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Serum level of antioxidant vitamins and minerals in patients with vitiligo, a systematic review and meta-analysis

Jing Huo[a], Taibin Liu[a], Yuchao Huan[b], Fenghua Li[c], Rui Wang[a,*]

[a] Department of Dermatology and Venereal Diseases, Dezhou People's Hospital, Dezhou, China
[b] Department of Dermatology and Venereal Diseases, Jinan City People's Hospital, Jinan, China
[c] Department of Endocrinology, Dezhou People's Hospital, Dezhou, China

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ABSTRACT

Background: Antioxidant status is considered as important factor in the pathogenesis of vitiligo. However, there are controversial findings about serum status of antioxidants in vitiligo patients. The purpose of this study was to systematically review the evidences comparing the serum levels of antioxidant vitamins and minerals between vitiligo patients and controls, and performing meta-analysis of the results.

Methods: A comprehensive search was performed for studies comparing the serum status of antioxidant vitamins and minerals using following databases since inception up to 30 April 2020; PubMed, EMBASE, Scopus, and Web of Science. Data extraction was done by two independent reviewers. The data was pooled for serum level of each antioxidant comparing between vitiligo and control groups.

Results: Thirteen studies were included in this systematic review. The serum level of vitamin A, C, E, selenium, zinc and copper were compared between vitiligo patients and controls in these studies. Eleven studies including 570 vitiligo cases and 580 controls were included in the meta-analysis. Serum vitamin A and copper level in vitiligo patients were only evaluated in single studies and not included in meta-analysis. Based on fixed effect model, there were no statistical difference between two groups regarding serum vitamin C (OR = 1.17, 95 % CI, 0.74–1.84, P = 0.495), and vitamin E (OR = 0.61, 95 % CI, 0.30–1.25, P = 0.180). Higher serum zinc can decrease the risk of vitiligo based on sensitivity analysis of the results. (OR = 0.29, 95 % CI 0.15 − 0.54, P < 0.001). Higher serum selenium level significantly increased the risk of vitiligo (OR = 4.31, 95 % CI, 2.72–6.81, P < 0.001). Vitamin A was not significantly different in two reported groups (6.35 ± 1.53 vs 6.77 ± 1.46 μg/mL, P > 0.05). Copper was significantly higher in vitiligo patients compared to controls (129 ± 33 vs 99 ± 19 μg /100 mL, P = 0.002).

Conclusion: The current meta-analysis of data on serum level of most studied antioxidants (vitamin C, vitamin E, zinc and selenium) in patients suffering vitiligo showed that higher serum selenium (OR = 4.31) and lower zinc level (OR = 0.29) can increased the risk of vitiligo. Potential mechanism associated with preventive effects of zinc and the depigmentation effect of selenium should be more elucidated in further studies.

1. Introduction

Vitiligo is a common acquired hypopigmentation disorder of the skin, mucous membranes and the retina [1]. The mean prevalence of vitiligo is estimated to be 0.2 % in population studies [2]. Vitiligo affects all age groups, all races and both sexes with higher prevalence in adult African females [2]. This disorder has major impact on quality of life of patients [3].

The pathophysiology of vitiligo is remained unclear. Oxidative stress has been evaluated as an important factor in the pathophysiology of vitiligo [4]. Some studies have demonstrated impaired antioxidant function in melanocytes of patients with vitiligo [5]. Melanocyte degeneration caused by free radical damage is shown in patients with vitiligo. Reduced catalase activity is previously demonstrated in the blood of vitiligo patients [6]. It is also shown to be associated with significant rise in epidermal free radicals [6] Serum level of different antioxidant vitamins and minerals including vitamin A, C, E, selenium, zinc and copper have been compared between patients with vitiligo and controls in different studies. However, the results are controversial.

The purpose of this study was to systematically review the evidences comparing the serum level of antioxidant vitamins and minerals between vitiligo patients and controls, and performing meta-analysis of

* Corresponding author.
E-mail address: ruiwangdermatology@gmail.com (R. Wang).

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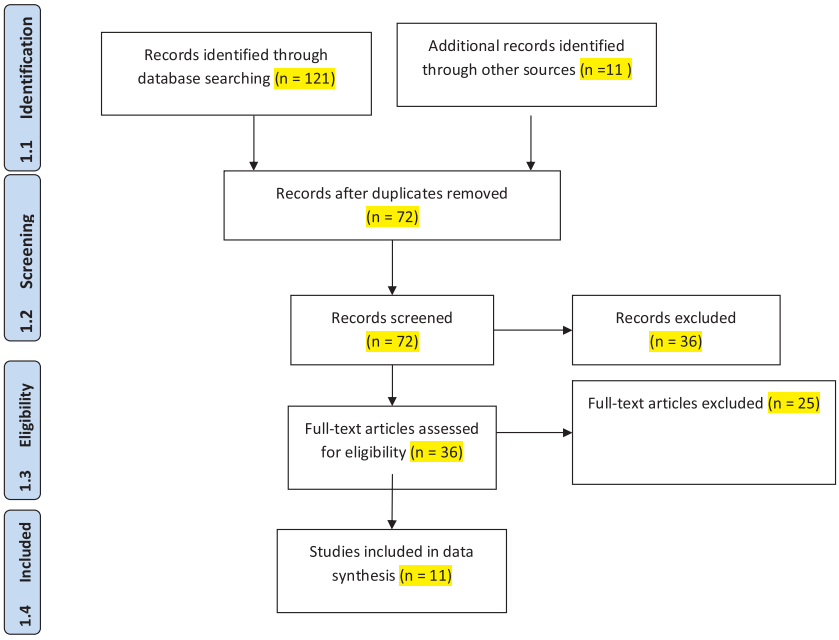

Fig. 1. PRISMA flow diagram for included studies.

the results.

2. Methods

2.1. Search strategy

A comprehensive search was performed to retrieve any study comparing the serum status of antioxidant vitamins and minerals from published literature. The following databases were evaluated since inception up to 30 April 2020; PubMed, EMBASE, Scopus, and Web of Science. The term “vitiligo” was added to keywords of antioxidants including “antioxidant”, “antioxidative”, “vitamin”, “zinc”, “selenium”, “copper” and “zinc” for database search. This review was restricted to studies reported in the English language.

2.2. Selection criteria

To meet the study objective, human studies on serum level of antioxidants in patients with vitiligo were included. Studies reported serum status of antioxidant vitamin or minerals in two study groups (patients with vitiligo and control groups) were included in the meta-analysis.

Following studies were excluded: (1) reviews presenting secondary data (2); animal and in-vitro studies (3); studies without control group (4); studies from which full text could not be sourced.

2.3. Data extraction

Bibliographic information of all articles found in literature search was imported into Endnotes V. × 6. Two independent reviewers performed data extraction. Third reviewer solved inconsistencies between the extracted data by the two reviewers.

Data was recorded on data extraction forms. Qualitative and quantitative data for the patient population, enrolment numbers in each group and type of antioxidant evaluated in serum in each group were extracted from each included study. The data was pooled for serum level of each antioxidant regardless of causality association. Review Manager (RevMan V.5.1) software was used for meta-analysis of the available data. The levels of mentioned antioxidant were compared between case and control groups for evaluating the effect of each antioxidant.

2.4. Quality assessment of included articles

The checklist provided by the Joanna Briggs Institute was used to check and control the quality of the articles [7]. The checklist consists of 8 questions that are categorized as "Yes, No, Not Specified and Not Applicable".

2.5. Statistical analysis

Cochran test was used for evaluation of the heterogeneity of the studies. The composition was assessed by I2 statistic. The random effect model was used to manage heterogeneity in the studies; otherwise, a fixed effect model was applied. The calculated odds ratio (OR) was used for comparison of differences between two groups. Sensitivity analysis was done by excluding each study separately and re-analysis of the results. Comprehensive Meta-Analysis (CMA) software (version 2) was used for analysis of data.

3. Results

3.1. Description of search

After searching all international databases, 132 articles were found and after removing duplicate articles, 72 articles were examined in terms of topic and abstract, out of which 36 articles entered the next stage. After reviewing their topics and abstracts at this stage, the full texts of the articles were examined and 13 articles entered the systematic review. The serum level of vitamin A, C, E, selenium, zinc and copper w ere compared between vitiligo patients and controls in these studies. Eleven studies including 570 vitiligo cases and 580 controls were included in the meta-analysis. The flowchart of the included studies is presented in Fig. 1.

3.2. Study characteristics

More specifically, the present review included studies published between 1999 and 2019. Based on geographical location, four studies were from Iran, one study from Bangladesh, one from Nepal, one from

Table 1
Characteristics of studies included in systematic review and meta-analysis.

Study	Antioxidant	Country	Year	Study design	Number in vitiligo group	Number in control group
(3)	Vitamin C and Zinc	Bangladesh.	2010	Cross-sectional	30	30
(8)	Vitamin C & Vitamin E	Nepal	2014	Cross-sectional	69	80
(9)	Vitamin E and Selenium	France	2002	Cross-sectional	11	11
(5)	Vitamin E and Selenium	Tunisia	2006	Cross-sectional	18	40
(10)	Vitamin E	India	2008	Cross-sectional	40	40
(11)	Vitamin E	Turkey	1999	Cross-sectional	23	23
(12)	Zinc	Iran	2018	Cross-sectional	63	103
(13)	Zinc	Iran	2017	Cross-sectional	100	100
(14)	Zinc	Iran	2019	Cross-sectional	98	98
(15)	Selenium	Iran	2011	Cross-sectional	60	45
(16)	Selenium	UK	1999	Cross-sectional	61	10
(17)	Vitamin A	Tunisia	2006	Cross-sectional	36	40
(18)	Copper	Bulgaria	1972	Cross-sectional	84	20

Table 2
JBI critical appraisal checklist applied for included studies.

Author Name/Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Overall Quality
Haider, 2010	Yes	Yes	N/A	No	No	No	Yes	Yes	4/8
Jain, 2008	Yes	Yes	N/A	Yes	No	No	Yes	Yes	5/8
Kockam, 1999	Yes	Yes	N/A	No	No	No	Yes	Yes	4/8
Mirnezami, 2018	Yes	Yes	N/A	Yes	No	No	Yes	Yes	4/8
Agrawal, 2014	Yes	Yes	N/A	No	No	No	Yes	Yes	4/8
Barikbin, 2011	Yes	Yes	N/A	No	Yes	Yes	Yes	Yes	6/8
Beazley, 1999	Yes	Yes	N/A	Yes	No	No	Yes	Yes	5/8
Boisseau-Garsaud, 2002	Yes	Yes	N/A	No	No	No	Yes	Yes	4/8
Ines, 2006	Yes	Yes	N/A	Yes	No	No	Yes	Yes	5/8
RostamiMogaddam, 2017	Yes	Yes	N/A	No	No	No	Yes	Yes	4/8
Saniee, 2019	Yes	Yes	N/A	Yes	Yes	No	Yes	Yes	6/8
Dammak, 2006	Yes	Yes	N/A	No	Yes	No	Yes	Yes	5/8
Genov, 1972	Yes	Yes	N/A	No	No	No	Yes	Yes	4/8

Q1. Were the criteria for inclusion in the sample clearly defined?.
Q2. Were the study subjects and the setting described in detail?.
Q3. Was the exposure measured in a valid and reliable way?.
Q4. Were objective, standard criteria used for measurement of the condition?.
Q5. Were confounding factors identified?.
Q6. Were strategies to deal with confounding factors stated?.
Q7. Were the outcomes measured in a valid and reliable way?.
Q8. Was appropriate statistical analysis used?.

France, one from Tunisia, one from India, one from Turkey, and one from UK. The characteristics of the studies are illustrated in Table 1.

3.3. Quality assessment

The studies included in the meta-analysis had overall quality score of 4–6 out of 8 based on JBI critical appraisal scores. The detailed information on quality evaluation of the studies is presented in Table 2.

3.4. Results of meta-analysis

3.4.1. Vitamin C

Among the included studies, three articles compare serum level of vitamin C in patients with vitiligo and control group. Base on fixed - effect model, there is no statistical difference between two groups (OR = 1.17, 95 % CI, 0.74–1.84, P = 0.495; I^2 = 0.0 %, P = 0.640) (Fig. 2).

3.4.2. Vitamin E

Base on fixed - effect model, serum level of vitamin E in vitiligo patients is lower than control group, but this finding was not statistically significant (OR = 0.61, 95 % CI, 0.30–1.25, P = 0.180; I^2 = 72.9 %, P = 0.001) (Fig. 3).

3.4.3. Zinc

Among the included studies, three articles compare serum level of zinc in patients with vitiligo and control group. Base on random - effect model, higher serum zinc can decrease the risk of vitiligo (OR = 0.47, 95 % CI, 0.19–1.16, P = 0.102; I^2 = 88.4 %, P < 0.001) (Fig. 4). However this clinically considerable OR only reaches statistical significance in sensitivity analysis of the results. (OR = 0.29, 95 % CI 0.15 − 0.54, P < 0.001) (Fig. 7).

3.4.4. Selenium

Base on fixed - effect model, serum level of selenium in vitiligo patients was higher than control group, and this finding was statistical significant (OR = 4.31, 95 % CI, 2.72–6.81, P < 0.001; I^2 = 33.8 %, P = 0.196) (Fig. 5).

3.5. Vitamin A and copper

Serum vitamin A and copper level in vitiligo patients were only evaluated in single studies and were not included in meta-analysis.

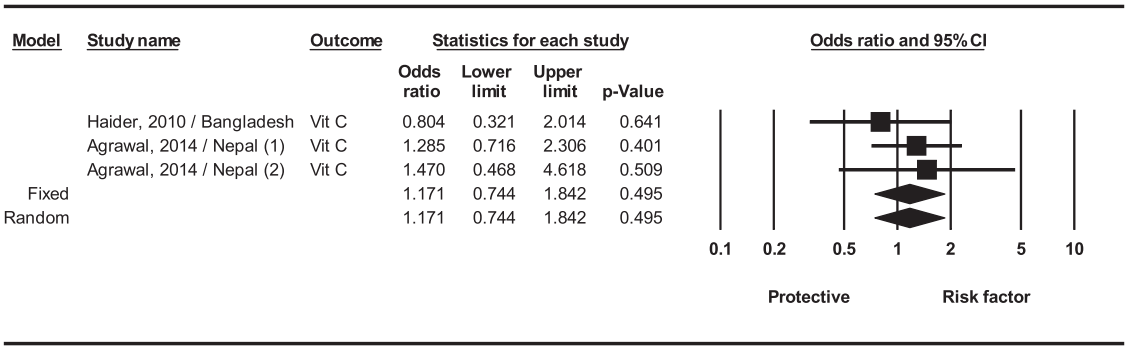

Fig. 2. Forest plot showing serum vitamin C level in patients with vitiligo compared to controls. Values are expressed as odds ratio with 95 % confidence interval (CI).

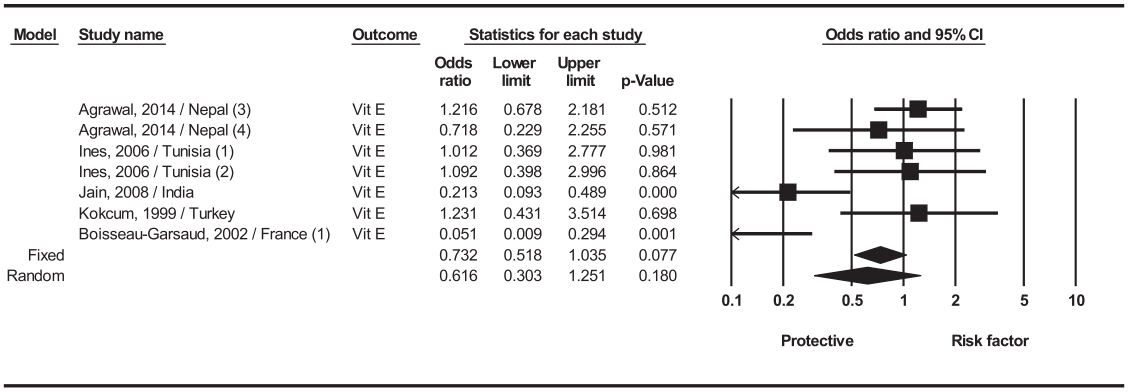

Fig. 3. Forest plot showing serum vitamin E level in patients with vitiligo compared to controls. Values are expressed as odds ratio with 95 % confidence interval (CI).

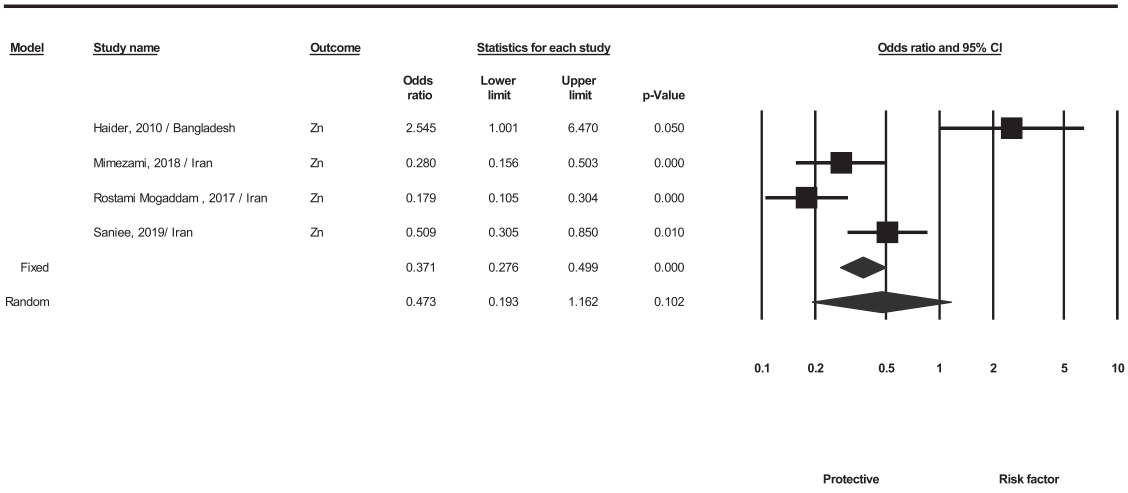

Fig. 4. Forest plot showing serum zinc level in patients with vitiligo compared to controls. Values are expressed as odds ratio with 95 % confidence interval (CI).

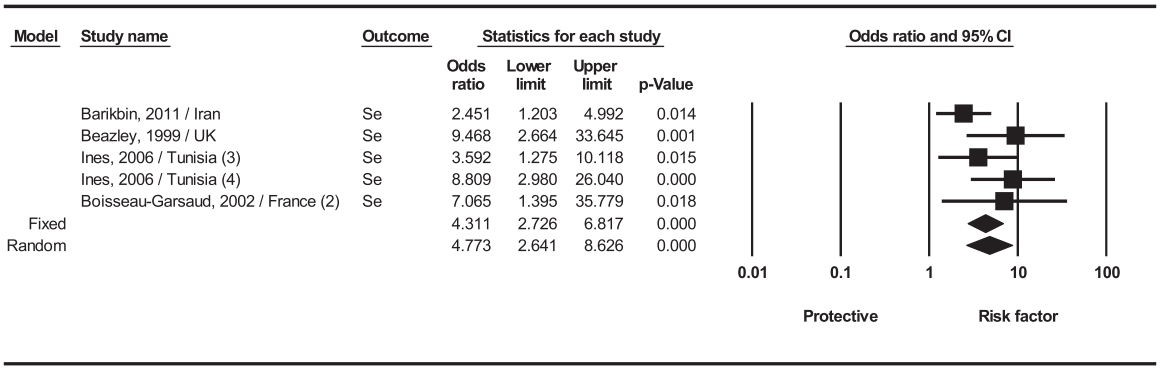

Fig. 5. Forest plot showing serum vitamin C level in patients with vitiligo compared to controls. Values are expressed as odds ratio with 95 % confidence interval (CI).

Vitamin A was not significantly different in two reported groups (6.35 ± 1.53 vs 6.77 ± 1.46 μg/mL, P > 0.05). [17] Copper was significantly higher in vitiligo patients compared to controls (129 ± 33 vs 99 ± 19 μg /100 mL, P = 0.002) [18].

3.6. Publication bias

Finally, according to the presented result by funnel plot and egger test (P = 0.09) no significant bias was observed (Fig. 6).

3.7. Sensitivity analysis

The findings were reanalyzed by deleting each study separately. The results were yielded regarding all outcomes (Fig. 7).Only for Zn has it been shown that a significant relationship is observed with the removal of Haider, 2010 study (OR = 0.29, 95 % CI 0.15−0.54, P < 0.001). Other findings did not change significantly with the removal of any of the studies.

4. Discussion

The importance of antioxidant activity in the pathogenesis of vitiligo has been evaluated in multiple investigations [19]. Stress, considered as initiating event in many patients with vitiligo, causes catecholamines rise in microenvironment of melanocytes [20] which is followed by sympathetic induced vasoconstriction of the dermis

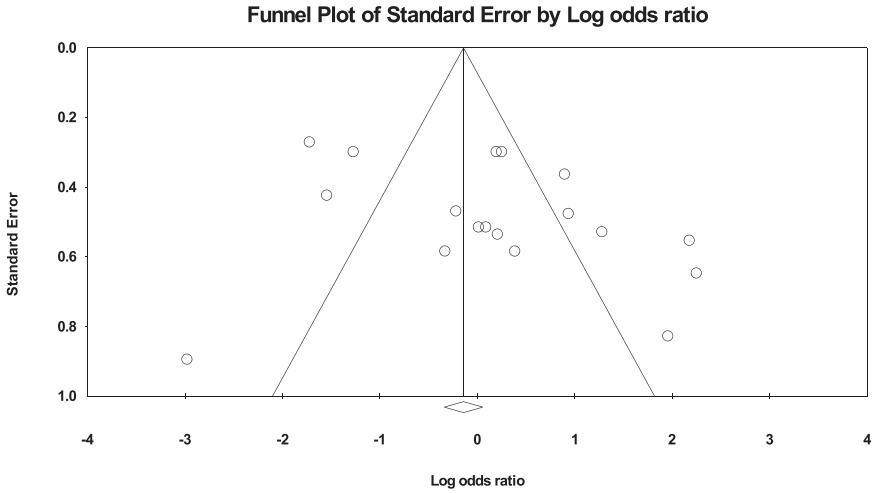

Fig. 6. Funnel plot showing publication bias of included studies.

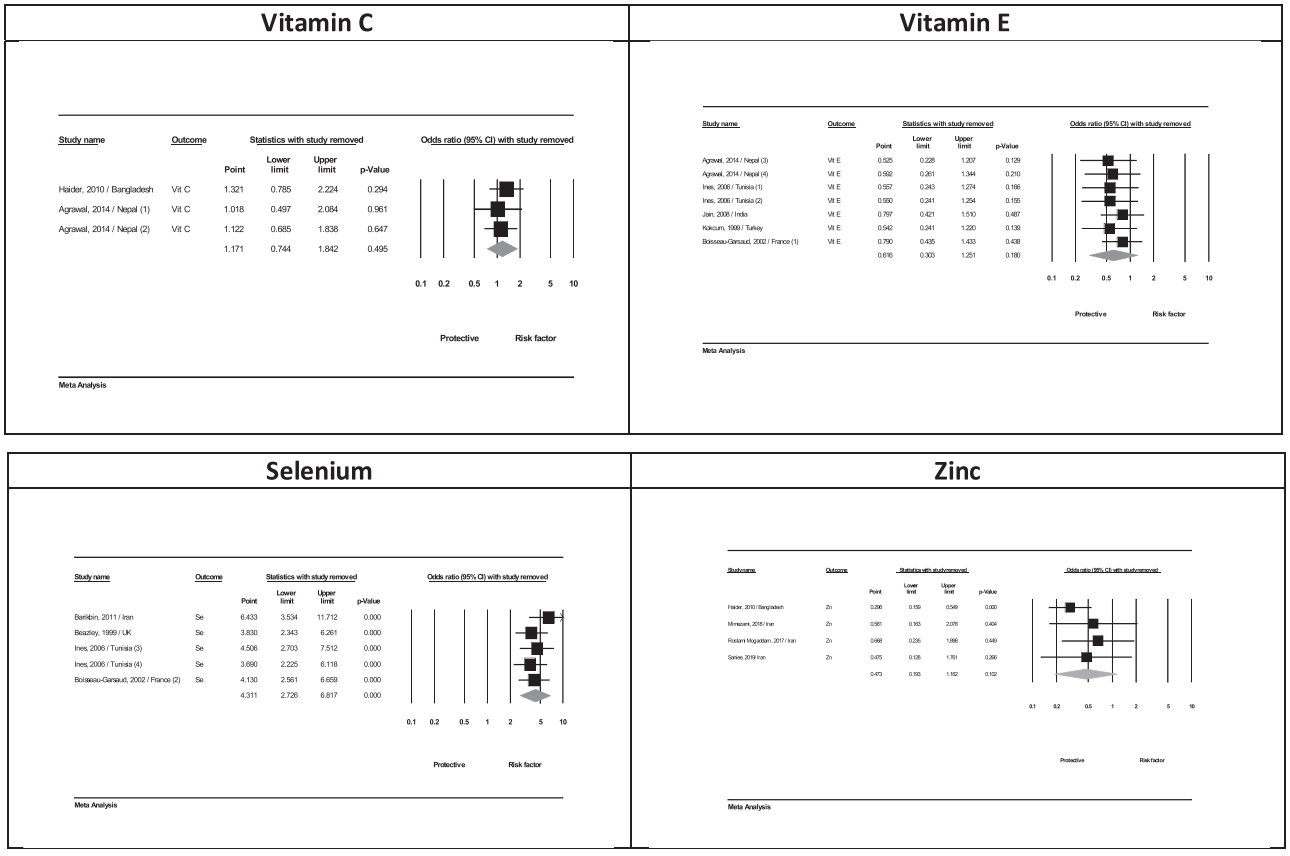

Fig. 7. Sensitivity analysis of studies included in meta-analysis. Values are expressed as odds ratio with 95 % confidence interval (CI) for exclusion of each study from analysis.

vasculature and cell damage by accumulation of free radicals [21].

Some researches on antioxidants status in vitiligo have shown no significant change in the systemic antioxidant status, but demonstrated a decreased antioxidants activity in the epidermis. [11,22,23] There are also some reports showed an increase in the global blood antioxidant status in patients with vitiligo compared to controls [9,24]. Our study, summing up the results of 10 studies on serum level of antioxidants in patients with vitiligo, showed no significant difference between serum level of antioxidants in these patients and controls, except for zinc and selenium.

Selenium has been demonstrated to be increased in the serum of vitiligo patients compared to controls in multiple studies [9,16,25,26]. Accumulation of these results was confirmed to be statistically significant in our meta-analysis. The significance of selenium elevation in vitiligo patients is unknown. However this evidence is against previous recommendations for selenium supplementation as an antioxidant in vitiligo [27]. The underlying association between higher serum selenium level and risk of vitiligo is unknown. Selenium is considered as important trace element in modulating oxidative stress pathway [28]. It is not known that how much glutathione peroxidase activity of melanocytes is by selenium-dependent isoenzymes [29]. On the other hand, some studies revealed depigmenting effect of selenium-containing

carbohydrates [30]. Some organic selenium compounds also showed to be able to decrease melanin production through inhibiting tyrosinase activity [31]. Potential mechanism associated with the depigmentation effect of selenium should be more elucidated in further studies.

Beside potential benefits of trace elements as antioxidants in skin there are also reports on toxic effects of these elements. For example multiple studies have shown that high dose of selenium may be associated with increased risk of melanoma [32–35]. This paradoxical effect can be explained as metalloids are not only antioxidants but also can act as pro- oxidants [36–39].

The potential effect of the disease status on the serum levels of the antioxidants should be also considered in the interpretation of the results. For instance it is previously suggested that systemic inflammatory response may be present in patients with active vitiligo [40]. On the other hand the serum level of antioxidant trace elements like selenium and zinc are showed to be decreased in inflammation [41,42]. Therefore the disease status may affect the level of antioxidants in patients with vitiligo. This reverse causation should also be mentioned in analysis of the study findings.

There are also some limitations which should be considered for interpretation of the results of this study. Depigmented patches of vitiligo can be an active autoimmune lesions or previous lesions of white scar with few viable melanocytes. It is important for the researches to consider stable versus active diseases, systemic versus local area of involvement, and comorbidities of other autoimmune diseases which are not considered in many of reports. The other limitation is that dietary antioxidants and trace elements can vary significantly by country, geographic locations, religions, and food culture [43]. Despite the effect of these variants on our results we could not enter them into meta-analysis because of limited number of studies.

5. Conclusion

The current meta-analysis of the results of 10 researches on serum level of most studied antioxidants in patients suffering vitiligo showed that higher serum selenium (OR = 4.31) and lower zinc level (OR = 0.29) can increased the risk of vitiligo. Potential mechanism associated with preventive effects of zinc and the depigmentation effect of selenium should be more elucidated in further studies.

Declaration of Competing Interest

No conflict of interest.

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