

Comparison of Serum Ferritin Levels in Children with Iron Deficiency Anemia with and without Early Childhood Caries Requiring Surgery: A Systematic Review and Meta-Analysis

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Abstract:

Background and Objective: Conflicting results in the literature indicate that there is no definitive association between ferritin levels and dental caries in childhood. However, several studies have suggested a close relationship between iron deficiency anemia and early childhood caries requiring surgical intervention. Given the correlation between ferritin levels and iron deficiency anemia, as well as the strong connection between iron deficiency anemia and early childhood caries in children needing surgery, this study aims to compare serum ferritin levels in children with iron deficiency anemia with and without dental caries that necessitate surgical treatment.

Materials & Methods: This study was a systematic review and meta-analysis conducted according to the PRISMA guidelines. The databases searched included Scopus, ProQuest, PubMed, and ISI Web of Science for studies published in English, and Magiran and SID for studies published in Persian. The defined keywords for this study were used in the searches across these databases.

Results: The results of the meta-analysis indicated that serum ferritin levels in children with early childhood caries requiring surgery were significantly lower than those in healthy children ($P = 0.008$, 95% CI: -0.230 to -0.446).

Conclusion: Early childhood caries requiring surgical intervention leads to poor dietary habits, which may be associated with anemia and low ferritin levels. Our study's findings clearly demonstrate that early childhood caries results in a significant reduction in serum ferritin levels.

Keywords: *Early Childhood Caries, Child, Iron Deficiency Anemia, Ferritin*

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Background and Objective

Early childhood caries (ECC) is a type of dental decay that affects the primary teeth in children under the age of 6 years.¹ Severe dental decay impacts the growth and health of children and can have a negative social and economic impact on parents and society. Dental caries can lead to oral pain, difficulty eating and sleeping, and may contribute to underweight and stunted growth in children.² It is believed that children with severe dental caries become anemic and malnourished, experiencing significant changes in their physical growth patterns, leading to iron deficiency anemia. On the other hand, iron deficiency anemia can also reduce the quality of life related to oral health.³

Anemia in children can have various causes. Common causes of anemia include iron deficiency anemia, acute blood loss anemia, chronic inflammatory anemia, malnutrition-related anemia, and anemia due to hereditary hemoglobinopathies.^{4,5}

Iron deficiency anemia is the most common cause of anemia. Several factors such as genetic influences, diet, inflammatory processes, and environmental factors like dental decay and low socio-economic status contribute to iron deficiency anemia.⁶

The relationship between early childhood caries and iron deficiency anemia is bidirectional. Diet is strongly associated with both early childhood caries and iron deficiency anemia. Prolonged breastfeeding may be linked to both caries in childhood and iron deficiency anemia.⁷ Tooth pain in early childhood can affect a child's overall health.⁸ Chewing difficulties due to caries can reduce the consumption of iron-rich foods such as meat and nuts. Furthermore, iron deficiency anemia may damage the developing central nervous system, potentially leading to disability and negatively affecting the quality of life in children.^{9,10}

Some studies have reported that children with severe early childhood caries are significantly more likely to develop iron deficiency anemia.¹¹ In contrast, other

studies have found no significant relationship between anemia and the number of teeth or caries severity, with no causal link between severe early childhood caries and anemia reported.^{12,13} Guronatan and colleagues¹⁴ also demonstrated in their study that children with severe early childhood caries appear to be significantly more likely to develop iron deficiency anemia. Notably, there is a close association between ferritin levels and iron deficiency anemia; correcting ferritin levels can alleviate iron deficiency anemia, making ferritin levels a potential predictor for iron deficiency anemia in early childhood caries.¹⁵

Conflicting results in the evidence suggest that no definitive connection exists between ferritin levels and childhood caries.¹⁶ However, several studies have indicated a close relationship between iron deficiency anemia and early childhood caries requiring surgery.¹⁷ According to the researchers, there is limited data on the connection between these two public health issues. Understanding this connection could help design low-cost and effective interventions using a shared risk factor approach and address at-risk children in regions with widespread issues. Furthermore, identifying the potential relationship between dental caries and ferritin levels could assist pediatricians, pediatric dentists, healthcare policymakers, and family physicians in improving children's health and implementing preventive policies.

Materials and Methods

Study Design

This study was designed as a systematic review and meta-analysis based on the PRISMA statement.

Search Strategy

Relevant studies were searched after defining a PECO question focused on inclusion and exclusion criteria related to the subject of the study. Due to inconsistencies in the results of various studies, this research utilized only case-control studies to obtain more reliable results. The included articles

evaluated ferritin levels (O, outcome) in children (P, population) with dental caries (E, exposure) compared to children without dental caries (C, comparison). Keywords were selected using simple or combined Boolean operators. The main keywords included "dental caries," "surgical dental caries," "dental surgery," "child," "ferritin," and "iron deficiency anemia." Databases searched included Scopus, ProQuest, PubMed, and ISI Web of Science for studies published in English, as well as MagIran and SID for studies published in Persian. No filters were applied other than age group (under 18 years). The search strategy retrieved articles related to (anemia or iron deficiency anemia or low serum iron levels or iron deficiency, ferritin levels, low ferritin * anemia or iron deficiency * anemia or low iron status) and (optimal ferritin level or control or absence of anemia or optimal ferritin status) and (caries or dental decay or cavitated lesion or cavitated dental decay) * or early childhood caries or dental caries in children* or severe early childhood caries) and (primary teeth or baby teeth or pediatric dentistry or pediatric dental care). Two authors independently performed a manual search of the aforementioned databases and reviewed the references of existing articles. This review included studies published between 1990 and 2021.

Inclusion and Exclusion Criteria

The inclusion criteria for this study were case-control studies published in Persian and English up until the end of 2021 that examined ferritin levels in children with and without early childhood caries requiring surgery. Exclusion criteria included review articles, clinical trials, letters to the editor, cohort studies, and pilot studies.

Study Selection

A reference management system in EndNote software was used to upload all potentially eligible studies and remove duplicates. Using the developed search strategy, two trained researchers independently searched the aforementioned databases. Article selection was based on the inclusion and exclusion criteria. The selected

abstracts were reviewed, and those meeting the inclusion criteria were chosen. The full texts of the selected abstracts were then screened, with some articles being excluded. Ultimately, the full text of eligible articles was reviewed by both researchers for inclusion in this systematic review.

Data Extraction

Two authors extracted data from the different studies into a table. Variables included author names, publication year, children's age, sample size in both the case and control groups, mean and standard deviation of ferritin levels in both groups, and a brief conclusion from each study.

Risk of Bias Assessment

Each study was assessed for risk of bias using the Newcastle-Ottawa Scale.¹⁸ The risk of bias in the included studies was evaluated using the criteria for observational studies. The scale included domains such as group comparison, measurement of exposure and outcomes, and selection of cases and controls. Scores less than 5, between 5 and 7, and above 7 were classified as low, moderate, and high methodological quality, respectively.

Data Analysis

Utilizing the comprehensive meta-analysis software RevMan, a meta-analysis was conducted to examine the relationship between low ferritin levels and the prevalence of dental caries in children. A random effects model was employed to calculate the standard mean difference for continuous data, accompanied by a 95% confidence interval. This model posits that the observed discrepancies among study results are not solely due to sampling error, but also represent authentic differences in populations or study conditions. By accommodating heterogeneity among studies, the random effects model provides an overall estimate that encapsulates the average true effect across all analyses. To evaluate the heterogeneity within the studies, we employed both the P-value (established at less than 0.05) and the I² statistic. The I² statistic is a key metric for

quantifying heterogeneity, indicating the percentage of the observed variability across studies that is attributable to genuine differences rather than mere sampling error. Values below 25% suggest low heterogeneity; values ranging from 25% to 50% indicate moderate heterogeneity; values between 50% to 75% signify high heterogeneity; and values exceeding 75% are regarded as indicative of very high heterogeneity. A high I^2 value may suggest substantial differences in study design, sample characteristics, or methodologies that warrant further examination. Moreover, a forest plot was employed to estimate the mean difference and visualize the results of the meta-analysis.

The forest plot serves as an essential visual instrument in meta-analysis, effectively presenting the results of all studies included in the analysis. Each study is depicted by a horizontal line, which indicates its 95% confidence interval (95% CI) for the effect size, with a square or dot located at the center to denote the effect size itself. The size of the square is typically proportional to the statistical weight of the study. At the base of the forest plot, a diamond shape represents the overall pooled effect size, with its width reflecting

the combined confidence interval. This visual representation facilitates a clear comprehension of how study results align or diverge, playing a critical role in assessing the heterogeneity and consistency of the findings. The Review Manager (RevMan) software (version 4-5) is an advanced and specialized tool for conducting systematic reviews and meta-analyses, developed by the Cochrane Collaboration. It is widely acknowledged as a premier tool for data analysis in systematic review studies on a global scale.

Findings

A total of 494 articles were retrieved in the initial search. After excluding duplicate and irrelevant articles, the abstracts of 29 studies were analyzed. Eventually, 17 articles underwent full-text analysis, of which 11 were excluded due to being cross-sectional and lacking a control group for comparison. As a result, six studies were included in this systematic review and meta-analysis. The quality assessment across the studies varied significantly. One study demonstrated low quality, three studies showed moderate quality, and two studies exhibited high quality (Figure 1).

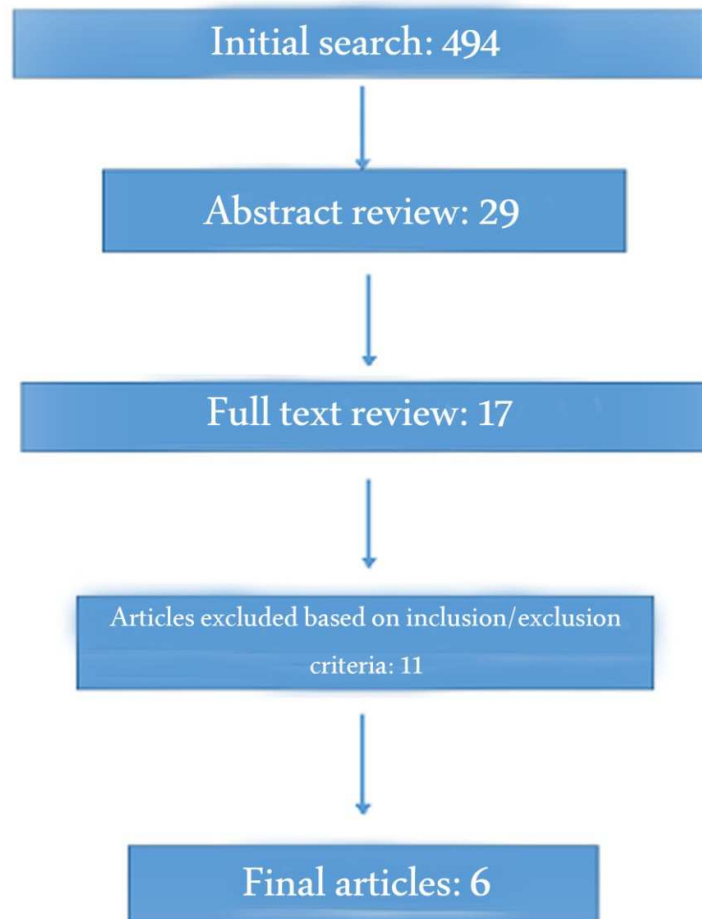


Figure 1- The process of inclusion and exclusion of studies in this systematic review and meta-analysis

The summary of the included studies indicated that six studies with a total sample size of 1,023 children under the age of 12, conducted between 2013 and 2017, were included in the study. In four out of the six studies, the authors reported that the serum ferritin levels in children with early childhood caries requiring surgery were significantly lower compared to serum ferritin levels in children without early childhood caries (P -value < 0.05). The summary of the studies included in this systematic review and meta-analysis is presented in Table 1.

Six articles assessed serum ferritin levels as mean and standard deviation using a similar method. The heterogeneity of the articles was reviewed, and it was found that the heterogeneity was high ($I^2 = 94.2\%$, $P = 0.029$). The results of the meta-analysis indicated that serum ferritin levels in children with early childhood caries requiring surgery were significantly lower than in healthy children (CI 95% = -0.230 to 0.446, $P = 0.008$).

The forest plot (Figure 2) below reflects the results of the meta-analysis.

Table 1- Summary of Studies Included in the Systematic Review and Meta-Analysis

Author/Year	Age Range	Study Quality	Sample Size	Ferritin Level (ng/ml)	Final Result
Abed/2014 ¹⁹	2 to 5 years	Score:6 Low	Intervention:100 Control:50	Intervention:31.86±18.2 Control:40.96±21.1	Serum ferritin levels in children with early childhood caries requiring surgery were significantly lower than in healthy children (P = 0.14)
Schroth/2013 ²⁰	Under 6 years	Score:5 Low	Intervention:144 Control:122	Intervention:29.1±18.4 Control:30.2±17.4	Serum ferritin levels in children with early childhood caries requiring surgery were significantly lower than in healthy children (P = 0.09)
Koppal/2013 ²¹	2 to 6 years	Score:6 Low	Intervention:30 Control:30	Intervention:29.33±24.22 Control:76.05±84.74	Serum ferritin levels in children with early childhood caries requiring surgery were significantly lower than in healthy children (P = 0.01)
Shamsaddin/2016 ²²	2 to 6 years	Score:7 Low	Intervention:157 Control:83	Intervention:34.58±25.01 Control:34.63±19.16	Serum ferritin levels in children with early childhood caries requiring surgery were non-significantly lower and very slightly lower than in healthy children (P = 0.56)
Jayakumar/2017 ²³	Under 6 years	Score:8 Low	Intervention:79 Control:35	Intervention:28.22±20.86 Control:37.40±24.20	Serum ferritin levels in children with early childhood caries requiring surgery were significantly lower than in healthy children (P = 0.035)
Nayak/2017 ²⁴	2 to 12 years	Score:8 Low	Intervention:119 Control:74	Intervention:30.71±21.54 Control:31.06±19.32	Serum ferritin levels in children with early childhood caries requiring surgery were non-significantly and slightly lower than in healthy children (P = 0.325)

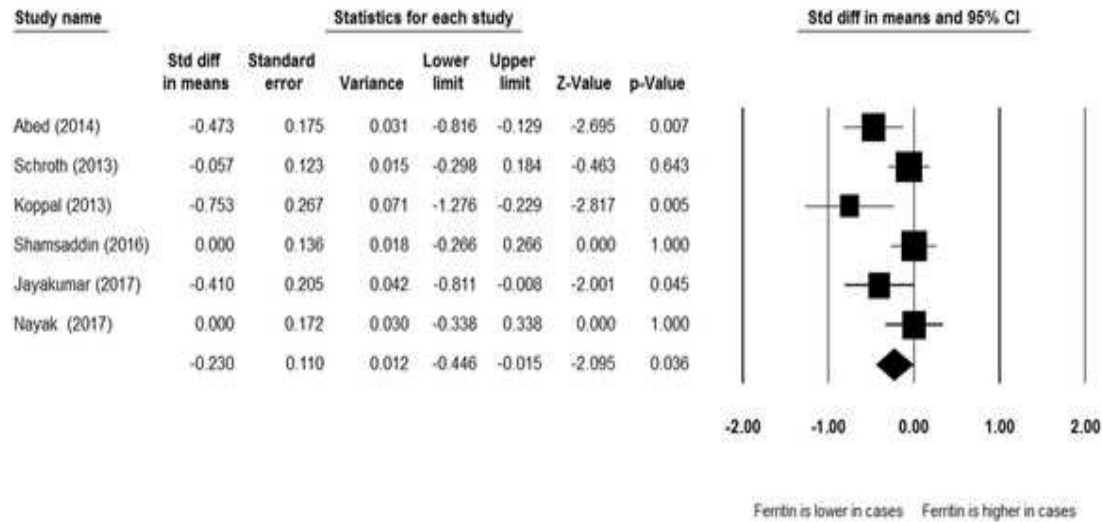


Figure 2- Forest plot derived from the articles included in this systematic review and meta-analysis.

Discussion

Early childhood caries requiring surgery is a severe dental decay affecting young children. These children suffer from malnutrition, poor ability to chew, and pain, leading to iron deficiency, stunted growth, and weight loss. Sleep disturbances affect the growth of these children due to reduced glucocorticoid production.²⁵

On the other hand, anemia can occur as a result of genetic factors (congenital), inflammatory processes, nutritional factors, and environmental factors such as dental decay and low socio-economic status. According to the World Health Organization, iron deficiency anemia is confirmed when at least two of the three parameters (MCV, serum ferritin, and Hb) are below the normal range.²⁷ This systematic review provides an accurate summary of the relationship between low serum ferritin levels and dental decay in children, considering all available case-control studies. It shows a significant association between low serum ferritin levels and early childhood caries, suggesting that

dental decay leads to a decrease in ferritin levels.

Various factors such as socio-economic conditions, diet, race, and sleep patterns can influence anemia. These factors vary across different populations.^{28,29} One of the differences in this study compared to similar studies is that it only includes case-control studies to reduce the potential effects of socio-economic status factors across different populations. Studies were conducted in communities with different socio-economic conditions, which may impact multifactorial variables such as dental decay and low ferritin levels.^{30,31} The existence of both case and control groups within each population and considering them in meta-analysis can help reduce the impact of community differences. Furthermore, the age group considered in this study differs from other studies. Our study included children up to the age of 18, whereas other studies usually focused on children with dental decay in early childhood.

Low ferritin levels may not be directly caused by early childhood caries but could be

associated with high milk consumption in early childhood.³² Given the inconsistencies in study results, this study conducted a meta-analysis of case-control studies to obtain more reliable outcomes. This systematic review showed that children with early childhood caries requiring surgery had a higher likelihood of low ferritin levels compared to the control group without decay. Dentists and primary care providers should be well-informed about this relationship and acknowledge that dental decay may serve as a risk factor for low ferritin levels when treating young children.³³ Physicians should be aware that nutritional deficiencies may follow dental decay in their patients. Dentists should also understand that children with dental decay are at risk for nutritional deficiencies that may affect their long-term health.

On the other hand, prolonged breastfeeding and the use of a bottle for more than two years can expose children to early childhood caries and malnutrition,³⁴ as they do not receive adequate iron and other essential nutrients. Therefore, early childhood caries, iron deficiency, and other nutritional complications are more likely to occur in this group of children.³⁵ Multiple dental caries make it difficult for children to chew foods, particularly meat, which impairs nutrient absorption in the intestine.^{36,37} As a result, children tend to consume sugary drinks to feel full, avoiding meat and iron-

containing foods.³⁸ Dietary factors leading to iron deficiency (excessive consumption of sweet drinks and insufficient meat intake) may also predict dental decay. In conclusion, whether dental decay causes iron deficiency in children or if low ferritin levels are a result of other factors remains unclear, highlighting the need for further cohort studies with larger sample sizes across different communities.^{39,40}

No study is without limitations. The first limitation in our study was the inclusion of patients with different age groups, particularly one study that included children up to 12 years of age, a different age range than typically defined for early childhood caries. The second limitation was the lack of knowledge regarding the nutritional status of the children, which is influenced by the economic status of the household. However, future studies are recommended for children with early childhood caries requiring surgery, with iron supplementation. Additionally, cohort studies are also recommended.

Conclusion

Early childhood caries requiring surgery leads to poor dietary habits that may be associated with anemia and low ferritin levels. Our study clearly demonstrated that early childhood caries requiring surgery results in a significant reduction in serum ferritin levels.

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