COHORT STUDY O

Improvement in Iron and Iron-Related Nutritional Status Following Pediatric Dental Surgery To Treat Severe Early Childhood Caries

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Abstract: ***Purpose:*** *To investigate improvement in iron and iron-related nutritional status of children with severe-early childhood caries (S-ECC) following dental rehabilitation under general anesthesia (GA).* ***Methods:*** *Children with S-ECC were recruited into a prospective study investigating changes in nutritional status before and after surgery. Parents completed a questionnaire, as their child had a venipuncture while under GA. Children returned for follow-up at a minimum of three months postsurgery, and parents completed a follow-up questionnaire and their child had an additional venipuncture and dental examination. Statistical analyses included descriptive, bivariate, and multivariable regression analyses.* ***Results:*** *A total of 150 children participated (mean age 47.7±14.1 months). The mean baseline ferritin concentration was 27.9±19.1 µg/L, while mean iron and hemoglobin levels were 12.3±4.3 µmol/L and 107.5±9.2 g/L, respectively. Overall, 53 percent were anemic, 30 percent had iron deficiency (ID), and 20 percent had iron deficiency anemia (IDA) at baseline. In total, 106 participants returned for follow-up. Paired t-tests revealed significant improvements in ferritin (27.0±18.4 µg/L versus 34.3±18.2 µg/L, P<0.001) and hemoglobin (108.2±8.3 g/L versus 123.7±9.4 g/L, P<0.001) levels. There was a 16 percent reduction in children with ID (P<0.001) and a 20 percent reduction in children experiencing IDA (P=0.011) from baseline to follow-up. Multivariable regression revealed that follow-up ferritin levels were associated with baseline ferritin concentrations, red meat intake, and difficulty purchasing food because of cost.* ***Conclusions:*** *Improvements in iron and iron-related nutritional status were observed post GA. Dental surgery for S-ECC may contribute to improved children's eating practices and resolve oral inflammation, thus leading to better nutritional status.* *(Pediatr Dent 2022;44(1):58-66) Received June 21, 2021 | Last Revision October 24, 2021 | Accepted October 29, 2021*

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Early childhood caries (**ECC**) is a common chronic disease of childhood that can pose a significant threat to overall health and well-being.[1] Severe early childhood caries (**S-ECC**) is a progressive manifestation of ECC that often requires rehabilitative surgery under general anesthesia (**GA**) due to the extent of dental decay and the very young ages of afflicted children. Currently, dental surgery to treat caries is the most frequently performed surgical day procedure among Canadian children.[2,3] While surgery may be effective at treating the outward manifestations of caries, knowledge about the burden ECC places on childhood health and development remains limited.

S-ECC can pose a significant threat to a child's overall quality of life. Pain associated with S-ECC is recognized to influence behavior, sleeping patterns, and alter eating habits, which can lead to underlying nutritional deficiencies.[1] In several recent cross-sectional studies, children with S-ECC were identified as being more likely to have anemia, in particular iron deficiency (**ID**), iron deficiency anemia (**IDA**), or lower levels of vitamin D.[4, 5] Multiple studies have also reported that S-ECC is associated with impaired growth and development.[5-8]

ID is the most common form of nutritional deficiency worldwide and can adversely affect a child's mental and physical development.[9,10] Anemia, which impacts nearly two billion people worldwide, is also indicative of poor nutrition and health.[10,11] ID is generally identified by insufficient hemoglobin and or ferritin levels.[10] While approximately 50 percent of anemia cases are attributable to a state of ID, individuals can have ID in the absence of anemia if its duration has not been prolonged or severe enough to depress hemoglobin levels below specific thresholds.[10] In cases where ID has been significant enough to give rise to a state of anemia, individuals can be considered to have IDA.[10]

Present literature reveals that poorer nutritional iron and vitamin D status is associated with S-ECC.[4,5,12,13] However, it is not apparent whether S-ECC is the direct source of these deficiencies or if it is a mediating factor that has a negative influence on dietary intake, thus contributing to nutritional deficiencies. Few prospective studies have assessed changes in iron status of children before and after GA; they involved small cohorts without appropriate power.[14,15]

The purpose of this study was to investigate whether there are any significant changes in the iron and iron-related nutritional status of preschool children with severe early childhood caries following rehabilitative dental surgery with a robust cohort.

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Methods

This prospective cohort intervention study investigated whether the iron status of preschool children with S-ECC would improve following dental surgery. This study was approved by the Health and Research Ethics Board and Misericordia Health Centre (**MHC**), University of Manitoba, Winnipeg, Manitoba, Canada. Recruitment of children older than 24 months but younger than 72 months with S-ECC occurred between November 2015 and January 2017 at the MHC on the day of their dental surgery. After providing informed consent, parents and caregivers completed a comprehensive questionnaire, including NutriSTEP and questions concerning the child's general health, oral health-related quality of life, dietary intake, use of supplements or medication, and socioeconomic status (**SES**).[16,17] At a minimum of three months postsurgery, children returned to the Children's Hospital Research Institute of Manitoba, Winnipeg, for a follow-up visit. The primary caregiver completed the same questionnaire provided at baseline analysis to assist in examining potential changes in diet and overall health and well-being.[16,17] Children's baseline dmft and dmfs (cumulative number of decayed, missing due to caries, and filled teeth/surfaces) scores were calculated from operative reports. As required for treatment at MHC, children fell into the American Society of Anesthesiologists (**ASA**) physical status classification system categories of ASA-1 or ASA-2.

Baseline venipunctures were performed in the operating room while follow-up venipunctures were drawn by a research nurse following the application of a topical anesthetic to minimize discomfort. Serum samples were analyzed by the Clinical Chemistry Laboratory at Winnipeg's Health Sciences Centre (**HSC**) for ferritin, total iron binding capacity (**TIBC**), and complete blood count (including hemoglobin, mean corpuscular volume [**MCV**], and red cell distribution width [**RDW**]). Hemoglobin, ferritin, TIBC, MCV, and RDW were used as indicators of nutritional iron status. Hemoglobin was specifically used as an indicator of anemia. To coincide with age-appropriate reference ranges for hemoglobin levels determined by the World Health Organization (**WHO**), children with hemoglobin concentrations less than 110 g/L were considered anemic.[18] Immunoassays of serum ferritin, iron, and TIBC further served as effective indicators of nutritional iron status and were performed in a Roche Cobas analyzer. Children with ferritin levels less than 20 µg/L were considered iron deficient. Additionally, participants with a combined deficit in serum iron (less than seven µmol/L) and an elevated level of TIBC (greater than 80 µmol/L) were also classified as iron deficient (**ID**). Lab results were reviewed by a pediatrician member of the team and letters sent to physicians when children had moderate or severe anemia.

A minimum of 110 children was required to provide 80 percent power to detect differences in mean ferritin at a significance level of α equals 0.05. Based on this and the potential for dropouts and loss to follow-up, the authors recruited 150 children. Participant laboratory and questionnaire data were recorded in Excel (Microsoft Office, Microsoft Corp., Redmond, Wash., USA) and analyzed using Number Cruncher Statistical Software (NCSS) 12.0 (Kaysville, Utah, USA). Data analysis included descriptive statistics (frequencies, 95% confidence intervals [**95% CI**], and means±standard deviations [**SD**]), bivariate analyses comprising *t*-tests, paired *t*-tests, and chi-square analysis, and multivariable linear regression. Principle component analysis (**PCA**) was also performed to evaluate the SES of the patient population more accurately due to the large number of variables recorded relative to this study's small sample size. PCA included variables on the level of education, receipt of government assistance, yearly income, community of residence, and difficulty buying food to feed children because food is expensive. This method of feature extraction enabled the authors to reduce the number of dimensions of their dataset to increase interpretability while also minimizing information loss. A *P*-value of ≤0.05 was significant.

Results

Baseline results. Overall, 150 children with a mean age of 47.7±14.2 months were recruited; 78 (52.0%) were female. Baseline results for nutritional iron status were not available for eight children. Descriptive characteristics, including oral health, and their parents/caregivers are presented in Table 1.

On average, children had normal hemoglobin, ferritin, TIBC, and MCV. The baseline mean iron concentration was 12.3±4.3 µg/L (range equals 2.5 to 24.6), while the mean

Table 1. DEMOGRAPHIC CHARACTERISTICS OF PARTICIPANTS (N=150)*

Variable name	All children baseline
Mean age (months)±SD	47.7±14.2
Mean dmfs±SD	39.9±17.3
Mean dmft±SD	10.2±3.4
Sex (%; 95% CI)	
Male	72 (48.0; 40.0-56.0)
Female	78 (52.0; 44.0-60.0)
Medication usage (%; 95% CI)	
Yes	13 (8.7; 4.2-13.2)
No	137 (91.3; 86.8-95.8)
Supplementation usage (multivitamin) (%; 95% CI)	
Yes	54 (64.0; 55.3-72.7)
No	64 (36.0; 27.3-44.7)
Letter about lab results sent to physician (%; 95% CI)	
Yes	51 (34.0; 26.4-41.6)
No	99 (66.0; 58.4-73.6)
Parent/caregiver education status (%; 95% CI)	
<Grade 12	92 (61.3; 53.5-69.1)
≥Grade 12	58 (38.7 30.9-46.5)
Receives government social assistance (%; 95% CI)	
Yes	86 (57.3; 49.4-65.2)
No	64 (42.7; 34.8-50.6)
Yearly household income (%; 95% CI)	
<$28,000	87 (58.0; 50.1-65.9)
>$28,000	54 (36.0; 28.3-43.7)
Don't know	9 (6.0; 2.2-9.8)
Receives government insurance coverage (%; 95% CI)	
Yes	144 (96.0; 92.9-99.1)
No	4 (2.7; 0.1-5.3)
Don't know	2 (1.3; 0.0-3.1)
Location of residence (%; 95% CI)	
Urban	95 (63.3; 55.6-71.0)
Rural	55 (36.7; 29.0-44.4)

* Abbreviations used in this table: SD=standard deviation; dmfs=decayed, missing, and filled primary tooth surfaces; CI=confidence interval.

Table 2. IRON STATUS OF PARTICIPANTS*†

Variable	Baseline overall value	Comparison of baseline and follow-up children		*P*-value
		Baseline matched	Follow-up matched	
Hemoglobin g/L (mean±SD)	107.53±9.19	108.20±8.30	123.74±9.43	<0.001‡
Iron µmol/L (mean±SD)	12.27±4.32	12.34±4.30	13.08±5.75	0.21‡
TIBC µmol/L (mean±SD)	52.03±8.50	52.21±8.38	62.70±9.20	<0.001‡
Ferritin µg/L (mean±SD)	27.92±19.19	27.03±18.44	34.30±18.16	<0.001‡
MCV fL (mean±SD)	78.60±5.09	78.46±4.96	79.90±4.78	<0.001‡
Hematocrit %(mean±SD)	0.32±0.02			<0.001‡
	(%; 95% CI)	(%; 95% CI)	(%; 95% CI)	
Anemia (low hemoglobin)				
Yes	76 (53.2; 45.0, 61.4)	45 (51.1; 40.7, 61.5)	5 (5.7; 0.9, 10.5)	<0.001§
No	67 (44.7; 36.6, 52.8)	43 (48.9; 38.5, 59.3)	83 (94.3; 89.5, 99.1)	
Iron deficiency				
Yes	43 (30.1; 22.6, 37.6)	30 (34.5; 24.5, 44.5)	16 (18.4; 10.3, 26.5)	<0.001§
No	100 (69.9; 62.4, 77.4%)	57 (65.5; 55.5, 75.5)	71 (81.6; 73.5, 89.7)	
Iron deficiency anemia				
Yes	29 (20.3; 13.7, 26.9)	20 (23.3; 14.4, 32.2)	3 (3.5; 0.0, 7.4)	0.001§
No	114 (79.7; 73.1, 86.3)	66 (76.7; 67.8, 85.6)	83 (96.5; 92.6, 1.0)	
Non-iron deficiency anemia				
Yes	44 (31.0; 23.4, 38.6)	23 (27.4; 17.9, 36.9)	2 (2.4; 0.0, 5.7)	<0.001§
No	98 (69.0; 61.4, 76.6)	61 (72.6; 63.1, 82.1)	82 (97.6; 94.3, 1.0)	
Low iron				
Yes	21 (14.6; 8.8, 20.4)	15 (17.1; 9.7, 25.7)	16 (18.2; 10.1, 26.3)	0.28§
No	123 (85.4; 79.6, 91.2)	73 (82.9; 75.0, 90.8)	72 (81.8; 73.7, 89.9)	
High TIBC				
Yes	3 (2.1; 0.0, 4.4)	1 (1.1; 0.0, 3.3)	3 (3.4; 0.0, 7.2)	0.32§
No	141 (97.9; 95.6, 1.0)	87 (98.9; 96.7, 1.0)	85 (96.6; 92.8, 1.0)	
Low ferritin				
Yes	48 (33.8; 26.0, 41.6)	30 (34.5; 24.5, 44.5)	16 (18.4; 10.3, 26.5)	< 0.001§
No	94 (66.2; 58.4, 74.0)	57 (65.5; 55.5, 75.5)	71 (81.6; 73.5, 89.7)	
Abnormal MCV				
Yes	22 (15.4; 9.5, 21.3)	14 (15.7; 8.1, 23.3)	5 (5.6; 0.8, 10.4)	<0.001§
No	121 (84.6; 78.7, 90.5)	75 (84.3; 76.7, 91.1)	84 (94.4; 89.6, 99.2)	

hemoglobin concentration was 107.5±9.2 g/L (range equals 67 to 124). Further, baseline mean ferritin and TIBC concentrations were 27.9±19.2 µg/L (range equals three to 122) and 52.0±8.5 µmol/L (range equals 32.9 to 87.5), respectively. The baseline MCV concentration was 78.6±5.1 fL (range equals 75 to 87 for children younger than 72 months of age and 77 to 95 for children at least 72 months of age). According to previously established thresholds for indicators of nutritional iron status, children had low or adequate nutritional levels based on their laboratory results (Table 2). At baseline, 76 (53.2%) participants had low hemoglobin and were anemic. Chi-square analysis revealed that females were more likely than males to have anemia ($P=0.006$). Furthermore, parents receiving government assistance were more likely to have children with anemia ($P=0.040$).

Overall, 43 (30.1%) children were iron deficient at baseline. In each instance, ID was accompanied by an inadequate level of serum ferritin. Thus, no participants met the condition for having ID based on low serum iron and high TIBC alone. Combined deficiencies in hemoglobin and iron status were used to identify children in a state of IDA. A total of 29 participants (20.3%) had IDA. Those who demonstrated inadequate concentrations of hemoglobin without experiencing ID were classified as having non-IDA. At baseline, 44 participants (31.0%) exhibited non-IDA, with a significantly higher proportion being female ($P<0.001$).

Nutritional intake and dietary habits were assessed to determine associations with baseline iron status. No associations were observed between dietary intake and anemia. However, those consuming white meat less than once per day were significantly more likely to exhibit inadequate concentrations of iron ($P=0.010$) and those consuming white or red meat demonstrated lower ferritin levels ($P=0.042$, $P=0.049$). Children whose level of red or white meat consumption was less than once daily were more likely to have ID ($P=0.038$, $P=0.045$) and IDA ($P=0.027$, $P=0.024$). Dietary intake of beans or lentils was not related to childhood nutritional status, despite being recognized sources of food rich in iron. Furthermore, children's use of supplements was not associated with nutritional iron status.

Baseline and follow-up comparison. A total of 106 participants completed both phases of the study. No significant descriptive or nutritional differences were recorded between those who returned and those who were lost to follow-up, except their place of residence ($P<0.001$). A higher rate of attrition was observed among those residing greater distances from Winnipeg. Paired *t*-tests for participants who completed both study phases revealed

* Abbreviations used in this table: TIBC=total iron binding capacity; MCV=complete blood count (including hemoglobin, mean corpuscular volume.

† Anemia=hemoglobin concentrations <110 g/L; low iron=concentrations <7 µmol/L; high TIBC=TIBC concentrations >80 µmol/L; low ferritin=ferritin concentrations <20 µg/L; iron deficiency=low ferritin or low iron and high TIBC; iron deficiency anemia=iron deficiency and anemia; non-iron deficiency anemia=anemia without iron deficiency.

‡ Paired *t*-test.

§ Chi-square.

significant improvements in the mean concentrations of ferritin (P<0.001), hemoglobin (P<0.001), TIBC (P<0.001), and MCV (P<0.001; Table 2). This was accompanied by a 45.5 percent reduction in participants experiencing anemia in those matched at baseline and follow-up (P<0.001). Significant improvements were also recorded in participants who had ID (16.1 percent reduction, P<0.001) and IDA (19.8 percent reduction, P=0.001) when compared at baseline and follow-up (Table 2). These changes paralleled a 25.0 percent decrease in participants impacted by non-IDA (P<0.001) (Table 2). There was no difference in ferritin or hemoglobin concentrations (data not shown) between children whose physician received a letter about their baseline lab results and those who did not (P=0.06 and P=0.17, respectively). Of the 41 children who did not receive supplements at baseline, 29 did at follow-up. However, there was also no difference in supplement use between baseline and follow-up among children whose doctors received a letter about baseline lab results (P=0.22). The mean difference in follow-up and baseline ferritin concentrations among children whose doctor received a letter was 5.6±15.0 μg/L (95% CI equals 0.1 to 11.1), and for those where no letters were sent the main difference was 8.2±17.7 (95% CI equals 3.5 to 12.8). For hemoglobin, the respective differences were 16.9±8.0 g/L (95% CI equals 14,1 to 19.8) and 14.8±6.4 g/L (95% CI equals 13.1 to 16.5).

PCA was performed to evaluate the socioeconomic status (**SES**) of the patient population. Principal component one (**PC1**), accounted for 53.9 percent of the explained variance and was primarily dominated by the seventh NutriSTEP question concerning how often families find food acquisition expensive. The second principal component (**PC2**), accounted for 21.1 percent of the variability in the SES and was composed of the caregiver's education, receipt of government social assistance, annual household income, and NutriSTEP question seven in roughly equal proportions.

Multiple linear regression analysis was performed with forward selection for follow-up ferritin levels, controlling for the time between baseline and follow-up assessments, and considered the location of residence, level of education, government assistance, and income. Results revealed that follow-up serum ferritin concentrations were significantly associated with baseline ferritin concentrations (P<0.001), red meat intake (P=0.020), and NutriSTEP question seven (which assessed the frequency by which families found food expensive to purchase) (P=0.027; Table 3). Significant relationships were also observed between the respective baseline and follow-up concentrations of serum iron (P<0.001) and hemoglobin (P=0.001), respectively. PC1 and PC2 were considered for their role in determining SES, yet neither PC1 nor PC2 was included in the final stepwise multiple regression models for iron or hemoglobin, suggesting that SES did not affect improvements in iron or hemoglobin levels. Further analysis via logistic regression was completed to measure variables associated with iron deficiency improvement. However, logistic regression did not yield any additional information, as the data proved to be too limited to build a model with a good fit (McFadden's adjusted R-squared less than 0.1).

Table 3. MULTIVARIABLE LINEAR REGRESSION MODELS OF FOLLOW-UP FERRITIN, HEMOGLOBIN, AND IRON LEVELS

Variable	Estimate	Standard error	Statistic (T-value)	*P*-value
Ferritin μg/L				
(Intercept)	4.10	6.12	0.67	0.51
Ferritin Level (baseline) μg/L	-0.50	0.085	-5.92	<0.001
Days between baseline and follow-up	0.013	0.017	0.77	0.45
Red meat intake (baseline) ≥1x/day	8.37	3.51	2.38	0.020
NutriSTEP question 7 (caregivers have difficulty purchasing food because of the cost at least some of the time)	6.81	3.02	2.26	0.027
Age (baseline)	0.18	0.11	1.65	0.10
Hemoglobin g/L				
(Intercept)	41.14	8.97	4.59	<0.001
Hemoglobin level (baseline) g/L	-0.28	0.085	-3.32	0.001
Days between baseline and follow-up	0.012	0.0079	1.50	0.13
Receiving supplements (baseline)	4.76	1.44	3.31	0.001
Chicken and turkey intake (baseline) ≥1x/day	4.71	1.83	2.57	0.012
Iron μmol/L				
(Intercept)	2.93	2.45	1.19	0.24
Iron level (baseline) μmol/L	-0.48	0.13	-3.67	<0.001
Days between baseline and follow-up	0.0085	0.0063	1.36	0.18
NutriSTEP question 5 (meat, fish, poultry or alternative intake ≥2x/day)	-2.02	1.11	-1.83	0.071
Age (baseline)	0.062	0.039	1.59	0.12

Discussion

Until recently, there has been limited research investigating the association between S-ECC and iron status in preschool children. To date, several studies have reported that children of various ages with caries are significantly more likely to demonstrate an abnormal iron status.[4,6,13,19-21] This prospective study provided an opportunity to further examine the relationship between S-ECC and iron status in Canadian children by investigating changes over time following dental surgery. Significantly noticeable improvements were observed for ferritin, hemoglobin, anemia, ID, and IDA.

Anemia (53.2 percent), ID (30.1 percent), and IDA (20.3 percent) were relatively common in children with untreated caries in this study. These findings were similar to a past study by the authors' team and considerably higher than the prevalence of ID and IDA observed in children with severe caries in a previous Canadian study.[4,13] An earlier case-control study determined that 14.6 percent of children with S-ECC were iron deficient while 18.9 percent had IDA.[4] However, differences were noted in how studies defined ID in children with both abnormal hemoglobin and ferritin concentrations. Additionally, these earlier Canadian studies defined IDA by the presence of two out of three abnormal blood tests for either serum ferritin, hemoglobin, or MCV.[4,13] Thus, observed differences in iron status among S-ECC patients are likely attributable to the alternative methods used to determine these outcomes.

Alternative markers of iron status were also evaluated, such as TIBC and MCV. TIBC is a measure of the blood's capacity to bind iron and, in combination with serum iron levels, serves as an indication of nutritional iron status. Previous use of TIBC to quantify iron status in association with caries has been sparse as ferritin is often the gold standard regarding the sensitivity and specificity with which it detects iron status.[22] Results from this present study were not an exception, as TIBC values combined with serum iron concentration provided no additional diagnostic information. In fact, this study's paired TIBC values generally increased in participants toward the classification of ID, despite widespread improvement in nutritional iron status. MCV is used to determine the oxygen-carrying capacity of the blood in response to the level of hemoglobin within the blood cells. Results indicated that the concentration of MCV improved significantly following dental surgery. Similar concentrations of MCV were observed in a past study of children with S-ECC.[4] However, unlike those participants, subjects in the current study were followed prospectively and demonstrated a marked increase in MCV concentration at follow-up.

Immunoassay of ferritin was used as the primary indicator of ID as it corresponds directly with the concentration of iron

Table 4. SUMMARY OF STUDIES ON IRON AND CARIES*

Type of study	No. of participants	Blood tests reported with reference ranges or cutoff values	Key findings and limitations
Clarke et al. 2006[13] Descriptive cross-sectional study of Canadian children with S-ECC	56 (blood testing only performed on 46)	Ferritin: 22-400µg/L Hemoglobin (Hgb): 110-140 g/L MCV: not defined Iron deficiency anemia defined as 2 out of 3 abnormal blood tests for Hgb, ferritin, and or MCV	80% had low ferritin levels; 28% had low hemoglobin levels 6% were iron deficient; 11% had iron deficiency anemia Limitations: pilot study; did not include a caries-free reference group
Shaoul et al. 2011[19] Observational cohort of children 3-18 years of age with severe dental caries (but not S-ECC)	30 children with microcytic anemia caused by iron deficiency	Ferritin Iron Hgb MCV Red cell distribution width No reference values provided	Improved Hgb, ferritin, and iron concentrations 4-6 months postsurgery Limitations: children were already diagnosed with microcytic anemia caused by iron deficiency; included children above preschool age
Sadeghi et al. 2012[20] Cross-sectional study involving a convenient sample of preschool children (24-71 months) with caries (but not necessarily S-ECC)	204 children	Ferritin: 7-140 ng/mL Iron: 50-120 µg/dL	Reported an inverse association between caries and serum iron levels; 94.1% of children with low iron had ECC; no association with ferritin concentrations was found Limitations: Mean number of teeth affected by decay was only 2.4±3.3, indicating that the average participant likely did not meet the case definition for S-ECC, but rather had a much milder form of ECC.
Schroth et al. 2013[4] Cross-sectional case-control study comparing preschool children with S-ECC and caries-free controls	144 children with S-ECC and 122 caries-free controls	Ferritin: 20-140µg/L Hgb: 115-135 g/L MCV: 75-78 fL Participants are considered to be iron deficient if they have abnormal Hgb and ferritin concentrations; iron deficiency anemia defined as 2 out of 3 abnormal blood tests for Hgb, ferritin, and or MCV	Children with S-ECC were significantly more likely to have low ferritin status (1.9X), low hemoglobin levels, and iron deficiency anemia (>6x) caries-free controls. Limitations: did not measure serum iron levels
Iranna et al. 2013[21] Cross-sectional pilot study of preschool children in India	30 children with S-ECC and 30 children without S-ECC (but not necessarily caries-free)	Ferritin: ≤10µg/L Hgb MCV	Children with S-ECC had significantly lower ferritin levels than those without S-ECC. Limitations: significantly underpowered to determine influences of confounders like age and sex; provided no statistical values for differences in Hgb levels and iron status between groups
Tang et al. 2013[6] Cross-sectional study of children with S-ECC from Taiwan	101 children with S-ECC ages 2-5 years	Hgb Hematocrit (Hct) Transferrin (TSF) Definitions of anemia and iron deficiency based on WHO standards: Children aged 6-59 months: anemia defined as Hgb <11g/dL and Hct <33% Children aged 5-11 years: anemia defined as Hgb <11.5g/dL and Hct <34% Iron deficiency defined as TSF saturation <16%	9% were anemic and 46% had iron deficiency Anemia more concentrated in children with highest decayed, extracted, filled primary tooth surface (defs) scores Limitations: did not include a reference group of children caries-free; arbitrarily chose the mean defs score to dichotomize children into 2 groups to assess differences in iron status and anemia. Therefore, their findings are entirely limited to children with the most extreme cases of S-ECC (not generalizable to all children with S-ECC).

* Abbreviations used in this table: S-ECC=severe early childhood caries; GA=general anesthesia; ECC=early childhood caries; IDA=iron deficiency anemia; MCV=mean corpuscle volume; WHO=World Health Organization; MCHC=mean cell hemoglobin concentration; PCV=packed cell volume; TIBC=total iron binding capacity; DMFT/dmft=decayed, missing, and filled permanent/primary teeth.

Table 4. CONTINUED*

Type of study	No. of participants	Blood tests reported with reference ranges or cutoff values	Key findings and limitations
Nur et al. 2016[24] Cross-sectional study in children with S-ECC from Turkey	160 children with S-ECC ages 2-6 years	Hgb: 11-13 g/dL & 12-18 g/dL Hct: 34%-40% MCV: 81-103 fl Children <5 years: Hgb <1g/dL, Hct <34%, and MCV <73fl Children ≥ 5 years: Hgb <11.5g/dL, Hct <35%, and MCV <75fl	19.3% (31 patients) have iron deficiency anemia defined by Hgb values 18.1% (29 patients) have iron deficiency anemia defined by Hct values 81.8% (131 patients) have iron deficiency anemia defined by MCV values Limitations: Blood samples were not able to be obtained from healthy children in the community. Thus, the prevalence of IDA between children with severe caries and caries-free children could not be compared.
Beltrame et al. 2016[8] A single case report	1 boy 3 years and 10 months old	Hct: 40%-52% Hgb: 14.0-18.0 g/dL Ferritin: 28-365 ng/mL Iron: 65-175 μg/dL From these evaluations, the child was diagnosed with S-ECC and anemia due to iron deficiency.	The patient had low Hct (25.9%; reference value=40%-52%), low Hgb (7.7g/dl; reference value=14-18g/dl), low ferritin (10.5 ng/mL; reference value=28- 365 ng/mL), and low serum iron (16μ/dL; reference value=65-175 μ/dL). Limitations: Being a single case study, the results cannot be generalized to the wider population. Treatment procedures and antibiotics used may not be as effective in alternative cases.
Bansal et al. 2016[25] Cross-sectional study conducted in a hospital setting in semi-urban India	60 children aged 2-6 years (30 with S-ECC and 30 controls with caries status <2)	Primary outcome: Ferritin Hgb MCV Iron deficiency anemia defined as 2 out of 3 abnormal blood tests for Hgb, ferritin, and or MCV using Clarke et al. 2006 reference values Secondary outcome with ranges used to diagnose anemia: Hgb: 12 d/dL MCV: 76-100 μm^3 MCHC: 33-37 d/dL PCV: 39-49%	13 children in the S-ECC group were found to have IDA with below normal Hgb and MCV values, whereas only 2 children in the control group were found to have IDA. Hgb, MCV, and PCV values differed significantly between both groups while MCHC levels did not. Limitations: The use of a cross-sectional design does not allow true cause-and-effect explanatory power. There was also a lack of age-matched caries-free controls. The sample size may be too small and underpowered.
Shamsaddin et al. 2017[26] Cross-sectional study conducted in a hospital setting in southeast Iran	240 children aged 2-6 years needing blood sampling for diagnostic reasons	Hgb MCV Ferritin Anemia in children <5 years: Hgb <11 g/dL, Hct <33% Anemia in children aged 5-11: Hgb <11.5g/dL, Hct <34% Iron deficiency in children <5 years: Ferritin <12 ng/mL Iron deficiency in children aged 5-11: Ferritin <15 ng/mL	No significant associations were observed between ECC and Hgb, MCV, and serum ferritin. Limitations: The study participants with and without ECC were not matched completely. The results of the community could not be extended to the greater community.
Nagarajan et al. 2017[14] Prospective cohort study conducted in a hospital setting in India	30 children aged 2-6 years with S-ECC and IDA	Hgb: <12 g/dL MCV: <76 μm^3 MCHC: <33 gm/dL Hct: <39% Serum ferritin: <24 ng/mL	Significant improvements were observed; positive correlation between S-ECC and low weight and presence of iron deficiency anemia Limitations: The sample size was undersized and did not have a caries-free control group. The sample population was not matched for sex. The sample was not matched for SES; a risk indicator for S-ECC.
Venkatesh and Bhanushali 2017[23] Cross sectional study conducted in a hospital setting in India	120 children aged 3-12 years with S-ECC	Iron: 50-120 μg/dL Ferritin: 7-140 ng/dL	There was an inverse association between serum iron and dental carries. There was no observed association between serum ferritin and dental caries. Limitations: The use of a cross-sectional design does not allow true cause-and-effect explanatory power. Dental caries has a multifactorial origin; a longitudinal study would be better able to assess the influence of any co-founding factors.

Table 4. CONTINUED*

Type of study	No. of participants	Blood tests reported with reference ranges or cutoff values	Key findings and limitations
Ferrazzano et al. 2020[15] Prospective study of uncooperative children requiring dental treatment under GA in Italy	43 children aged 3-14 years; did not mention if treatment was all due to caries	Reported changes in ferritin but did not provide reference ranges	68.6% of children showed improved ferritin, 14.3% remained unchanged, and 17.1% had worse ferritin levels at follow-up. Limitations: Included children above preschool age; did not report actual baseline and follow-up concentrations of ferritin
Shafi et al.[27] 2020 Cross-sectional study of children in Saudi Arabia	122 children 3-12 years	Hgb MCV	Strong inverse correlation between Hgb levels and DMFT/dmft index scores; no association between MCV levels and DMFT/dmft index scores
Mohamed et al. 2021[28] Cross-sectional study in Egypt investigating the association between ECC and IDA	40 children with IDA and 40 healthy age and sex-matched children <72 months old	Definition of anemia based on WHO criteria Severe anemia Hgb <7.0 g/dL; moderate anemia 7.0-8.9 g/dL; mild anemia 9.0-10.9 g/dL (<60 months of age) and 9.0-11.4 g/dL (>60 months) Ferritin: 30-400 ng/ml Iron: 65-175 μg/dl (males) and 50-150 μg/dl (females) TIBC: 262-400 μg/dl IDA: ferritin <12 mg/dl and Hgb <11 g/dl	Negative correlation between dmft scores and both Hgb and mean corpuscular hemoglobin levels; mean dmft score higher in anemic versus non-anemic group; positive correlation between dmft score and presence of anemia Limitations: The use of a cross-sectional design does not allow true cause-and-effect explanatory power.

* Abbreviations used in this table: S-ECC=severe early childhood caries; GA=general anesthesia; ECC=early childhood caries; IDA=iron deficiency anemia; MCV= mean corpuscle volume; WHO=World Health Organization; MCHC=mean cell hemoglobin concentration; PCV=packed cell volume; TIBC=total iron binding capacity; DMFT/dmft=decayed, missing, and filled permanent/primary teeth.

in the blood. At baseline, 33.8 percent of participants possessed inadequate ferritin concentrations (less than 20 μg/L) and were ID. These findings corresponded with the authors' earlier study of children undergoing dental surgery for S-ECC, where 32.1 percent of children demonstrated inadequate ferritin levels.[4] Meanwhile, Clarke et al. (2006) reported that 80 percent of their study participants had ID.[13] In the present investigation, ferritin levels were strongly related to the burden caries. Following dental rehabilitation, ferritin levels improved significantly (27.03±18.4μg/L versus 34.3±18.2 μg/L, $P<0.001$). These results agree with the conclusions reached by other studies reporting that children with S-ECC were significantly more likely to demonstrate low ferritin levels than caries-free controls.[4,21] However, the overall findings remain inconsistent as several studies have failed to report an association between caries experience and serum ferritin levels. In fact, two reports observed a strong inverse correlation between dental caries and serum iron, which are findings that were largely absent from the present study.[20,23] A summary of findings from various studies on caries and iron status in children appears in Table 4.[4,6,8,13-15,19-21,23-28]

Anemia can be triggered by numerous factors and can pose a significant threat to neurological development. According to WHO, the highest prevalence of anemia occurs in preschool children influencing over 47 percent of children worldwide.[9] In Canada, only 7.6 percent of preschoolers have anemia.[9] When applying the WHO cutoffs for anemia to the current group of study participants, 53.2 percent were anemic. Therefore, S-ECC may account for a significant proportion of those having anemia, especially within Manitoba.

Multiple regression analysis was completed to identify the presence of any significant changes in nutritional iron status following dental surgery while controlling for confounding variables, including the time between baseline and follow-up and SES. Children whose households found it difficult to purchase food at least some of the time were significantly more likely to demonstrate a 6.8 μg/L increase in ferritin levels compared with children whose households did not have trouble purchasing food. This suggests that, while dental surgery may be influential in improving one's ferritin status, the cost associated with purchasing foods rich in iron might also have a detrimental impact on one's baseline iron status. Further support for this argument can be found through the observed association with red meat intake, whereby those who consumed red meat at least once per day were more likely to see an 8.3 μg/L increase in ferritin levels at follow-up. Interestingly, neither PC1 nor PC2 was included in the final regression models investigating serum iron status and hemoglobin concentrations. Therefore, SES did not lead to an improvement in iron or hemoglobin levels when keeping other covariates of interest constant. Ultimately, further research is needed to understand how SES and diet interact to influence one's overall iron status.

To date, few studies have investigated changes in the nutritional iron status of children following dental surgery.[14,15,19] In addition, those studies that have been performed often have significant limitations that hinder their ability to draw definitive conclusions (Table 4). For example, one study only obtained blood samples at baseline, even though children were followed longitudinally, preventing the authors from being able to assess changes in serum iron status.[24] In another study, children with severe caries were recruited based on having microcytic anemia caused by ID.[19] Thus, it was expected that children in this cohort would possess lower serum iron concentrations at baseline regardless of the association with underlying caries pathology. That study, along with a more recent prospective study, was also greatly underpowered and lacked comparable control populations to allow for more conclusive findings.[14,19] However, notwithstanding these limitations, both studies reported a significant increase in hemoglobin and ferritin concentrations postsurgery.[14,19] In the prior study, this was further accompanied by a significant increase in serum iron status.[19] Together, both accounts offer validation for the results documented in the present study as the authors reported significant improvements in all domains related to nutritional iron status, including decreases in anemia, ID, and IDA at follow-up. In each study, treatment of the underlying caries often corresponded with a concomitant resolution of IDA without additional iron supplementation.

Several hypotheses have been proposed to explain how the presence of S-ECC may be related to a child's iron status.[4] Most notably, pain associated with S-ECC may influence a child's eating habits, predisposing them to nutritional deficiencies such as low iron.[1,4,10] Alternatively, low socioeconomic status has also been documented as a risk factor for anemia.[29] Specifically, a financially restrictive situation may hinder a family's ability to purchase healthy foods that are rich in iron. A second hypothesis is that low hemoglobin levels that are often observed in children with S-ECC may be due to the body's inflammatory response, which frequently accompanies severe decay.[4,6] Chronic inflammation resulting from pulpitis or dental abscesses can alter metabolic pathways, leading to an increase in the production of cytokines that inhibit erythropoiesis.[30] This reduces the level of hemoglobin in the blood, thus decreasing the level of serum iron.[30] Others have hypothesized that the salivary gland function is impaired in those with iron deficiency.[23,31] Reduced salivary gland secretion leads to a lower resting oral pH with less buffering capacity. This has been proposed to increase the risk of developing caries as the tooth enamel is more susceptible to acid demineralization. In addition, the treatment of IDA and concomitant increase in markers of nutritional iron status have led to significant improvements in salivary pH buffering capacity.[31]

This study is not without limitations. A convenience cohort sampling method was used. Thus, children who were not undergoing surgery to treat S-ECC were not able to serve as controls. The lack of a systematic random sampling method may have also limited the ability to obtain an entirely representative sample of all the children with S-ECC receiving rehabilitative dental surgery in Manitoba. Response bias was also possible in the parents' self-reported ratings of child oral health or personal demographic characteristics. Complications associated with obtaining blood samples meant that the nutritional status of some study participants could not be determined, potentially influencing the overall findings of the study. While several children in this study were Indigenous Canadians, with over 50 percent being Registered First Nation based on insurance information, the authors did not specifically collect information on children's ethnicity. Additional permissions would have been required to do so. Another limitation is that the authors' ferritin cutoff, used by Winnipeg's Health Sciences Centre, of less than 20 ug/L to denote iron deficiency may slightly differ from what others have adopted. Lastly, as part of this study's protocol, letters were sent to physicians of children with baseline lab results outside of normal ranges. Some may have initiated supplementation that might have influenced their follow-up concentrations.

Conclusions

Based on the results of this study, the following conclusions can be made:

1. Children with severe early childhood caries demonstrated significant improvements in their iron and iron-related nutritional status following rehabilitative dental surgery. Specifically, children exhibited improvements in ferritin and hemoglobin levels following dental surgery. Significantly fewer children were found to have anemia, iron deficiency, and iron deficiency anemia after receiving dental rehabilitation to treat S-ECC.
2. These results provide further support for the oral-systemic relationship between a child's iron status and their overall health. This study also suggests that, for children who already have S-ECC, rehabilitative dental surgery may serve as a useful form of treatment that can simultaneously improve one's iron status.
3. Further investigations will be necessary to understand the role diet and SES have on influencing one's oral health.

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