

Meta analysis of the relationship between serum ferritin levels and diabetes

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Abstract

To provide reference for the prevention, diagnosis and treatment of diabetes by means of comprehensively analyzing the relationship between serum ferritin level and diabetes. The software of review manager 5 (Revman 5) was applied to analyze the data for meta analysis. Based on the screening of the criteria about literature inclusion and exclusion, there were 23 case-control studies eventually included in the Meta-analysis, which referred to 3,269 subjects, including 1,888 diabetic cases and 1,808 non-diabetic cases. In terms of the meta-analysis, the D-L method (DerSimonian & Laird) of random effects model was used in the statistical analysis data because the heterogeneity test results suggested that the heterogeneity between studies was significant. The effect size showed that the serum ferritin levels in patients with diabetes was higher than that in non-diabetic patients and the difference represented the statistical significance (WMD = 105.60, 95% CI (87.23, 123.97), $P < 0.00001$). The results remained unchanged after the sensitivity analysis of the study. It also showed a good symmetry of the funnel diagram in this study with the fail-safe factor of $Nfs_{0.05} = 3874$, suggesting that this study was less affected by the publication

bias and indicating the stable and reliable results of meta-analysis. Serum ferritin level was closely related to diabetes and may be one of the important risk factors of diabetes.

Keywords: serum ferritin, diabetes, heterogeneity

Introduction

Iron, one of the important trace metals elements necessary for the body, is extremely important for ensuring the normal physiological functions of the body and maintains the balance of iron in the body. Too much iron could promote and amplify the damage of the free radicals to the tissues and organs and could cause the lesions of various organs such as liver, heart, diabetes, hormonal disorders and immune abnormalities, etc., which is called iron overload. More than 90% of iron in the body binds to proteins and iron-containing proteins are characterized by many important biological functions in the body (1). Ferritin is the main storage form of iron in the body, so serum ferritin (SF) is commonly used as an effective indicator to predicate the iron storage in the body in clinical practice.

With the rapid development of the economy, changes in lifestyle, and acceleration of the aging process, diabetes has become another kind of disease to seriously endanger people's health except cardio-cerebrovascular diseases and tumors. The epidemiological survey (2) demonstrates that the number of global diabetes in 2013 has reached 382 million and is expected to increase to 592 million by 2035, obviously showing the prevalence of diabetes in China is rising rapidly. In 2010, the National Center for Disease Control and Endocrinology of the Chinese Medical Association investigated the prevalence of diabetes in people over 18 years old in China and took the WHO diagnostic criteria in 1999 in to use, showing the prevalence of diabetes was 9.7%. China has been home to the most cases of diabetes worldwide. Among the patients in our country, the patients with T2DM account for more than 90% and a lot of studies have reported that the ferritin was overloaded in the patients with T2DM. The studies (3-5) indicated that elevated SF levels are closely related to T2DM. In order to objectively evaluate the correlation between serum ferritin and diabetes, this study conducted the meta-analysis about the relevant studies at home and abroad.

Materials and methods

Source of information

Case-control studies on on serum ferritin and diabetes published at home and abroad could be collected by using computer to retrieve Wanfang Database, China National Knowledge Infrastructure (CNKI), VIP Database, Pub Med database, EMBASE database, and Web of Science database. The searching date is set from January 2008 to May 2018. The search keywords are “serum ferritin levels and diabetes mellitus”.

Literature inclusion criteria

1) Chinese or English literature published from January 2008 to May 2018 at home and abroad; 2) The research should refer to a case-control study with rigorous design, unlimited quantities of the research subjects and the reliable method about serum ferritin detection; 3) Complete report about the literature data in the aspects of the data needed for the analysis of this study, such as the number of cases in diabetic case group and the non-diabetic case group, as well as the corresponding serum ferritin levels (mean value and standard deviation); 4) Patients mentioned in the literature did not use drugs that affect serum ferritin; 5) The diagnostic criteria of disease discussed in the literature are clear: Diabetes meets WHO diagnostic criteria; 6) Select one of the articles for which the same sample population are repeatedly reported.

Literature Exclusion Criteria

1) The literature on the mean value and standard deviation of serum ferritin levels cannot be obtained according to the reports data; 2) review literature; 3) Repeated literature or the reports to the same population; 4) Exclude the literature with poor quality, repeated reports, little information and unusable information.

Data Extraction

The data extracted from the literature include: 1) General information: author's name and the publication date; 2) Research data: the grouping and number of the patients, the proportion of men and women, and the average age, etc.; 3) Measurement index: Correlation measurement data of serum ferritin levels (mean and

standard deviation).

Statistical analysis

This paper adopted the statistical software Rev Man 5.3 provided by the Cochrane Collaboration to conduct statistical analysis, inputting the extracted literature data in the software Revman 5, establishing a meta-analysis database, and then carefully checking the data to ensure an accurate data entry. The weighted mean difference (WMD) was selected as the effect index because the data in this study were continuous variables. The research data should be performed with the test for heterogeneity before calculating the combined statistics of the effect indicators. According to the results, we chose to use the fixed effect model or the random effect model to complete the statistical analysis of the data in the software Revman 5.0 to obtain the combined statistical values of WMD and 95% of the CI. Completing the forest plots and the sensitivity analysis of the study data, we evaluated the publication bias through making the funnel plot and calculating the safety factor to estimate the reliability of the overall effect values.

Results

Features of literature including

According to the inclusion and exclusion criteria of the research literature, there were 23 (6-28) references included in Meta-analysis in this study, including 5 Chinese documents and 18 English documents. The cumulative number of cases was 3696, including 1888 patients with diabetes and 1808 without diabetes.

Meta Analysis Results

The heterogeneity test firstly performed on the 23 references included in the analysis showed that there was no homogeneity among the including studies (chi-square value for heterogeneity test referred to $\chi^2= 625.79$, $P<0.00001$, $I^2 = 96\%$). Therefore, the combined statistics of the effect indicators in software Revman 5.3 were calculated by the random effects model - D-L method. The results of the statistical analysis were: WMD = 105.60, including 95% CI (87.23, 123.97), P

<0.00001 (Figure 1). It showed that the difference in serum ferritin levels between the diabetic and non-diabetic cases was statistically significant, which presented that the serum ferritin levels in the diabetic group were remarkably higher than those in the non-diabetic group. The result reflected that high serum ferritin levels were related to diabetes.

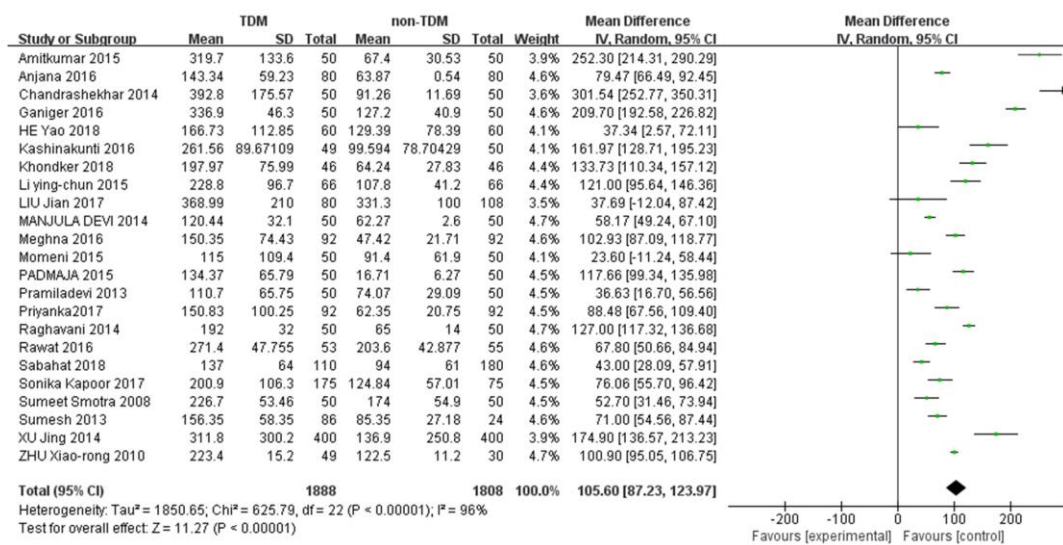


Figure 1 Meta analysis of the relationship between serum ferritin level and diabetes mellitus.

The combined statistics of the effect indicators in software Revman 5.3 were calculated by the random effects model - D-L method. The results of software Revman 5.3 shew that WMD = 105.60, including 95% CI (87.23, 123.97), P < 0.00001. There was significant difference in serum ferritin levels between the diabetic and non-diabetic cases. Compared with the non-diabetic group, the serum ferritin levels in the diabetic group were significantly increased.

Sensitivity analysis

Based on the combined analysis between the fixed-effect model and the 23 literature included in this study, the OR value (95% CI) referred to 95.26 (92.07 -98.46), Z = 58.44, P < 0.00001. This result was consistent with the random effect model results, suggesting that the results of this study are reliable.

Analysis of the publication bias

The software Revman 5.3 was firstly used to draw a funnel diagram for this

meta-analysis (Figure 2) and then the plot was adopted to evaluate the publication bias of this study. It could be seen that the graph of the funnel diagram was basically symmetric an inverted funnel shape in the study, indicating that the research was less affected by the publication bias.

When the fail-safe factor evaluation was used again in the publication bias, the calculation formula was as follows: if $P = 0.05$, $Nfs = (\sum Z/1.645)^2 - k$, k was the number of included studies. According to the formula mentioned above, we calculated that $Nfs_{0.05} = 3874$ for the fail-safe factor of the Meta-analysis, which indicated that 3874 negative results were needed to overturn the conclusion about the relationship between high serum ferritin levels and diabetes. The large Nfs value in the meta-analysis shows that this study is less affected by the publication bias and has better reliability.

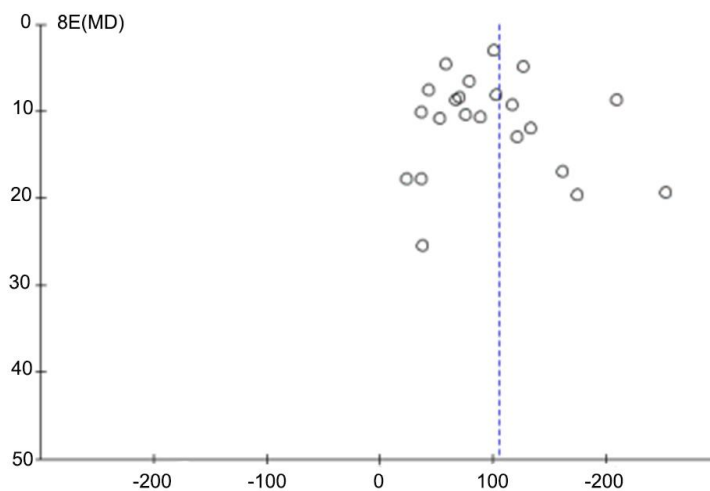


Figure 2. Analysis of the publication bias.

The graph of the funnel diagram was in basically symmetric inverted funnel shape, and the research was less affected by the publication bias.

Discussion

Ferritin, a globular protein, could be expressed in almost all types of cells. It could be soluble in water, cytoplasm or plasma, and is stable in the fluids both inside and

outside of the cell (1). SF refers to an indicator commonly used in clinical to reflect the body's iron store. The studies have shown that there is a correlation between SF and FPG & TDM, but the results are not completely consistent. Most of the results show that SF concentration is positively correlated with the occurrence of TDM. The studies like Yeap (4) found that the level of ferritin is an independent diabetes-related factor in adults. Moreover, some scholars (5) found that ferritin is a powerful marker that can be used to predict the risk of diabetes. Some related studies have demonstrated that the levels of serum ferritin in patients with diabetes is closely related to the fasting insulin levels and insulin sensitivity index of patients, which may have a serious impact on the patient's insulin function (29). The levels of serum ferritin show a certain relationship with the patient's own insulin resistance and there would be a sedimentation phenomena between iron and the pancreas islet, which would cause a damage to β cells in the islet. Iron could promote the formation of free radicals in the body of the patient, which would cause the atherosclerosis and lipid oxidation, and the patient would suffer from cell damage (30). If there is too much iron in patient's body, the saturation of plasma and ferrin will cause chromium deficiency in the patient's tissues and impair his insulin function. Finally, the patient would suffer from the symptom of carbohydrate metabolism disorders (31). In order to further confirm the relationship between serum ferritin and diabetes, Meta-analysis was used to analyze the results of the 23 literature studies. The results suggest that elevated serum ferritin is associated with diabetes. Therefore, as for the diabetic patients, we should also pay attention to patients' serum ferritin levels and improve the treatment of hyperferritinism in clinical work while strictly controlling the blood glucose, blood pressure, blood lipids and other risk factors since it may be one of the effective measures of the prevention and reduction for the risk of diabetes.

The Meta-analysis in this study was retrieved according to well-recognized and effective searching strategies. It should be provided with a rigorous searching strategy and comprehensive searching database when retrieving the documents. All the documents related to the research topic should be collected as much as possible with a

high recall rate to avoid the missed searches and make an effective control of the sampling bias. This study establishes strict criteria for literature inclusion and exclusion, making clear provisions on the types of research designs, study subjects, and the age of inclusion and adopting strict screening of the initial examination literature as well as the control of selection bias. As a result, there were 23 case-control studies used for Meta-analysis. In the process of Meta-analysis, sensitivity analysis was performed on the study to explore the degree of influence of individual studies on the combined effect when there was statistical heterogeneity among independent studies. We also made the reliability of the evaluation results to avoid the decisive influence of few studies on the results of Meta-analysis. On the other hand, the publication bias of the Meta-analysis in this study was evaluated by plotting the funnel plot and calculating the safety factor. According to the analysis results mentioned above, the results of Meta-analysis are stable, reliable, and of good reference. However, the following limitations still exist in this study: (1) Although the study is full of rigorous searching strategy, relatively extensive searching method and comprehensive searching database, some unpublished literature (such as supplements and conference documents) was still inevitably left out. Therefore, there may be publication bias; (2) there may exist language bias because the searching language used in this study was Chinese and English, and other language literature may be missed; (3) The literature included in this study all refers to the case-control study data, only presenting a correlation between high serum ferritin levels and diabetes, but the evidence for causality is lack of conviction. Therefore, the relationship between the two aspects needs to be proved by prospective randomized intervention trials and cohort studies.

Ferritin is the most abundant protein in human body and is often used as an effective indicator to predicate the iron stores in the body. Iron metabolism disorder is one of the risk factors of diabetes since ferritin plays a role in the regulation of body iron homeostasis. The Meta-analysis was used in this study to confirm the close relationship between high serum ferritin level and diabetes, which may be one of the

important risk factors of diabetes. It also provides objective evidence of evidence-based medicine for the prevention of diabetes.

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