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# Pagophagia in men with iron-deficiency anemia

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ABSTRACT

Few case series of pagophagia and iron deficiency include men. We performed a retrospective study of non-Hispanic white men with iron-deficiency anemia whose anemia and pagophagia, thrombocytosis, and thrombocytopenia (if present) resolved after iron replacement. Iron-deficiency anemia was defined as transferrin saturation (TS) < 15%, serum ferritin (SF) < 30 μg/L, and hemoglobin (Hb) < 13.0 g/dL. We excluded men with: anemia, thrombocytosis, or thrombocytopenia due to non-iron-deficiency causes; malignancy; chronic inflammatory conditions; hemochromatosis; or creatinine > 1.1 mg/dL. We computed univariate and multivariable pagophagia associations with: age; gastrointestinal bleeding; TS; SF; Hb; red blood cell (RBC) count; mean corpuscular volume (MCV); RBC distribution width (RDW); and platelet count. Median age of 41 men was 54 y (range 18–81). Fourteen men (34.1%) had pagophagia. Thirty-six men (87.8%) had gastrointestinal bleeding. Mean Hb was 9.4 ± 2.2 g/dL. Six men (14.6%) had thrombocytosis; two (4.9%) had thrombocytopenia. Logistic regression on pagophagia revealed: age ($p = 0.0158$; odds ratio 0.92 [95% confidence interval: 0.85, 0.99]) and platelet count ($p = 0.0187$; 0.98 [0.97, 1.00]) (41.4% of pagophagia occurrence; ANOVA $p = 0.0053$). We conclude that pagophagia occurred in 34% of men with iron-deficiency anemia and was negatively associated with age and platelet count, after adjustment for other variables.

## 1. Introduction

Pica is the daily compulsive eating of food or non-food items not part of one's habitual diet or preferences [1]. Pagophagia, the excessive habitual consumption of ice, is the type of pica most closely associated with iron deficiency in adults and rapidly reversible with iron therapy [1–6], especially parenteral iron [3]. In 1640, Lazare Rivière (1589–1655), French physician of Louis XIII, reported that women and girls with chlorosis consume ice, snow, and cold water [7]. Case series reports of pagophagia in adults with iron deficiency in US medical literature emerged in the 1960s [2,3]. Pagophagia is the most commonly reported type of pica in US adults with iron depletion or deficiency [1–3,6,8]. Pagophagia variants in adults with iron deficiency include excessive habitual consumption of freezer frost [9,10], snow [4], frozen bottled water [11], popsicles [1], iced drinks [1,4], and cold water [1,12]. Pagophagia in rats with iron deficiency is similar to that in humans [13].

The prevalence of iron deficiency in adults is greatest in pregnant and non-pregnant pre-menopausal women [14]. Accordingly, pagophagia is common in pregnant [15] and non-pregnant pre-menopausal [1,16] women with iron deficiency and has been reported during lactation [17]. Pagophagia also occurs in women with iron deficiency of all ages due to non-reproductive iron losses [1,6,8]. Pagophagia and iron deficiency occur in US non-Hispanic white, African-American, and Hispanic women [1,6,18].

Few case series reports of pagophagia and iron deficiency include substantial observations on men [1,19,20]. To learn more, we performed a retrospective study of 41 previously unreported US non-Hispanic white men ages ≥18 y with iron-deficiency anemia who were evaluated to identify causes of iron deficiency and whose anemia and pagophagia, thrombocytosis, and thrombocytopenia (if present) resolved after intravenous iron dextran therapy. Using data obtained at diagnosis, we computed clinical and laboratory associations of pagophagia using univariate and multivariable analyses. We compare and discuss clinical and laboratory associations of pagophagia in adults with iron deficiency identified in this and other reports.

*Abbreviations:* ANOVA, analysis of variance; CI, confidence interval; Hb, hemoglobin; MCV, mean corpuscular volume; OR, odds ratio; RBC, red blood cell; RDW, red blood cell distribution width; SD, standard deviation; SF, serum ferritin; TS, transferrin saturation

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## 2. Methods

### 2.1. Ethics statement

This work was performed according to the principles of the Declaration of Helsinki [21]. Western Institutional Review Board granted an exemption for performance of this study under 45 CFR 46.101(b)(4) on 4 March 2019 (submission no. 2554968-44265830). Obtaining informed consent was not required because this study involved retrospective chart review and analyses of observations recorded in routine medical care.

### 2.2. Patient selection

We reviewed computerized and paper charts of consecutive self-identified non-Hispanic white men ages ≥18 y referred to an out-patient clinic who were diagnosed to have iron-deficiency anemia. Each man reported not taking oral iron supplements and not having received erythrocyte transfusion before referral. All men underwent: history regarding blood loss, pica, pagophagia, sore mouth or tongue, dysphagia, gastrointestinal symptoms, and medications; physical examination; blood testing; fecal occult blood testing; gastrointestinal endoscopy and other evaluations to identify sites of blood loss, as appropriate; and evaluation for causes of anemia or abnormal platelet counts other than iron deficiency. Other inclusion criteria stipulated that each man had resolution of pagophagia (if present), anemia, low serum ferritin (SF), and abnormal platelet counts (if present) after therapy with intravenous iron dextran (INFed®; Watson Pharma, Inc., Morristown, NJ, USA).

### 2.3. Patient exclusions

We excluded men who had: non-iron deficiency causes of anemia and other red blood cell (RBC) abnormalities, thrombocytosis, and thrombocytopenia; malignancy or myelodysplastic syndrome; autoimmune, infectious, or other chronic inflammatory conditions; hemochromatosis; serum creatinine > 1.1 mg/dL; or incomplete evaluations or data. We excluded men with non-ice pica or polypica and men whose data were previously published [1].

### 2.4. Definition of iron-deficiency anemia

Anemia was defined as hemoglobin (Hb) < 13.0 g/dL [22]. Iron-deficiency anemia was defined as combined transferrin saturation (TS) < 15%, SF < 30 μg/L, and Hb < 13.0 g/dL.

### 2.5. Definition of pagophagia

Pagophagia was defined as the daily compulsive eating of ice not ordinarily part of the patient's habitual diet or preferences, for more than one month, and not reasonably attributable to causes other than iron deficiency by the patient or treating physician [1].

### 2.6. Definition of gastrointestinal bleeding

Gastrointestinal bleeding was defined as positivity of fecal occult blood tests without other explanation or a site of bleeding visualized by esophagogastroduodenoscopy, camera enteroscopy, or colonoscopy.

### 2.7. Laboratory

Complete blood counts were measured using Cell-Dyn 1800 (Abbott Diagnostics, Chicago, IL, USA). Mean platelet volume and platelet crit were not measured. Blood samples were obtained for measurement of TS and SF without regard for state of fasting. Measurements included spectrophotometric serum iron and unsaturated iron-binding capacity, calculated total iron-binding capacity and TS, and turbidimetric immunoassay of SF (Laboratory Corporation of America, Burlington, NC, USA). Serum creatinine was measured as part of renal or comprehensive metabolic profiles (Laboratory Corporation of America, Burlington, NC, USA). Normal platelet counts were defined as 140–400 × $10^3$/μL. Thrombocytosis was defined as platelet count > 400 × $10^3$/μL. Thrombocytopenia was defined as platelet count < 140 × $10^3$/μL.

### 2.8. Statistics

The dataset for analysis included complete observations on 41 men at diagnosis: age; pagophagia (dichotomous); gastrointestinal bleeding (dichotomous); TS; SF; Hb; RBC; mean corpuscular volume (MCV); RBC distribution width (RDW); and platelet count. Data are displayed as enumerations, percentages, mean ± 1 standard deviation (SD) (range), or median (range).

We used the Shapiro-Wilk test to determine normality of data distributions. Normally distributed data were compared using the Student's *t*-test (two-tailed) and results are displayed as mean ± 1 standard deviation (SD). Other continuous data were compared using the Mann-Whitney *U* test and results are displayed as median (range). We used Fisher's exact test (two-tailed) to compare proportions. We compared independent variables in men with and without pagophagia using univariable techniques. We performed logistic regression on pagophagia using independent variables identified in univariate comparisons. We computed the odds ratio (OR) and 95% confidence interval [95% CI] of significant independent variables and analysis of variance (ANOVA) of the regression. Values of $p < 0.05$ were defined as significant. Bonferroni corrections were applied to control the type I error rate at 0.05 for multiple univariate comparisons. Analyses were performed with Excel 2000® (Microsoft Corp., Redmond, WA, USA) and GB-Stat® (v. 10.0, 2003, Dynamic Microsystems, Inc., Silver Spring, MD, USA).

## 3. Results

### 3.1. General characteristics

Median age at diagnosis of iron-deficiency anemia in 41 men was 54 y (range 18–81). Fourteen men (34.1%) had pagophagia. Each of the 14 men reported excessive habitual consumption of ice cubes, pellets, or flakes, or crushed ice. No man reported non-ice pica. No man had cheilosis, glossitis, stomatitis, or dysphagia. No man reported symptoms of restless legs syndrome.

Thirty-six men (87.8%) had gastrointestinal bleeding. Eighteen men had bleeding from non-malignant sites in the gastrointestinal tract alone. Two men had gastrointestinal bleeding and epistaxis due to hereditary hemorrhagic telangiectasia. Sixteen men had positive fecal occult blood tests, but no site of bleeding was visualized by gastrointestinal endoscopy or camera enteroscopy. Of these 16 men, four took aspirin and clopidogrel, two took aspirin alone, and another took omeprazole. In three men without evidence of bleeding, iron deficiency was attributed to malabsorption (two atrophic gastritis, one gastric bypass operation). No site of bleeding or cause of iron malabsorption was detected in two men ages 75 y and 81 y, respectively.

### 3.2. Laboratory results

Laboratory results for all 41 men are displayed in Table 1. Median TS was 5% (range 2, 19) and median SF was 10 μg/L (range 2, 27). Mean Hb level was 9.4 ± 2.2 g/dL (1 SD) (range 4.7, 12.6) and mean RBC count was 4.11 ± 0.84 × $10^6$/μL (1 SD) (range 2.06, 5.06). Mean MCV was 74.1 ± 9.8 fL (1 SD) (range 58.5, 97.7) and median RDW was 17.9% (range 14.2, 31.0). Mean platelet count was 296 ± 97 × $10^3$/μL (1 SD) (range 122, 511). Six men (14.6%) had thrombocytosis. Two men (4.9%) had thrombocytopenia.

**Table 1**
Clinical and laboratory characteristics of 41 men with iron-deficiency anemia[a]

| Characteristic[b] | Pagophagia ($n$ = 14) | No pagophagia ($n$ = 27) | Value of p[c] (14 pagophagia vs. 27 no pagophagia) | All men ($n$ = 41) | Value of p (14 pagophagia vs. all 41 men) |
|---|---|---|---|---|---|
| Mean age, y ± 1 SD | 49 ± 20 | 60 ± 18 | 0.1017 | 56 ± 19 | 0.2402 |
| Gastrointestinal bleeding, % (n) | 92.9 (13) | 85.2 (23) | 0.6648 | 87.8 (36) | ~1.0000 |
| Median TS, % (range) | 4 (2, 10) | 6 (2, 14) | 0.2317 | 5 (2, 14) | 0.3962 |
| Median SF, μg/L (range) | 10 (2, 26) | 10 (3, 27) | 0.2716 | 10 (2, 27) | 0.5288 |
| Mean Hb, g/dL ± 1 SD | 9.7 ± 1.9 | 9.3 ± 2.3 | 0.5978 | 9.4 ± 2.2 | 0.6946 |
| Mean RBC x $10^6$/μL (SD) | 4.49 ± 0.77 | 3.91 ± 0.82 | 0.0412 | 4.11 ± 0.84 | 0.1338 |
| Mean MCV, fL ± 1 SD | 71.2 ± 8.9 | 75.5 ± 9.8 | 0.1784 | 74.1 ± 9.6 | 0.3389 |
| Median RDW, % (range) | 18.1 (15.7, 31.0) | 17.4 (14.2, 25.7) | 0.3949 | 17.9 ± 9.6 | 0.5535 |
| Mean platelets x $10^3$/μL ± 1 SD | 256 ± 69 | 317 ± 103 | 0.0343 | 296 ± 97 | 0.1124 |

[a] Iron-deficiency anemia was defined as combined TS < 15%, SF < 30 μg/L, and Hb < 13.0 g/dL. No man had cheilosis, glossitis, stomatitis, or dysphagia. Abbreviations: SD, standard deviation; TS, transferrin saturation; SF, serum ferritin; Hb, hemoglobin; RBC, red blood cells; MCV, mean corpuscular volume; RDW, red blood cell distribution width.

[b] We used the Shapiro-Wilk test to determine normality of data distributions. Normally distributed data were compared using the Student's $t$-test (two-tailed) and results are displayed as mean ± 1 standard SD. Other continuous data were compared using the Mann-Whitney $U$ test and results are displayed as median (range).

[c] Bonferroni correction for nine comparisons yielded a revised p for significance of < 0.0056.

### 3.3. Univariate associations with pagophagia

Ten of 21 men ages 18–55 y had pagophagia (47.6%). Four of 20 men ages 56–81 y had pagophagia (20.0%). The difference between these proportions was not significant ($p$ = 0.1001). Mean RBC count was higher in men with than without pagophagia in an initial comparison (Table 1). Mean platelet count was lower in men with than without pagophagia in an initial comparison (Table 1). After Bonferroni correction, neither of these differences was significant (Table 1). A comparison of respective characteristics of 14 men with pagophagia and all 41 men revealed no significant differences (Table 1).

### 3.4. Regression on pagophagia

We selected three independent variables associated with uncorrected values of $p \leq 0.1017$ in univariate comparisons (age, red blood cell count, platelet count; Table 1). Logistic regression on pagophagia revealed two significant associations: age ($p$ = 0.0158; OR 0.92 [95% CI: 0.85, 0.99]) and platelet count ($p$ = 0.0187; OR 0.98 [95% CI: 0.97, 1.00]). This regression accounted for 41.4% of pagophagia occurrence (ANOVA $p$ = 0.0053).

## 4. Discussion

The prevalence of pagophagia in the present 41 non-Hispanic white men with iron-deficiency anemia was 34%. In previous reports, the prevalence of pagophagia in white men with iron deficiency was 32% [1] and 42% [20]. In two studies, the prevalence of pagophagia in adults with iron deficiency was significantly lower in men than women [1,20]. Pagophagia in all 14 of the present men resolved rapidly after intravenous iron dextran therapy (an inclusion criterion), consistent with previous reports of pagophagia resolution in men and women treated for iron deficiency [1,2,19,20]. In 23 adults with iron deficiency due to chronic blood loss, pagophagia resolved when iron replacement treatment elevated serum iron levels > 70 μg/dL [2].

In this study, regression on pagophagia revealed a significant negative association of age, after adjustment for other variables, although the OR was not especially low. In a study that included 230 nonpregnant women with iron deficiency, the prevalence of pica reports (86% pagophagia) was significantly greater in women ages 19–59 y (56%) than women ages 60–91 y (35%) [1].

Iron deficiency is associated with histologic changes of oral mucosa and depletion of heme-containing enzymes therein that are reversed rapidly by iron replacement therapy [23,24]. None of the present men had cheilosis, glossitis, or stomatitis, although it has been postulated that some adults habitually consume ice or cold water to soothe these manifestations of iron deficiency [25]. In another study, the prevalence of epithelial abnormalities in adults with iron deficiency was significantly lower in those with pagophagia than those with non-ice pica [1]. In a small randomized trial, adults with iron-deficiency anemia who chewed ice had improved response times and decreased errors in a continuous performance test [26]. It was hypothesized that increased blood flow to the brain via peripheral vasoconstriction or sympathetic nervous system activation could explain these observations [26].

The predominant cause of iron-deficiency anemia in the present men was gastrointestinal bleeding, consistent with other reports of men with iron deficiency [1,14,20], but gastrointestinal bleeding was not significantly associated with pagophagia. In another report, the site of gastrointestinal bleeding in men or women was not significantly associated with pica (88% pagophagia) [20]. In another study, the prevalence of diverse causes of blood loss and iron malabsorption did not differ significantly between adults with iron deficiency who had pagophagia and those who had non-ice pica [1]. In two men, no site of bleeding or cause of iron malabsorption was detected, in agreement with previous reports [1,27,28].

Hb, MCV, and RDW were not significantly associated with pagophagia in this study. Pica occurs in some adults who have iron deficiency without anemia [29]. Pagophagia in adults with iron deficiency resolves with iron treatment long before Hb is normal [2,3]. In 262 men and non-pregnant women with iron deficiency, pica (87% pagophagia) was associated with lower values of MCV and higher values of RDW, after adjustment for other variables [1]. In a study of deferred US blood donors with iron depletion or deficiency, MCV was the variable most strongly associated with pica (93% pagophagia) [19]. The common *TMPRSS6* allele p.A736V (rs855791) is associated with lower TS, Hb, and MCV in general adult populations [30,31]. In 46 non-pregnant US women with iron depletion or deficiency, of whom 46% had pagophagia, there was no significant relationship of p.A736V with pagophagia, TS, or erythrocyte measures [8].

Concentrations of iron in drinking water are typically < 0.3 mg/L and thus adults consume ~0.6 mg of iron daily in drinking water [32]. Greater concentrations of iron may occur in drinking water obtained from rivers, facilities that utilize iron salts as water purification coagulants, or iron pipes [32]. Although drinking water (or ice) may provide small quantities of iron daily, we found no report that pagophagia alleviates iron deficiency. Iron absorption from oral doses in adults with iron-deficiency anemia with and without pagophagia did not differ significantly [33].

Eighty percent of the men in this study had normal platelet counts, 15% had thrombocytosis, and 5% had thrombocytopenia, consistent

with findings in other adults with iron deficiency [34]. Resolution of thrombocytosis and thrombocytopenia with iron dextran therapy in the present eight men (an inclusion criterion) suggests that iron influences platelet counts [34]. In a study of women with iron deficiency, 28% had thrombocytosis and 2% had thrombocytopenia [35]. In adults from the general US population matched for age, mean platelet counts were lower in men than women and lower in whites than non-Hispanic blacks [36]. In the present study, there were significant negative associations of platelet counts with pagophagia in univariate and multifactorial analyses, although these associations were not strong, in agreement with a previous report [1].

A strength of the present study is the presentation of observations on non-Hispanic white men with a broad range of ages who had iron-deficiency anemia, with or without pagophagia, and who lacked other common conditions that influence TS, SF, erythrocyte, and platelet measures. Some men may have not reported pagophagia due to embarrassment or the belief that pagophagia is an idiosyncrasy, not a symptom [6,12]. Thus, our prevalence estimate of pagophagia may be conservative. Analysis of a larger cohort may have revealed other significant findings. Measuring serum erythropoietin, serum transferrin receptor, and erythrocyte protoporphyrin or examining bone marrow was not indicated in most of the present men. We did not assess dietary iron intake. We did not perform mutation analyses to detect common alleles of *TMPRSS6* [30] and *HFE* [37,38] that influence TS, SF, Hb, and MCV. In another report, common *TF* polymorphisms were not associated with significant differences in TS, SF, Hb, or MCV [39].

## 5. Conclusions

We conclude that pagophagia occurred in 34% of men with iron-deficiency anemia and was negatively associated with age and platelet count, after adjustment for other variables.

## Author contributions

JaCB conceived the study, evaluated patients, performed statistical evaluations, and drafted the manuscript. JClB compiled data and performed statistical evaluations. LFB evaluated patients. All authors contributed to the final manuscript.

## Conflicts of interest

None of the authors has a conflict of interest to report.

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