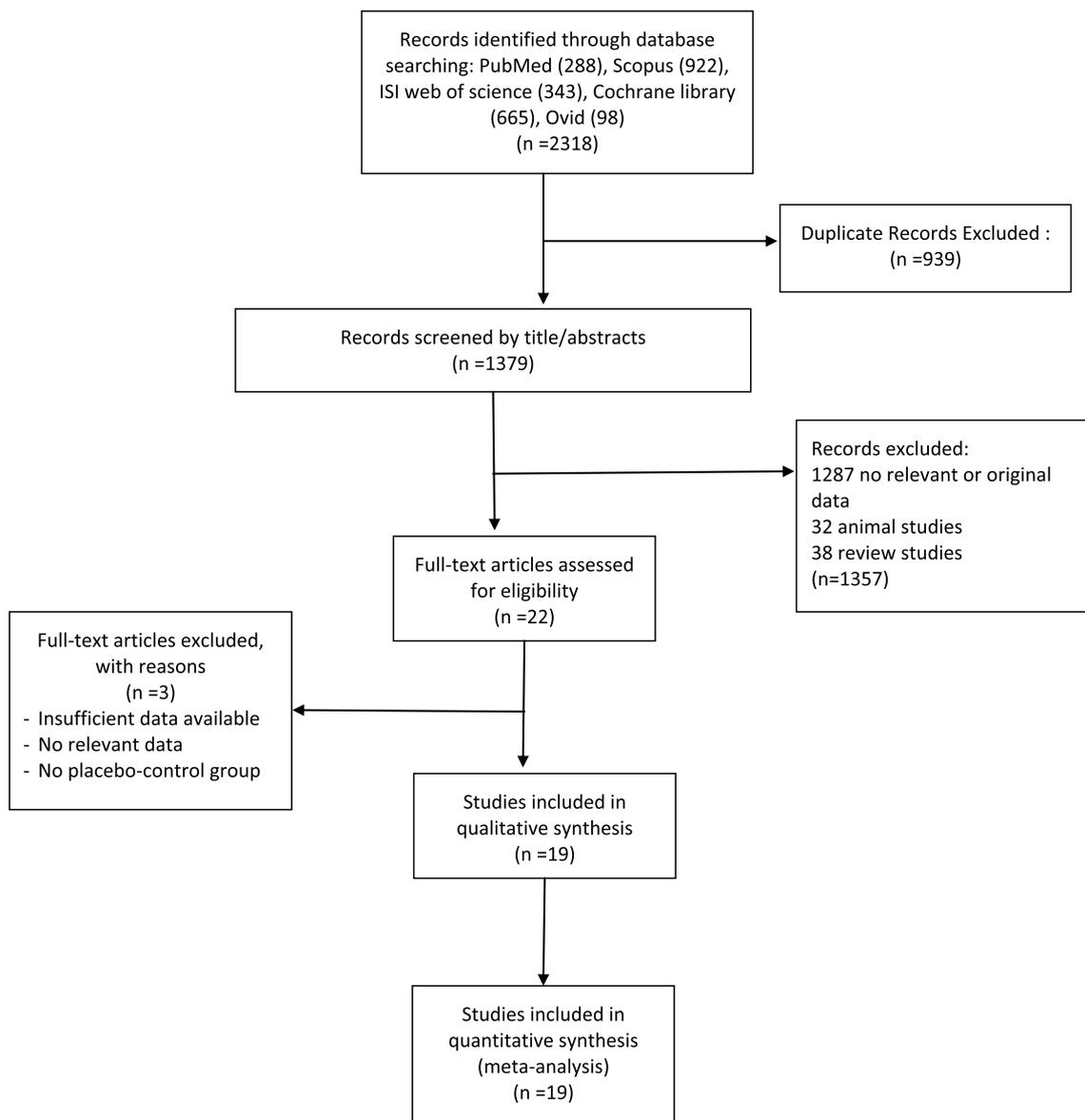
Fig. 1. Flowchart of study selection for inclusion in the systematic review.

200 μg/day selenium for six months decreased significantly TC and non-HDL-C in men and women with low selenium status. However, a higher dose of selenium (300 μg/day) could not successfully decrease TC and non-HDL-C levels while significantly increased HDL-C in these subjects (Rayman et al., 2011). The lipid profile response to selenium supplementation seems to depend on to baseline levels of these risk factors, dose and duration of the supplementation, age, sex and BMI of patients receiving this supplement. Two previous meta-analysis studies were assessed the effects of selenium supplementation on lipid profile levels in clinical trial studies. Tabrizi et al. showed that selenium supplement had no significant decreasing effects on lipid profile levels in patients with metabolic diseases. Only five studies included in this meta-analysis (Tabrizi et al., 2017). Another meta-analysis study by Hasani et al. with the ending search time of 2016 evaluated the effects of selenium supplementation on lipid profile levels in all type of diseases included nine clinical trials in final analysis and concluded that selenium supplementation could decrease significantly TC, TG and VLDL levels (Hasani et al., 2018). Because of these conflicting results and existence of new clinical trials respected this topic, this updated systematic review and meta-analysis was carried out to assess the effects of selenium supplementation on lipid profile levels in clinical trial studies.

2. Materials and methods

2.1. Search strategy

This study was carried out based on to the pattern of reporting systematic review and meta-analysis (PRISMA). A comprehensive searching of databases including PubMed, Scopus, ISI web of science, Ovid and Cochrane library in titles, keywords and abstracts were performed by two independent authors (EY, SS) up to January 19, 2019 with the following combinations of key terms: (selenium OR se OR trace element OR selenium supplementation) AND (randomized controlled trial OR clinical trial OR randomized OR placebo) AND (cholesterol OR triglyceride OR TG OR total cholesterol OR TC OR low-density lipoprotein OR LDL OR LDL-C OR LDL-cholesterol OR high-density lipoprotein OR HDL OR HDL-C OR HDL-cholesterol OR lipoprotein OR lipid). Search was not limited to language. Reference list of selected papers were also searched manually for finding more related articles.

Table 1
Characteristics of included studies in meta-analysis.

Author	year	country	Study design	participants	sex	Mean age (intervention/control)	Mean BMI (intervention/control)	Trial duration (week)	Daily dose of selenium (µg)	Type of selenium	Sample size (intervention/control)
PV Luoma	1985	Finland	DB/R/PL	Healthy subjects	F/M	25/23	22/22	2	96	Selenium	10/13
G Ravn-Haren	2008	Denmark	DB/R/PL	Healthy subjects	M	26.8/26.8	23.4/23.4	4	300	Selenium yeast	20/20
						26.8/26.8	23.4/23.4	1	300	Selenium yeast	20/20
						26.8/26.8	23.4/23.4	4	300	Selenate	20/20
						26.8/26.8	23.4/23.4	1	300	Selenate	20/20
R Schnabel	2008	Germany	DB/R/PL	Patients with coronary artery disease	F/M	66/66	28.4/28.1	12	200	Sodium selenite	148/144
						66/66	27.8/28.1	12	500	Sodium selenite	141/144
F Tara	2010	Iran	DB/R/PL	Patients with preeclampsia	F/M	21.6/21.6	23.8/23	24	100	Selenium yeast	61/64
M Alizadeh	2011	Iran	DB/R/PL	Patients with Cardiovascular Disease	F	36.7/36.6	> 25- > 25	3	200	Selenium yeast	21/21
						36.7/36.6	> 25/ > 25	6	200	Selenium yeast	21/21
M P Rayman	2011	UK	DB/R/PL	Healthy subjects	F/M	67/67	27.7/27.5	25	100	Selenium yeast	1233/107
						67/67	27.4/27.5	25	200	Selenium yeast	124/107
						67/67	27.8/27.5	25	300	Selenium yeast	120/107
M Salehi	2013	Iran	DB/R/PL	Hemodialysis patients	F/M	50/55	22.86/22.37	12	200	Selenium yeast	40/40
T Faghihi	2014	Iran	DB/R/PL	Patients with Type 2 Diabetes	F/M	53/55	28.31/27.89	12	200	Selenium	33/27
M Jamilian	2015	Iran	DB/R/PL	Patients with polycystic ovary syndrome	F	25.4/25.7	25/25.2	8	200	Selenium	35/35
M Karamali	2015	Iran	DB/R/PL	Patients with cervical intraepithelial neoplasia	F	38.9/38.3	28.6/28.7	24	200	Selenium yeast	28/28
Z Asemi	2015	Iran	DB/R/PL	Patients with gestational diabetes	F	27.6/29.6	27.3/28.5	6	200	Selenium	35/35
F Bahmani	2015	Iran	DB/R/PL	Patients with Diabetic Nephropathy	F/M	63/61	29.8/30.4	12	200	Selenium yeast	30/30
F Cold	2015	Denmark	DB/R/PL	Healthy subjects	F/M	66.4/65/4	27.1/26.5	25	100	Selenium yeast	124/126
						66.3/65.4	27.2/26.5	25	200	Selenium yeast	122/126
						66.5/65.4	26.5/26.5	25	300	Selenium yeast	119/126
						66.4/65.4	27.1/26.5	260	100	Selenium yeast	124/126
						66.3/65.4	27.2/26.5	260	200	Selenium yeast	122/126
						66.5/65.4	26.5/26.5	260	300	Selenium yeast	119/126
A Farrokhian	2015	Iran	DB/R/PL	Patients with Type 2 Diabetes and Coronary Heart Disease	F/M	40-85/40/85	NR/NR	8	200	Selenium	30/30
HR Omrani	2016	Iran	DB/R/PL	Hemodialysis patients	F/M	58/60	24.18/23.35	12	200	Selenium	42/42
E Mesdaghinia	2016	Iran	DB/R/PL	pregnant	F	18-40/18-40	21.2/22.5	10	100	Selenium yeast	30/30
OR Tamtaji	2018	Iran	DB/R/PL	Patients with Alzheimer's	F/M	78.8/78.5	21.2/21.5	12	200	Selenium	26/26
F Raygan	2018	Iran	DB/R/PL	Patients with congestive heart failure	F/M	70.7/68.5	25.7/26.2	12	200	Selenium yeast	26/27
A Kamali	2019	Iran	DB/R/PL	Patients with Coronary Artery Bypass Grafting Surgery	F/M	62.6/61.2	26.4/26.2	4	200	Selenium yeast	17/16

Abbreviations: DB, double-blinded; PC, placebo-controlled; R, randomized; NR, not reported; F, Female; M, Male.

Table 2
Risk of bias assessment of studies included in the meta-analysis.

Other sources of bias	Reporting bias	Incomplete Outcome Data (Attrition bias)	Blinding of Outcome Assessment	Blinding of Participants and Personnel	Allocation Concealment	Random Sequence Generation	Author
U	U	L	U	U	U	L	PV Luoma
U	U	U	U	L	L	L	G Ravn-Haren
L	U	L	U	U	U	L	R Schnabel
L	U	L	U	U	U	L	F Tara
L	U	L	U	L	U	L	M Alizadeh
L	U	L	L	L	L	L	M P Rayman
L	U	L	L	L	L	L	M Salehi
L	U	L	L	L	L	L	T Faghihi
L	U	L	L	L	L	L	M Jamilian
L	U	L	U	U	L	L	M Karamali
L	U	L	L	L	L	L	Z Asemi
L	U	L	L	L	L	L	F Bahmani
L	U	L	U	U	L	L	F Cold
L	U	L	L	L	L	L	A Farrokhian
L	U	L	U	U	L	L	HR Omrani
L	U	U	L	L	U	L	E Mesdaghinia
L	U	L	L	L	L	L	OR Tamtaji
L	U	L	L	L	L	L	F Raygan
L	U	L	L	L	L	L	A Kamali

Abbreviations: H, high risk of bias; L, low risk of bias; U, unclear risk of bias.

Study ID	WMD (95% CI)	% Weight
PV Luoma (1985)	-13.00 (-29.93, 3.93)	1.12
G Ravn-Haren (2008)	-6.18 (-18.41, 6.05)	2.03
G Ravn-Haren (2008)	0.00 (-11.49, 11.49)	2.27
G Ravn-Haren (2008)	-5.40 (-17.43, 6.63)	2.09
G Ravn-Haren (2008)	3.86 (-7.08, 14.80)	2.47
F Tara (2010)	4.90 (-7.24, 17.04)	2.05
M Alizadeh (2011)	-12.30 (-26.71, 2.11)	1.51
M Alizadeh (2011)	-1.40 (-17.59, 14.79)	1.21
M P Rayman (2011)	-10.42 (-17.46, -3.38)	5.03
M P Rayman (2011)	-9.26 (-15.74, -2.78)	5.67
M P Rayman (2011)	0.40 (-5.99, 6.79)	5.78
M Salehi (2013)	-5.68 (-29.87, 18.51)	0.56
T Faghihi (2014)	0.84 (-11.82, 13.50)	1.91
M Jamilian (2015)	-0.00 (-11.21, 11.21)	2.37
M Karamali (2015)	11.80 (-0.02, 23.62)	2.15
Z Asemi (2015)	-2.68 (-15.25, 9.89)	1.93
F Bahmani (2015)	6.30 (-2.67, 15.27)	3.45
F Cold (2015)	-2.71 (-8.16, 2.74)	7.13
F Cold (2015)	2.32 (-3.07, 7.71)	7.22
F Cold (2015)	0.77 (-4.63, 6.17)	7.20
F Cold (2015)	-3.08 (-8.85, 2.69)	6.63
F Cold (2015)	-5.78 (-11.25, -0.31)	7.09
F Cold (2015)	-0.39 (-6.53, 5.75)	6.10
HR Omrani (2016)	-6.14 (-18.28, 6.00)	2.06
E Mesdaghinia (2016)	5.30 (-9.65, 20.25)	1.41
A Farrokhian (2015)	-2.10 (-14.02, 9.82)	2.12
OR Tamtaji (2018)	-8.70 (-21.00, 3.60)	2.01
F Raygan (2018)	-1.54 (-7.88, 4.80)	5.84
A Kamali (2019)	-2.30 (-16.30, 11.70)	1.59
Overall (I-squared = 19.8%, p = 0.173) Test for overal effect: Z=2.14 (p=0.032)	-2.02 (-3.86, -0.17)	100.00

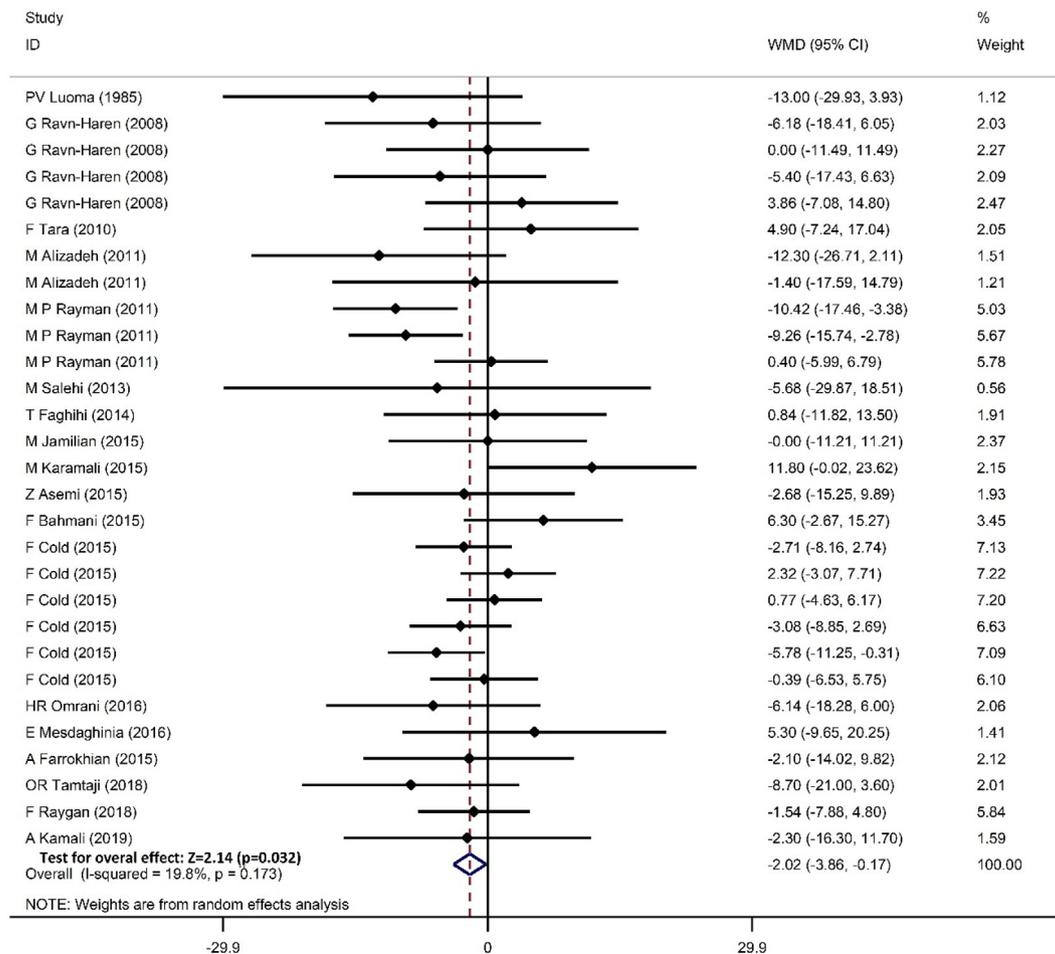NOTE: Weights are from random effects analysis

Fig. 2. Forest plot of the random-effects model meta-analysis of selenium supplementation on blood total cholesterol concentration (mg/dl). WMD, weighted mean difference.

2.2. Study selection

The inclusion criteria for selection of eligible studies included 1) randomized control trials with parallel design; 2) reported serum/plasma level of lipid profile in intervention and control groups; and 3) reported sufficient information on baseline and after post-intervention plasma/serum lipid concentrations in selenium supplementation and control groups. The exclusion criteria were 1) studies with combined supplementation of selenium with other antioxidants and vitamins or lifestyle modification; 2) trials with no control or placebo group; 3)
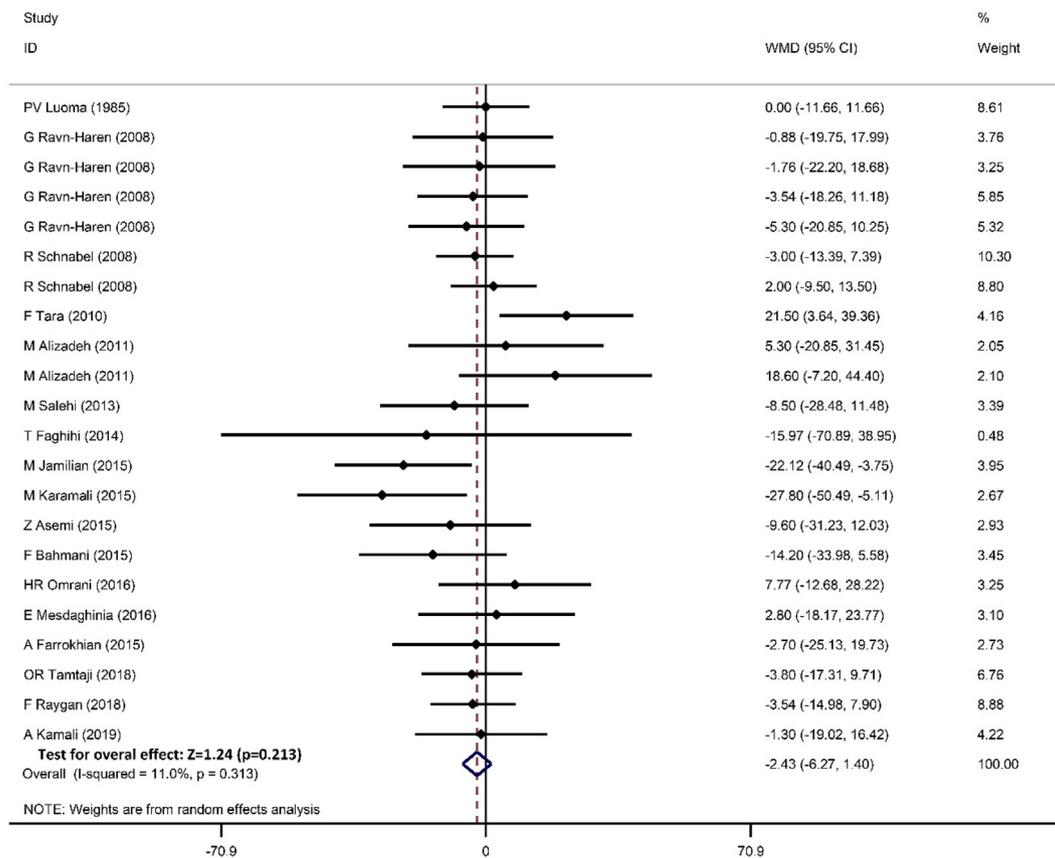
Fig. 3. Forest plot of the random-effects model meta-analysis of selenium supplementation on blood triglyceride concentration (mg/dl). WMD, weighted mean difference.

studies without sufficient data on plasma/serum concentration of lipid profile in baseline and post-intervention; 4) non-interventional studies; 5) use of lipid-lowering drugs in the study groups without appropriate controlling.

2.3. Data extraction and quality control

Two authors (SH, MA) independently screened titles and abstracts of all identified studies for relevance to the topic and then more relevant studies were selected for data extraction using the screening form. A third author (OA) solved any disagreement between these authors at the step of screening and data extraction process. Quality control of selected trials was carried out using Cochrane collaboration modified tool. This tool can perform trial quality assessment based on randomization and allocation concealment, participants, personnel and outcome assessment blinding, selective reporting and attrition bias (Higgins et al., 2011).

Characteristics of the included articles were first author, publication year, original country, journal name, design of study, sample size in intervention and control groups and dose of daily supplementation with selenium. Characteristics of the participants in studies included sex, mean age, mean body mass index, baseline, post-intervention and net changes of lipid profile levels. Studies with more independent arms were considered as separate trials. GetData Graph Digitizer software (www.robotical.ir) was used for the extraction of reported data in form of graphs. All values of lipid profile concentration were reported in the same unit (mg/dl).

2.4. Data synthesis and statistical analysis

Mean and standard deviation of the changes in serum/plasma concentration of lipid profile were considered in control and treatment groups for the meta-analysis. Cochran's Q-test at significance of $P < 0.05$ was used for testing the statistical heterogeneity in the studies and I^2 statistics was used to calculate the percent of variation among studies (Cochran, 1954). The pooled effect size was estimated using fixed effects model and random effects model was used in the presence of heterogeneity. Moreover, Funnel plot analysis and begg and egger's regression test were used for estimating of publication bias. All analyses were carried out using STATA version 12.0 (Stata Corporation, College Station, TX, USA). P-value < 0.05 was considered as statistically significant.

3. Results

Flow diagram of the study selection process is shown in Fig. 1. Of 2318 articles found in the first step of database searching, 939 articles excluded because of being duplicated. In the second step, 1308 articles which did not meet the inclusion criteria were excluded and 22 articles remained for the assessment of eligibility. At the end of the selection process, 19 trials with 31, 21, 29 and 22 arms were used for assessing the effects of selenium supplementation on serum levels of HDL-C, LDL-C, TC and TG, respectively.

3.1. Characteristics of included studies

Characteristics of the included studies in this meta-analysis are shown in Table 1. Of 3881 participants included in the meta-analysis, 1951 participants were organized in the intervention group and other 1930 participants stayed in the control group from different countries including (Iran (Mesdaghinia et al., 2017; Bahmani et al., 2016; Salehi et al., 2012; Jamilian et al., 2015; Faghihi et al., 2014; Karamali et al.,
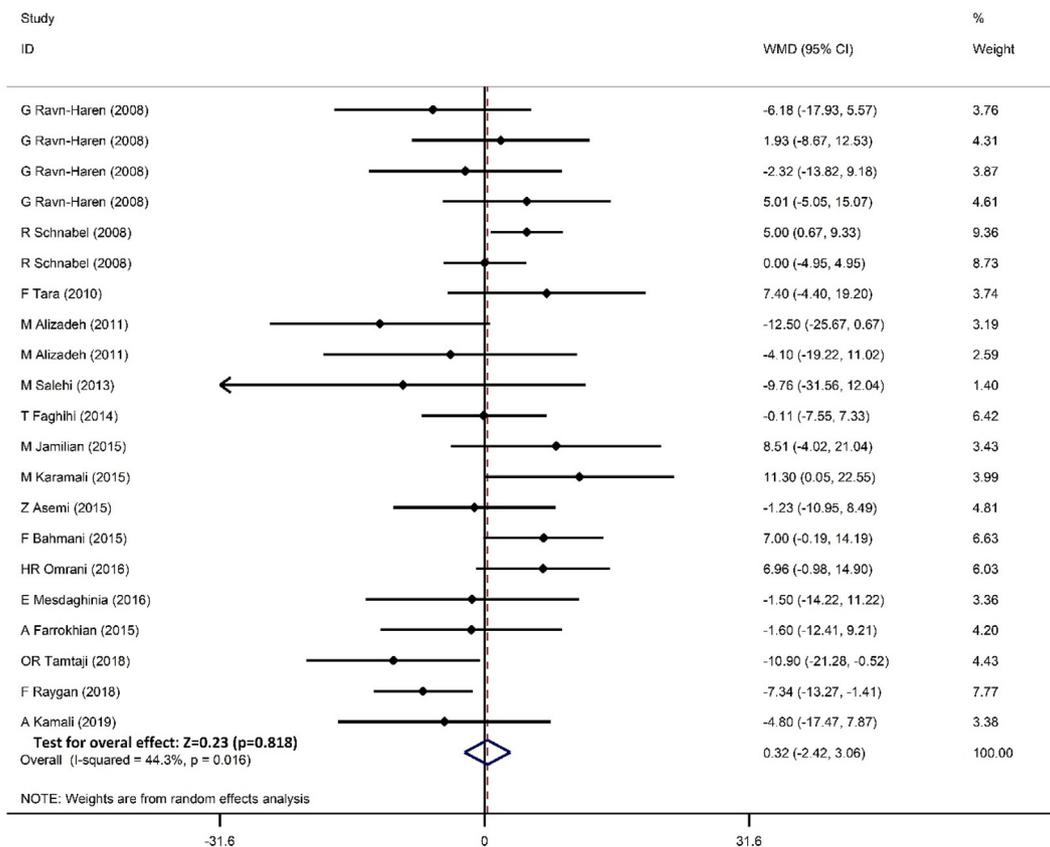
Study
ID

%

WMD (95% CI)

Weight

Study ID	WMD (95% CI)	Weight
G Ravn-Haren (2008)	-6.18 (-17.93, 5.57)	3.76
G Ravn-Haren (2008)	1.93 (-8.67, 12.53)	4.31
G Ravn-Haren (2008)	-2.32 (-13.82, 9.18)	3.87
G Ravn-Haren (2008)	5.01 (-5.05, 15.07)	4.61
R Schnabel (2008)	5.00 (0.67, 9.33)	9.36
R Schnabel (2008)	0.00 (-4.95, 4.95)	8.73
F Tara (2010)	7.40 (-4.40, 19.20)	3.74
M Alizadeh (2011)	-12.50 (-25.67, 0.67)	3.19
M Alizadeh (2011)	-4.10 (-19.22, 11.02)	2.59
M Salehi (2013)	-9.76 (-31.56, 12.04)	1.40
T Faghihi (2014)	-0.11 (-7.55, 7.33)	6.42
M Jamilian (2015)	8.51 (-4.02, 21.04)	3.43
M Karamali (2015)	11.30 (0.05, 22.55)	3.99
Z Asemi (2015)	-1.23 (-10.95, 8.49)	4.81
F Bahmani (2015)	7.00 (-0.19, 14.19)	6.63
HR Omrani (2016)	6.96 (-0.98, 14.90)	6.03
E Mesdaghinia (2016)	-1.50 (-14.22, 11.22)	3.36
A Farrokhian (2015)	-1.60 (-12.41, 9.21)	4.20
OR Tamtaji (2018)	-10.90 (-21.28, -0.52)	4.43
F Raygan (2018)	-7.34 (-13.27, -1.41)	7.77
A Kamali (2019)	-4.80 (-17.47, 7.87)	3.38
Overall (I-squared = 44.3%, p = 0.016)	0.32 (-2.42, 3.06)	100.00

Test for overal effect: Z=0.23 (p=0.818)

NOTE: Weights are from random effects analysis

Fig. 4. Forest plot of the random-effects model meta-analysis of selenium supplementation on blood LDL-C concentration (mg/dl). WMD, weighted mean difference.

2015; Tara et al., 2010; Alizadeh et al., 2012; Asemi et al., 2015; Kamali et al., 2019; Raygan et al., 2018; Tamtaji et al., 2018; Farrokhian et al., 2016; Omrani et al., 2016), Germany (Schnabel et al., 2008), Finland (Luoma et al., 1985), Denmark (Cold et al., 2015; Ravn-Haren et al., 2008) and United Kingdom (Rayman et al., 2011)). Publication year of the included studies were recorded from 1985 to 2019. Various forms of selenium supplementation were used with doses of 96–500 mg/day and duration times of 1–260 weeks. Risk of bias assessment of studies included in this meta-analysis are shown in Table 2.

3.2. Effects of selenium supplementation on plasma lipid concentrations

Meta-analysis of the effects of selenium supplementation on plasma concentrations of HDL-C, LDL-C, TC and TG were carried out in 31, 21, 29 and 22 effect size studies, respectively. Results of the pooled effects size meta-analysis showed significant decreasing effect of selenium supplementation on plasma concentrations of TC (WMD -2.02 mg/dl; 95% CI = −3.86, −0.17; P = 0.032; Fig. 2). Selenium supplementation could not influence significantly serum levels of other lipid profiles including TG (P = 0.21, Fig. 3), LDL-C (P = 0.82, Fig. 4) and HDL-C (P = 0.45, Fig. 5) concentrations. Results of subgroup analysis showed that when the dosage of selenium supplementation was 200 μg/day or when the baseline level of serum TC was > 200 μg/dl, selenium supplementation could decrease significantly TG and TC concentrations, respectively. Trial duration and selenium supplement type had no significant effect in lipid profile responses to selenium supplementation (supplementary file 1).

3.3. Publication bias

No publication bias was found using Begg test (P = 0.2 for HDL-C, P = 0.08 for LDL-C, P = 0.2 for TC, P = 0.8 for TG) and egger test

(P = 0.25 for HDL-C, P = 0.23 for LDL-C, P = 0.4 for TC, P = 0.9 for TG). The funnel plots are shown in Fig. 6).

4. Discussion

Effects of vitamins, minerals and other dietary compounds on lipid profile levels were shown previously in clinical trial studies which revealed the beneficial effects of these compounds on lipid profile level (Askari et al., 2013; Rad et al., 2014; Saboori et al., 2016; Guerrero-Romero et al., 2004). While Tabrizi et al. in one meta-analysis study concluded that selenium supplementation had no significant decreasing effects on lipid profile levels in metabolic diseases (Tabrizi et al., 2017), another meta-analysis study showed that selenium supplementation could decrease significantly TC, TG and VLDL levels (Hasani et al., 2018). Similarly, results of the current meta-analysis showed that except for TC concentration, selenium supplementation had no significant effects on the lipid profile including serum levels of HDL-C, LDL-C and TG. This study showed that consuming selenium supplements could decrease TC level only 2 mg/dl which was not clinically important. Since factors including baseline levels of lipid profile, dose of selenium supplementation and duration of intervention could possibly affect the net influence of supplementation, subgroup analysis based on the highlighted factors was carried out as well.

Results showed that when selenium dosase was 200 μg/day or when the baseline level of TC level was > 200 μg/dl, selenium supplementation could decrease TG and TC level up to 5 and 3 mg/day, respectively which was statistically significant. Although the exact mechanisms associating selenium with lipid metabolism are not clearly explained, small amounts of this element have been found in human lipoproteins (Ducros et al., 2000). Moreover, selenium could incorporate into special proteins, so-called seleno-proteins containing amino acid seleno-cysteine and exert its biological function (Hatfield
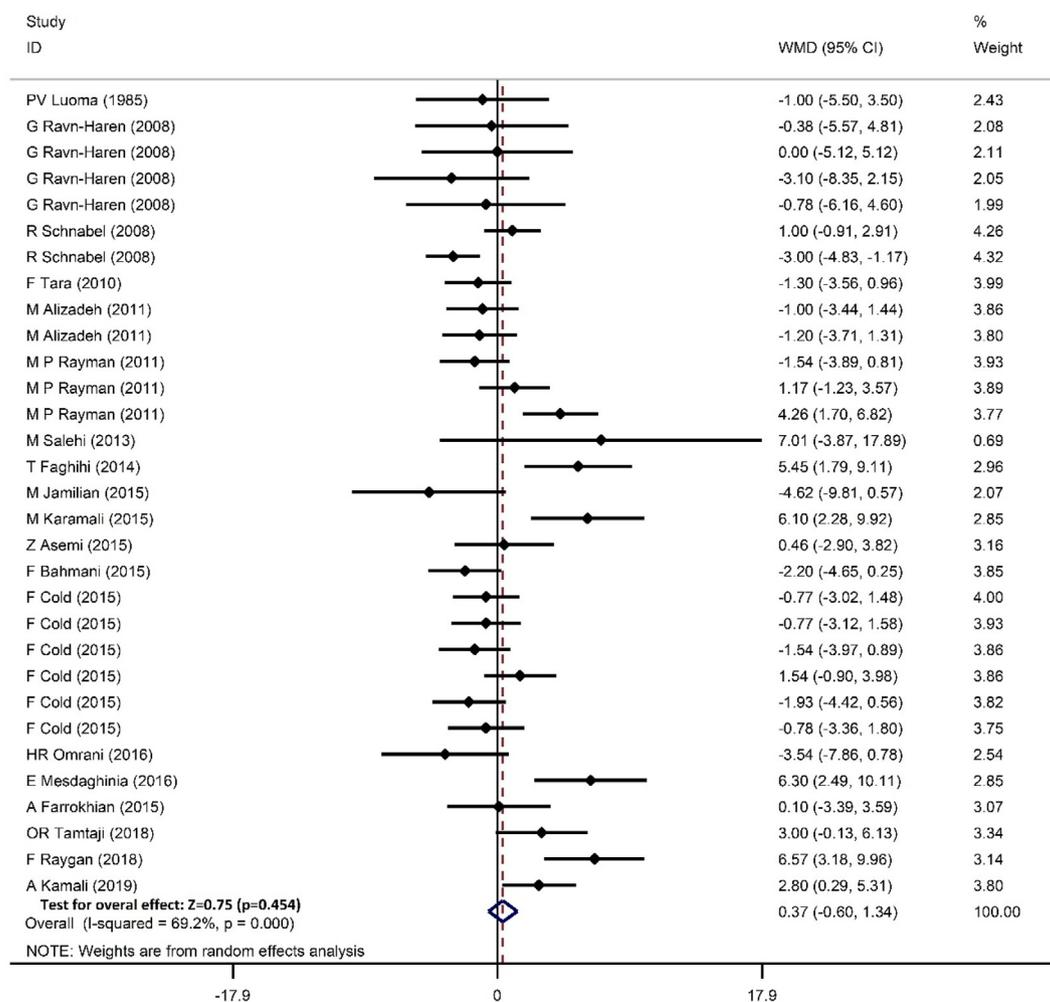
Study ID		WMD (95% CI)	% Weight
PV Luoma (1985)		-1.00 (-5.50, 3.50)	2.43
G Ravn-Haren (2008)		-0.38 (-5.57, 4.81)	2.08
G Ravn-Haren (2008)		0.00 (-5.12, 5.12)	2.11
G Ravn-Haren (2008)		-3.10 (-8.35, 2.15)	2.05
G Ravn-Haren (2008)		-0.78 (-6.16, 4.60)	1.99
R Schnabel (2008)		1.00 (-0.91, 2.91)	4.26
R Schnabel (2008)		-3.00 (-4.83, -1.17)	4.32
F Tara (2010)		-1.30 (-3.56, 0.96)	3.99
M Alizadeh (2011)		-1.00 (-3.44, 1.44)	3.86
M Alizadeh (2011)		-1.20 (-3.71, 1.31)	3.80
M P Rayman (2011)		-1.54 (-3.89, 0.81)	3.93
M P Rayman (2011)		1.17 (-1.23, 3.57)	3.89
M P Rayman (2011)		4.26 (1.70, 6.82)	3.77
M Salehi (2013)		7.01 (-3.87, 17.89)	0.69
T Faghihi (2014)		5.45 (1.79, 9.11)	2.96
M Jamilian (2015)		-4.62 (-9.81, 0.57)	2.07
M Karamali (2015)		6.10 (2.28, 9.92)	2.85
Z Asemi (2015)		0.46 (-2.90, 3.82)	3.16
F Bahmani (2015)		-2.20 (-4.65, 0.25)	3.85
F Cold (2015)		-0.77 (-3.02, 1.48)	4.00
F Cold (2015)		-0.77 (-3.12, 1.58)	3.93
F Cold (2015)		-1.54 (-3.97, 0.89)	3.86
F Cold (2015)		1.54 (-0.90, 3.98)	3.86
F Cold (2015)		-1.93 (-4.42, 0.56)	3.82
F Cold (2015)		-0.78 (-3.36, 1.80)	3.75
HR Omrani (2016)		-3.54 (-7.86, 0.78)	2.54
E Mesdaghinia (2016)		6.30 (2.49, 10.11)	2.85
A Farrokhian (2015)		0.10 (-3.39, 3.59)	3.07
OR Tamtaji (2018)		3.00 (-0.13, 6.13)	3.34
F Raygan (2018)		6.57 (3.18, 9.96)	3.14
A Kamali (2019)		2.80 (0.29, 5.31)	3.80
Test for overall effect: Z=0.75 (p=0.454)		0.37 (-0.60, 1.34)	100.00
Overall (I-squared = 69.2%, p = 0.000)			

NOTE: Weights are from random effects analysis

-17.9   0   17.9

Fig. 5. Forest plot of the random-effects model meta-analysis of selenium supplementation on blood HDL-C concentration (mg/dl). WMD, weighted mean difference.

and Gladyshev, 2002). Animal studies have shown increases in plasma levels of cholesterol and apolipoprotein E and a higher level expression of genes involving in cholesterol biosynthesis pathway in Knock-out mice having specific designated tRNA[Ser]Sec (Sengupta et al., 2008). Another study showed that selenium supplementation could increase the production of 15-deoxy prostaglandin J2 which is a known ligand for peroxisome proliferator-activated receptor (PPAR-γ) (Vunta et al., 2007). It is clear that the activation of PPAR-γ could result in reduced cholesterol synthesis via decreasing the concentration of sterol regulatory element-binding Protein-2 (SREBP-2) (Klopotek et al., 2006). Effects of selenium supplementation in animal and human studies were quite different. Selenium supplementation in experimental studies resulted in decreased plasma levels of TC and LDL-C while increased plasma levels of HDL-C (Wojcicki et al., 1991; Wolf et al., 2010). However, human studies showed different results. Laclaustra et al. in the National Health and Nutrition Examination Survey (NHANES) concluded that the serum selenium levels were positively associated with TC and LDL-C concentrations (Laclaustra et al., 2010). Similarly, another study showed a positive association between selenium plasma level with LDL-C and TC in men. In women, selenium level was correlated to the levels of HDL-C and Apo-lipoprotein A1 (Coudray et al., 1997). In a study by Yang et al. serum selenium levels included a positive association with serum levels of TC, LDL-C, TG and glucose in elderly patients (Yang et al., 2010).

There are studies have shown that high consumption of selenium, even doses considered to be adequate, can increase the risk of diabetes type-2 development (Wei et al., 2015) and supplementation with

200 μg/day of selenium for three months could result in worsened hyper-glycaemia in these patients (Faghihi et al., 2014).

5. Conclusions

In conclusion, results of the current meta-analysis study showed that selenium supplementation could decrease significantly serum levels of TC and TG. However, the magnitude of these reductions were not seem to be clinically important.

Conflicts of interest

The authors declare no conflicts of interest.

Author contributions

SS and EY designed and searched for the study. SH and MA reviewed and selected the articles and extracted data from articles under the supervision of OA. SS and MB performed data analysis and interpretation. EY, OA and SS drafted the manuscript. EF revised the article for important intellectual content.
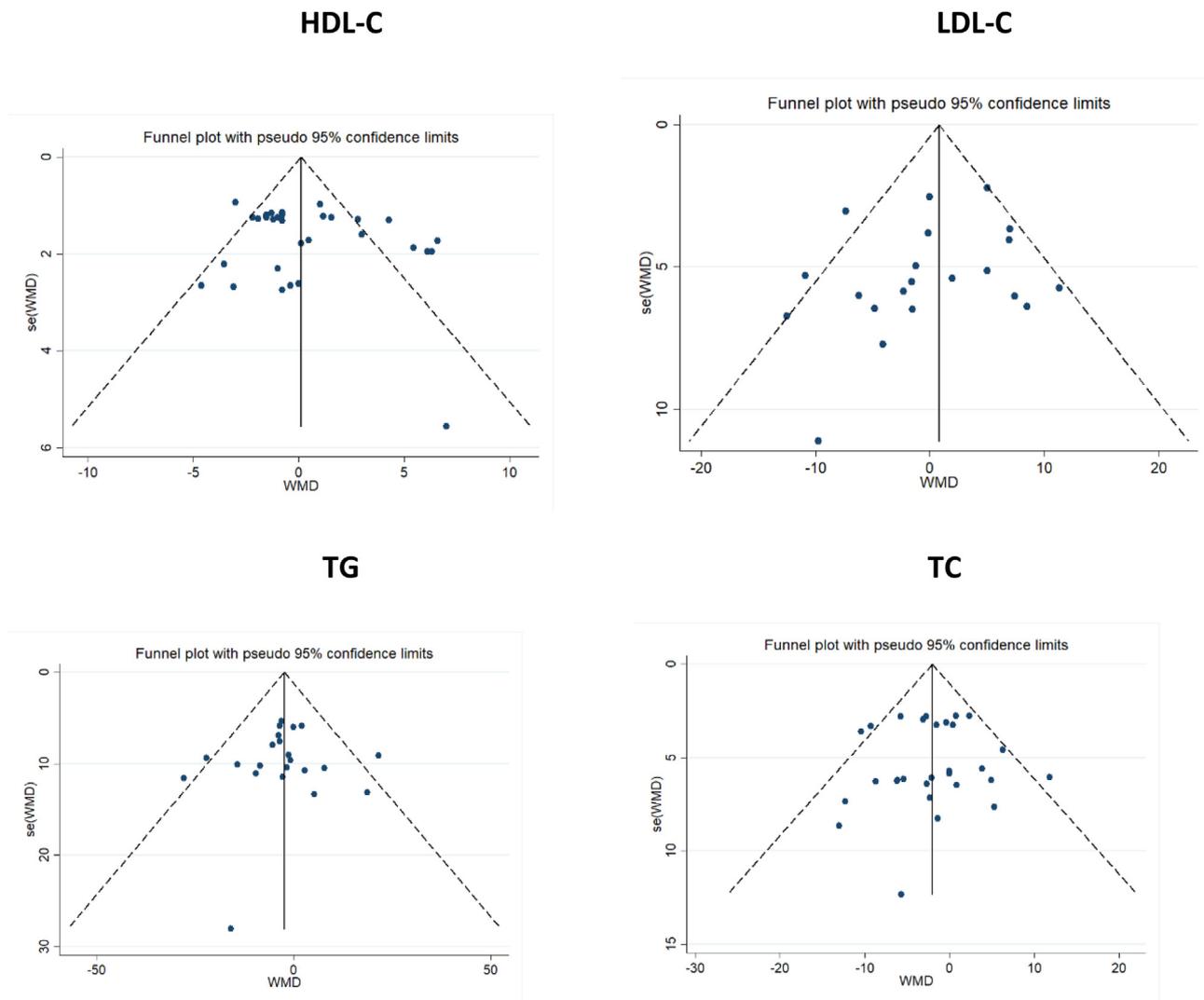
HDL-C

LDL-C

TG

TC

Fig. 6. Funnel plots of trials measured lipid profile.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.obmed.2019.100113.

References

Alizadeh, M., et al., 2012. Effect of L-arginine and selenium added to a hypocaloric diet enriched with legumes on cardiovascular disease risk factors in women with central obesity: a randomized, double-blind, placebo-controlled trial. Ann. Nutr. Metabol. 60 (2), 157–168.

Asemi, Z., et al., 2015. Effects of selenium supplementation on glucose homeostasis, inflammation, and oxidative stress in gestational diabetes: randomized, double-blind, placebo-controlled trial. Nutrition 31 (10), 1235–1242.

Askari, G., et al., 2013. Quercetin and vitamin C supplementation: effects on lipid profile and muscle damage in male athletes. Int. J. Prev. Med. 4 (Suppl. 1), S58.

Bahmani, F., et al., 2016. Effect of selenium supplementation on glycemic control and lipid profiles in patients with diabetic nephropathy. Biol. Trace Elem. Res. 172 (2), 282–289.

Chen, J.-S., 2012. An original discovery: selenium deficiency and Keshan disease (an endemic heart disease). Asia Pac. J. Clin. Nutr. 21 (3), 320–326.

Cochran, W.G., 1954. The combination of estimates from different experiments. Biometrics 10 (1), 101–129.

Cold, F., et al., 2015. Randomised controlled trial of the effect of long-term selenium supplementation on plasma cholesterol in an elderly Danish population. Br. J. Nutr. 114 (11), 1807–1818.

Coudray, C., et al., 1997. Lipid peroxidation level and antioxidant micronutrient status in a pre-aging population; correlation with chronic disease prevalence in a French epidemiological study (Nantes, France). J. Am. Coll. Nutr. 16 (6), 584–591.

Ducros, V., et al., 2000. Selenium determination in human plasma lipoprotein fractions by mass spectrometry analysis. J. Inorg. Biochem. 81 (1), 105–109.

Faghihi, T., et al., 2014. A randomized, placebo-controlled trial of selenium supplementation in patients with type 2 diabetes: effects on glucose homeostasis, oxidative stress, and lipid profile. Am. J. Therapeut. 21 (6), 491–495.

Farrokhian, A., et al., 2016. Selenium supplementation affects insulin resistance and serum hs-CRP in patients with type 2 diabetes and coronary heart disease. Horm. Metab. Res. 48 (04), 263–268.

Flores-Mateo, G., et al., 2006. Selenium and coronary heart disease: a meta-analysis. Am. J. Clin. Nutr. 84 (4), 762–773.

Guerrero-Romero, F., et al., 2004. Oral magnesium supplementation improves insulin sensitivity in non-diabetic subjects with insulin resistance. A double-blind placebo-controlled randomized trial. Diabetes Metab. 30 (3), 253–258.

Hasani, M., et al., 2018. Effect of selenium supplementation on lipid profile: a systematic review and meta-analysis. Horm. Metab. Res. 50 (10), 715–727.

Hatfield, D.L., Gladyshev, V.N., 2002. How selenium has altered our understanding of the genetic code. Mol. Cell. Biol. 22 (11), 3565–3576.

Higgins, J.P., et al., 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343, d5928.

Jamilian, M., et al., 2015. Metabolic response to selenium supplementation in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Clin. Endocrinol. 82 (6), 885–891.

Kamali, A., Amirani, E., Asemi, Z., 2019. Effects of selenium supplementation on metabolic status in patients undergoing for coronary artery bypass grafting (CABG) surgery: a randomized, double-blind, placebo-controlled trial. Biol. Trace Elem. Res. 1–7.

Karamali, M., et al., 2015. The favourable effects of long-term selenium supplementation on regression of cervical tissues and metabolic profiles of patients with cervical intraepithelial neoplasia: a randomised, double-blind, placebo-controlled trial. Br. J. Nutr. 114 (12), 2039–2045.

Kieliszek, M., Błażejak, S., 2016. Current knowledge on the importance of selenium in food for living organisms: a review. Molecules 21 (5), 609.

Kipp, A.P., et al., 2015. Revised reference values for selenium intake. J. Trace Elem. Med.

Biol. 32, 195–199.

Klopotek, A., Hirche, F., Eder, K., 2006. PPARγ ligand troglitazone lowers cholesterol synthesis in HepG2 and Caco-2 cells via a reduced concentration of nuclear SREBP-2. Exp. Biol. Med. 231 (8), 1365–1372.

Laclaustra, M., et al., 2010. Serum selenium and serum lipids in US adults: national health and nutrition examination Survey (NHANES) 2003–2004. Atherosclerosis 210 (2), 643–648.

Luoma, P., et al., 1985. Serum selenium, glutathione peroxidase, lipids, and human liver microsomal enzyme activity. Biol. Trace Elem. Res. 8 (2), 113–121.

Mesdaghinia, E., et al., 2017. Clinical and metabolic response to selenium supplementation in pregnant women at risk for intrauterine growth restriction: randomized, double-blind, placebo-controlled trial. Biol. Trace Elem. Res. 178 (1), 14–21.

Nordberg, J., Arnér, E.S., 2001. Reactive oxygen species, antioxidants, and the mammalian thioredoxin system. Free Radic. Biol. Med. 31 (11), 1287–1312.

Omrani, H., et al., 2016. Effect of selenium supplementation on lipid profile in hemodialysis patients. J. Ren. Inj. Prev. 5 (4), 179.

Rad, E.Y., et al., 2014. The effects of vitamin D supplementation on glucose control and insulin resistance in patients with diabetes type 2: a randomized clinical trial study. Iran. J. Public Health 43 (12), 1651.

Ravn-Haren, G., et al., 2008. A short-term intervention trial with selenate, selenium-enriched yeast and selenium-enriched milk: effects on oxidative defence regulation. Br. J. Nutr. 99 (4), 883–892.

Raygan, F., et al., 2018. Selenium supplementation lowers insulin resistance and markers of cardio-metabolic risk in patients with congestive heart failure: a randomised, double-blind, placebo-controlled trial. Br. J. Nutr. 120 (1), 33–40.

Rayman, M.P., 2008. Food-chain selenium and human health: emphasis on intake. Br. J. Nutr. 100 (2), 254–268.

Rayman, M.P., et al., 2011. Effect of supplementation with high-selenium yeast on plasma LipidsA randomized trial. Ann. Intern. Med. 154 (10), 656–665.

Saboori, S., et al., 2016. Various effects of omega 3 and omega 3 plus vitamin E supplementations on serum glucose level and insulin resistance in patients with coronary artery disease. Iran. J. Public Health 45 (11), 1465.

Salehi, M., et al., 2012. Selenium supplementation improves the nutritional status of hemodialysis patients: a randomized, double-blind, placebo-controlled trial. Nephrol. Dial. Transplant. 28 (3), 716–723.

Salonen, J., et al., 1982. Association between cardiovascular death and myocardial infarction and serum selenium in a matched-pair longitudinal study. The Lancet 320 (8291), 175–179.

Schnabel, R., et al., 2008. Selenium supplementation improves antioxidant capacity in vitro and in vivo in patients with coronary artery disease: the SElenium Therapy in Coronary Artery disease Patients (SETCAP) Study. Am. Heart J. 156 (6), 1201. e1–1201. e11.

Sengupta, A., et al., 2008. Loss of housekeeping selenoprotein expression in mouse liver modulates lipoprotein metabolism. Biochem. Biophys. Res. Commun. 365 (3), 446–452.

Tabrizi, R., et al., 2017. The effects of selenium supplementation on glucose metabolism and lipid profiles among patients with metabolic diseases: a systematic review and meta-analysis of randomized controlled trials. Horm. Metab. Res. 49 (11), 826–830.

Tamtaji, O.R., et al., 2018. Probiotic and selenium co-supplementation, and the effects on clinical, metabolic and genetic status in Alzheimer's disease: a randomized, double-blind, controlled trial. Clin. Nutr. https://doi.org/10.1016/j.clnu.2018.

Tara, F., et al., 2010. Selenium supplementation and the incidence of preeclampsia in pregnant Iranian women: a randomized, double-blind, placebo-controlled pilot trial. Taiwan. J. Obstet. Gynecol. 49 (2), 181–187.

Vunta, H., et al., 2007. The anti-inflammatory effects of selenium are mediated through 15-deoxy-Delta12,14-prostaglandin J2 in macrophages. J. Biol. Chem. 282 (25), 17964–17973.

Wei, J., et al., 2015. The association between dietary selenium intake and diabetes: a cross-sectional study among middle-aged and older adults. Nutr. J. 14 (1), 18.

Wojcicki, J., et al., 1991. Effect of selenium and vitamin E on the development of experimental atherosclerosis in rabbits. Atherosclerosis 87 (1), 9–16.

Wolf, N.M., et al., 2010. Study of molecular targets influencing homocysteine and cholesterol metabolism in growing rats by manipulation of dietary selenium and methionine concentrations. Br. J. Nutr. 104 (4), 520–532.

Xun, P., et al., 2010. Longitudinal association between toenail selenium levels and measures of subclinical atherosclerosis: the CARDIA trace element study. Atherosclerosis 210 (2), 662–667.

Yang, K.-C., et al., 2010. Serum selenium concentration is associated with metabolic factors in the elderly: a cross-sectional study. Nutr. Metabol. 7 (1), 38.