Int J Clin Exp Med 2016;9(3):6086-6092
www.ijcem.com /ISSN:1940-5901/IJCEM0018009

Original Article

Association between deficient selenium levels and myocardial infarction: a meta-analysis

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Received October 16, 2015; Accepted January 6, 2016; Epub March 15, 2016; Published March 30, 2016

Abstract: There are conflicting reports as to the correlation between selenium (Se) levels and myocardial infarction (MI). The aim of this study is to clarify the relationship between serum Se levels and MI using a meta-analysis approach. We searched related articles in the Pubmed, and Science direct published as of October 2015. Seven eligible articles with 920 subjects from 12 case-control studies were included in the meta-analysis. Overall, pooled analysis indicated that subjects with MI had lower serum Se levels than healthy controls (SMD = -6.120, 95% CI = [-7.770, -4.471], $P < 0.001$). Further subgroup analysis found that subjects with MI had lower serum Se levels than healthy controls among the population in Asia (SMD = -10.168, 95% CI = [-14.698, -5.637], $P < 0.001$), but not similar pattern was found in Europe (SMD = -1.259, 95% CI = [-2.521, 0.003], $P = 0.051$). In conclusion, this meta-analysis indicates that there is a significant relationship serum Se deficiency and MI. We suggest that a long-term observation in a cohort design should be performed to obtain better understanding of causal relationships between Se and MI, through measuring Se at baseline to investigate whether the highest Se category versus lowest was associated with MI risk.

Keywords: Selenium, myocardial infarction, meta-analysis

Introduction

Atherosclerosis is a well-known precursor of ischemic heart disease due to accumulation of lipids and fibrous elements in arteries [1]. The development of atherosclerosis depends on a balance between pro-inflammatory stimuli, anti-inflammatory and antioxidant defence mechanisms [2]. Myocardial infarction (MI) occurs when myocardial ischemia, a diminished blood supply to the heart, exceeds a critical threshold and overwhelms myocardial cellular repair mechanisms designed to maintain normal operating function and homeostasis [3]. Trace elements, for example selenium (Se), are being increasingly recognized as essential mediators of the development and progression of MI [4-6]. The disturbance of Se may cause MI, because of a direct effect on the vascular system, or indirectly via lipoprotein metabolism [7, 8]. Lipoprotein oxidation is inhibited by enzymatic antioxidants, such as glutathione peroxidase and selenoenzyme glutathione peroxidase, the activities of which depend on an adequate Se supply [9]. The selenium-binding antioxidants are designed to prevent the occurrence of free radical-induced injury under normal conditions [10, 11]. Any significant modification of Se status would lead to changes in the activity of these enzymes and have important consequences on the susceptibility of tissues to oxidative stress [12].

Epidemiological studies support the possibility that the deficiency of certain essential element may increase the risk of MI. Some clinical studies found that there was a significant relationship between Se deficiency and MI risk [13, 14]. However, some studies suggest that there is no correlation between Se levels and MI risk [15]. Although Se deficiency is plausibly linked to an increase risk of MI, the inconsistency among the findings of previous studies precludes definitive recommendations at present. Meta-analysis is an important tool for revealing trends that might not be apparent. Therefore, we performed a comprehensive and critical meta-analysis of the studies, in order to draw a more

clear and evidence-based conclusion on the association between Se levels and MI.

Materials and methods

Search strategy

We searched the medical literature published in English in the Pubmed, and Science direct up to October 2015. Literature searches were applied by using the following search terms: "selenium" AND "myocardial infarction". Reference lists of all eligible studies were screened to identify potentially eligible studies. We contacted authors directly for crucial rude data that were unavailable in the original publications.

Selection criteria

Two authors independently selected eligible studies for inclusion possibility. Where there was a disagreement for study inclusion, a discussion was held to reach a consensus. Titles and abstracts were screened for subject relevance. Studies that could not be definitely excluded based on abstract information were also selected for full text screening. Eligible studies had to meet the following criteria: (1) human study; (2) case-control study or cohort study; (3) subjects with no other diseases and no drugs intake which might influence the levels of Se; (4) studies providing data of Se levels for both subjects with MI and healthy controls. Exclusion criteria included: (1) in vitro, laboratory study or animal study; (2) review or case report; (3) subjects with diseases/drugs (Keshan disease, Kashin-Beck disease, heart disease, high blood pressure, breast cancer) which might influence the serum levels of Se; (4) studies not providing serum levels of Se for both subjects with MI and healthy controls.

Data extraction and quality assessment

Two authors independently extracted data using a standard form. The following information was extracted from each included study: first author's family name, year of publication, type of study, country, demography of subjects (age and number of patients), data on serum levels of Se, type of Se measurement. For studies that included subjects of a different racial descent, we extracted data separately for each group and categorized these groups as Europe, and Asia.

The methodological quality of the included studies was independently and appraised twice by two authors. The qualities of all included studies were assessed using the Newcastle-Ottawa Scale (NOS) [16]. The assessment tool focused on three aspects, including participant selection, comparability and exposure. The studies would be assigned stars of 9 if all items were satisfied.

Statistical analysis

The extracted data were used to perform meta-analysis to obtain the standardized mean difference (SMD) and 95% confidence intervals (CI). The SMDs were calculated using either fixed-effects models or, in the presence of heterogeneity, random-effects models. We evaluated heterogeneity via the Chi-square and I-square tests. If the I^2 value was greater than 50% and the p value was less than 0.1, the meta-analysis was considered as homogeneous. Subgroup analyses were used to identify associations between Se levels and other relevant study characteristics as possible sources of heterogeneity. The stability of the study was detected by sensitivity analysis, through re-meta-analysis with one involved study excluded each time. Publication bias was measured using Begg's tests and visualization of funnel plots. All statistical analyses were performed with Stata version 11.0 (StataCorp, College Station, TX, USA).

Results

Literature search

The literature search yielded a total of 122 primary articles, of which 105 were excluded for one of the following reasons: (1) irrelevant to our topic (n = 59); (2) non-human studies (n = 36); (3) non-original studies (reviews, etc.) (n = 17); (4) articles not providing serum levels of Se for both subjects with MI and healthy controls (n = 3). Overall, 7 eligible articles with 12 case-control studies involving 920 subjects met the inclusion criteria for meta-analysis [13-15, 17-20]. A flow diagram of the study selection process is presented in **Figure 1**.

Study characteristics and quality assessment

By geographic location, 7 articles with 12 case-control studies were conducted in 7 different

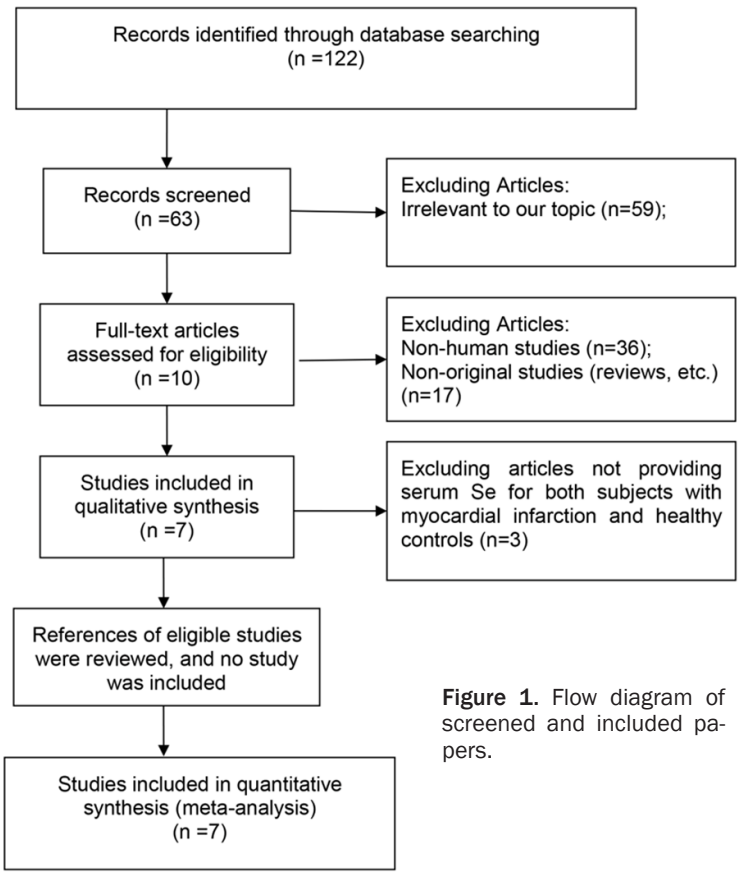

Figure 1. Flow diagram of screened and included papers.

countries (Finland, Germany, Norway, France, Spain, Iran and Pakistan). The earliest study was published in 1983, and the latest in 2014. The number of subjects in each study ranged from 70 to 162. All studies measured Se concentration by atomic absorption spectrophotometry (AAS). The overall study quality averaged 6 stars on a scale of 0 to 9. The characteristics of the included studies and the results of the quality assessment were listed in **Table 1**.

Serum se and myocardial infarction

The random-effects meta-analysis results indicated that patients with MI had lower serum levels of Se than the healthy controls (SMD = -6.120, 95% CI = [-7.770, -4.471], $P < 0.001$). The 12 sets of results showed a statistically significant amount of heterogeneity ($I^2 = 98.7\%$, $P < 0.001$) (**Figure 2**).

The subgroup analysis showed that the geographical location had an influence on the serum Se in MI and healthy controls. Further subgroup analysis stratified by geographical location indicated that subjects with MI had lower serum Se levels than healthy controls among the population in Asia (SMD = -10.168, 95% CI = [-14.698, -5.637], $P < 0.001$), but not similar pattern was found in Europe (SMD = -1.259, 95% CI = [-2.521, 0.003], $P = 0.051$) (**Figure 3**).

Publication bias and sensitivity analysis

Publication bias was determined by Begg's test and visualization of funnel plot. There was no evidence of publication bias ($P = 0.891$) (**Figure 4**). Sensitivity analysis showed that excluding any one study from the pooled analysis did not vary the results substantially (**Table 2**).

Discussion

Atherosclerosis is a well-known precursor of MI due to accumulation of lipids and fibrous elements in arteries, which can be caused by the disturbance between pro-inflammatory stimuli, anti-inflammatory and antioxidant defence mechanisms [21]. In recent years, studies have investigated the possible role of antioxidant index, for example Se, in the etiology and pathogenesis of MI [13, 17]. In the present study, our meta-analysis of 920 participants from 12 case-control studies found that the low serum levels of Se were associated with MI, which may reflect the increased risk of MI in patients with low Se levels.

Selenium (Se) is a trace element and an essential part of the enzyme glutathione peroxidase (GSH-Px), which protects cells from oxidative damage [22]. Oxidative damage is thought to play an important role in atherosclerosis, which is a well-known precursor of MI. Reactive oxygen species (ROS) bring about lipid peroxidation, and oxidized low-density lipoprotein promotes atherogenesis and destabilizes plaque via several pathways, including the induction of apoptosis of vascular wall cells. The free radical comes in contact with the inner lining of the arteries, where microscopic injuries occur. Eventually, the buildup of fat, cholesterol, met-

Table 1. Characteristics of subjects in eligible studies

Studies	Country	Measurement	Myocardial infarction			Healthy controls			Quality score
			Age (year)	N	Concentration (mean ± SD)	Age (year)	N	Concentration (mean ± SD)	
Miettinen 1983	Finland	AAS	48	33	75.2±3.3 μg/L	48	64	72.9±1.8 μg/l	5
Koehler 1987	Germany	AAS	NR	54	670±266 nmol/L	18-70	93	981±209 nmol/l	6
Ringstad 1987	Norway	AAS	NR	59	1.57±0.21 μmol/L	NR	59	1.61±0.27 μmol/l	6
Auzepy 1987	France	AAS	NR	31	73.55±2.33 μg/L	NR	48	84.73±1.79 μg/l	6
Navarro-Alarcon 1999	Spain	AAS	65	32	58.67±27.16 μg/L	NR	130	74.9±27.3 μg/l	6
Hassanzadeh 2006	Iran	AAS	NR	25	74.08±11.31 μg/L	NR	50	105.36±32.52 μg/l	7
Afridi 2014-1	Pakistan	AAS	45~60	35	120±9.67 μg/L	45~60	51	215±15.6 μg/l	6
Afridi 2014-2	Pakistan	AAS	45~60	23	109±8.73 μg/L	45~60	56	208±11.5 μg/l	6
Afridi 2014-3	Pakistan	AAS	45~60	25	76.9±5.92 μg/L	45~60	51	215±15.6 μg/l	6
Afridi 2014-4	Pakistan	AAS	45~60	15	65.9±6.82 μg/L	45~60	56	208±11.5 μg/l	6
Afridi 2014-5	Pakistan	AAS	45~60	23	33.8±4.5 μg/L	45~60	51	215±15.6 μg/l	6
Afridi 2014-6	Pakistan	AAS	45~60	14	30.6±2.81 μg/L	45~60	56	208±11.5 μg/l	6

NR, not reported. AAS, atomic absorption spectrophotometry.

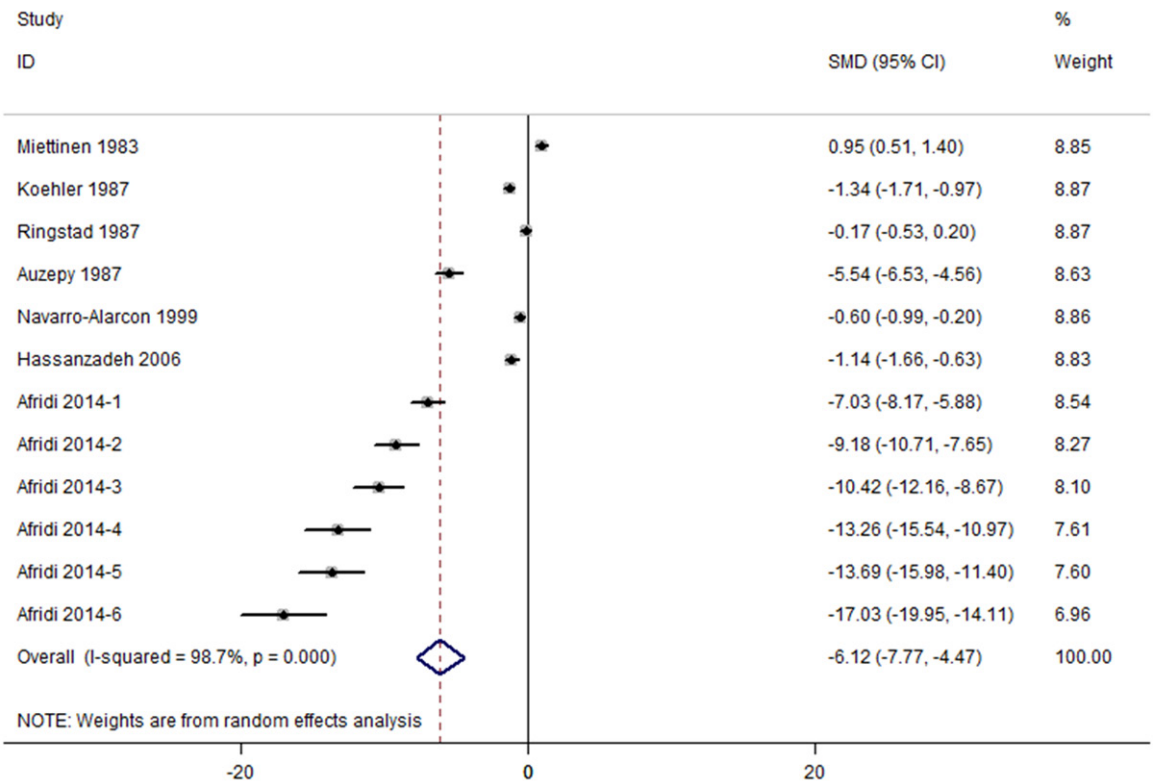

Figure 2. Forest plot of studies in Se levels for subjects with MI versus healthy controls. The combined SMD and 95% confidence intervals (CIs) were calculated using the random-effects model.

als, and other substance at the site of injury narrows the arteries, which leads to MI. ROS produced by various processes in peripheral blood are inhibited by enzymatic and non-enzymatic antioxidants, which protect DNA and other important molecules from oxidative damage which would otherwise induce apoptosis [23, 24]. Se, as a cofactor of enzyme glutathione peroxidase (GSH-Px), is an important antioxidant enzyme which protects the DNA and main cellular components from the damage of the free radicals by decreasing ROS generation

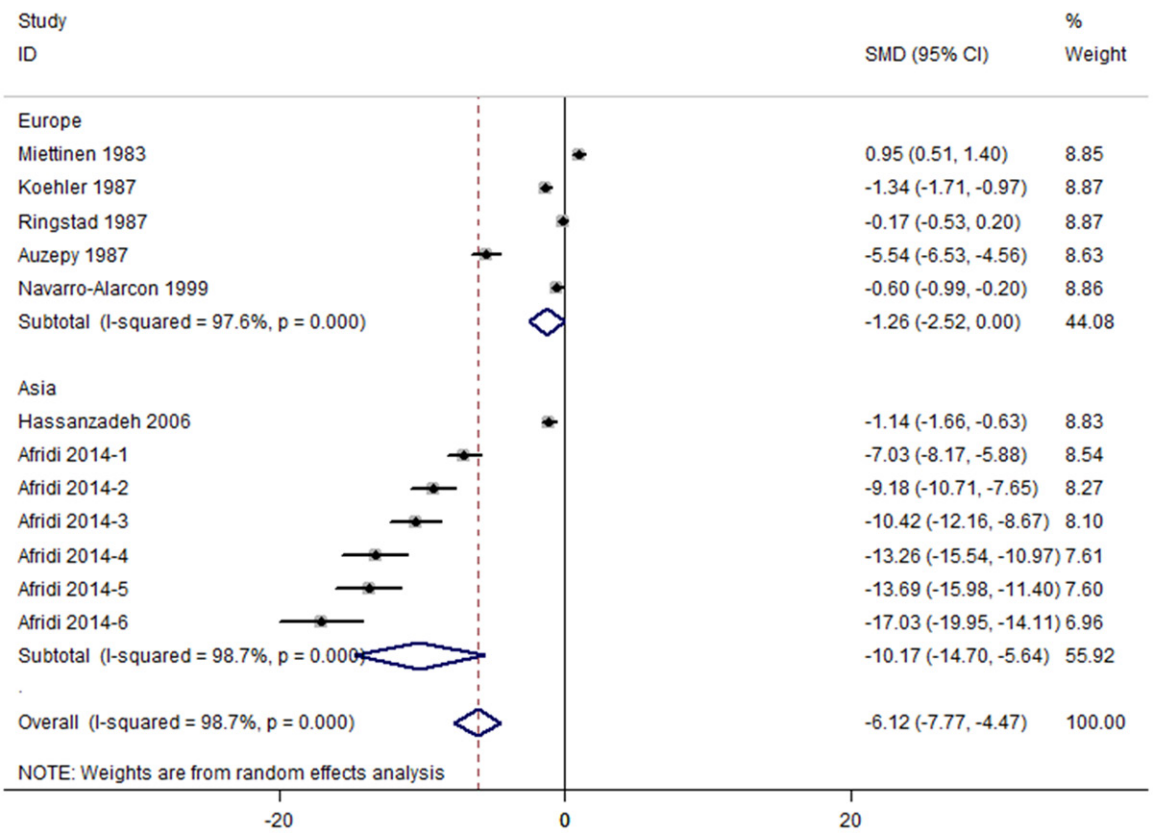

Figure 3. Subgroup analysis stratified by geographical location of studies in levels of Se for subjects with MI versus healthy controls.

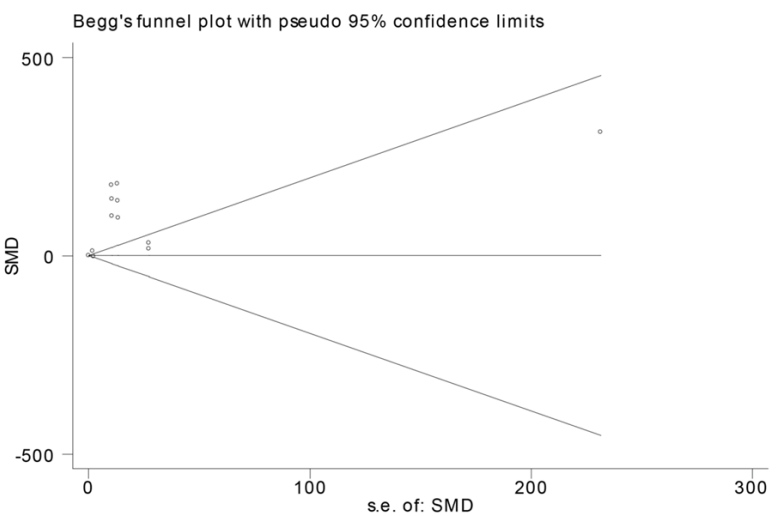

Figure 4. Funnel plot for studies in Se levels for subjects with MI versus healthy controls.

[25, 26]. Thus, it is possible that Se acting as an antioxidants and free radical scavenger provide protection against MI, and the deficiency of Se may directly result in the increased risk of MI.

To the best of our knowledge, this is the first meta-analysis to estimate the association between serum levels of Se with MI. We made sure to minimize the bias by means of study procedure. Publication bias was also absent, as determined by Begg's test. Sensitivity analysis showed that excluding any one study from the pooled analysis did not vary the results substantially. However, the limitations of present study should be noted. To begin with, significant heterogeneity was observed in overall and subgroup analyses. Otherwise, the observation of heterogeneity should not reduce the confidence in the find-

Table 2. The stability of the study was detected through sensitivity analysis

Excluded study	SMD (95% CI)	I^2	*P*
Before excluding	-6.120 (-7.770, -4.471)	98.7%	< 0.001
Miettinen 1983	-6.834 (-8.626, -5.043)	98.7%	< 0.001
Koehler 1987	-6.682 (-8.663, -4.701)	98.8%	< 0.001
Ringstad 1987	-6.784 (-8.729, -4.838)	98.8%	< 0.001
Auzepy 1987	-6.154 (-7.839, -4.469)	98.7%	< 0.001
Navarro-Alarcon 1999	-6.741 (-8.685, -4.798)	98.8%	< 0.001
Hassanzadeh 2006	-6.659 (-8.521, -4.796)	98.8%	< 0.001
Afridi 2014-1	-5.996 (-7.646, -4.346)	98.7%	< 0.001
Afridi 2014-2	-5.796 (-7.428, -4.165)	98.7%	< 0.001
Afridi 2014-3	-5.692 (-7.317, -4.068)	98.7%	< 0.001
Afridi 2014-4	-5.487 (-7.103, -3.871)	98.7%	< 0.001
Afridi 2014-5	-5.448 (-7.057, -3.840)	98.6%	< 0.001
Afridi 2014-6	-5.266 (-6.868, -3.665)	98.6%	< 0.001

ing but just add some uncertainty about the magnitude of that [27]. In present study, the further subgroup analysis indicated that the geographical location was the possible source of heterogeneity. We found that subjects with MI had lower serum Se levels than healthy controls in Asia, but not in Europe. Second, only 920 participants from 12 case-control studies and no randomized clinical trial included in the meta-analysis might weaken the quality of the results. Despite these limitations, our findings point out new directions for future research. The present study raised new question why there was no relationship with Se deficiency and MI in Europe, just as in Asia. Thus, we suggest that a trans-regional multicenter, community-based and long-term observation in a cohort design should be performed to obtain better understanding of causal relationship between serum Se with MI of different human races or regions.

Conclusion

In conclusion, this meta-analysis supports a significant association between deficient serum Se concentration and MI. However, this finding needs further confirmation by a trans-regional multicenter study to obtain better understanding of causal relationship between serum Se with MI of different human races or regions.

Disclosure of conflict of interest

None.

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