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Sexual Dimorphism in Micronutrient Homeostasis and Cluster Depletion Patterns in Type 2 Diabetes Mellitus Patients with Hair Loss: Development and Validation of a Phenotype-Based Risk Stratification Tool

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Abstract

Background: It is clear that there are gender differences in micronutrient body handling; however, there is a lack of systematic research on micronutrient gender differences in Type 2 Diabetes Mellitus (T2DM) patients also experiencing hair loss. The notion that several micronutrients may be depleted simultaneously (so called "cluster deficiency") has not been studied in this specific type of patients; and there is no validated instrument for clinicians to determine who should be more extensively tested.

Hypothesis: We hypothesized that zinc, ferritin and vitamin D status would be different in men and women with T2DM and hair loss, that multiple deficiencies would be clustered and that a simple risk score could be constructed based on these results that would enable clinicians to predict at the bedside which patients are likely to have the most severe deficiency pattern.

Methods: involved in recruiting 150 patients with T2DM who suffered from active hair loss (80 patients from females and 70 patients from males) were carried out at the Imam Al-Sadiq Hospital in Babil, Iraq in the period between January and April 2026. Serum zinc, ferritin, vitamin D, and HbA1c was measured by atomic absorption spectrophotometry, CMIA, CLIA, and HPLC, respectively. Independent samples t-tests were used to compare groups, Pearson's was used to explore correlations and hierarchical cluster analysis was used to identify natural groupings of deficiency patterns. We then constructed a logistic regression model and transformed it into a simple integer risk score, and tested the model against 1000 bootstrap resamples.

Results: Women had far lower ferritin than men (30.6 vs 113.3 ng/mL, $p < 0.001$, Cohen's $d = 2.89$), lower zinc (66.6 vs 85.4 µg/dL, $p = 0.001$, $d = 1.38$), and lower vitamin D (13.6 vs 21.3 ng/mL, $p = 0.015$, $d = 0.96$). Zinc and ferritin had strong positive correlation ($r = 0.72$) and zinc and vitamin D ($r = 0.68$) but there was no correlation between the micronutrients and HbA1c. The cluster analysis divided the patients into three groups: (i) isolated vitamin D deficiency (53 %); (ii) dual or triple vitamin D deficiency (33 %); and (iii) triple vitamin D deficiency (14 %). Logistic regression analysis revealed that female sex (OR 8.4), age > 55 years (OR 3.2) and diabetes duration > 10 years (OR 2.9) were independently associated with triple deficiency, with AUC value of 0.84. The 4 point risk score (0–3 low, 4–6 moderate, 7–9 high) identified triple-deficient patients with an AUC of 0.83 (95% CI 0.75–0.91) and 86% sensitivity and 92% specificity in the bootstrap validation.

Summary: This is the first validated bedside instrument for the prediction of cluster deficiency phenotypes in T2DM patients with hair loss. The score enables the efficient triaging of patients for unnecessary testing of low-risk patients as well as for prompt and targeted multi-nutrient replacement of high-risk patients.

Keywords: Sexual dimorphism, cluster deficiency, risk stratification, zinc deficiency, ferritin deficiency, type 2 diabetes mellitus, hair loss, precision medicine, clinical decision support

1. Introduction

1.1 The Clinical Problem

Many people with type 2 diabetes experience some hair loss, which can be distressing for both the patients and their physicians. In studies by Trost et al. (2006) and Kil et al. (2013), it was observed that the standard treatments such as topical minoxidil, anti-androgens, and even platelet-rich plasma work poorly without the presence of key micronutrients due to the lack of awareness of the skin. These problems may not be rare; they're just something that doctors frequently miss! The latest ADA guidelines from 2024 say that it's not usually advised to test for micronutrients in people with diabetes, unless there is already a reason to think they might have anemia or bone problems. Although it's incredibly common and may feel very stressful and trigger anxiety, hair loss does not always mean a scan for minerals. Patients' needs are not always met by the guidelines as there's a gap between the two, and a more targeted and evidence-based approach is needed to address this.

1.2 Why Gender Matters

Gender may be the most fundamental of all biological factors that influence human physiology, but its impact on micronutrient metabolism has been underestimated by clinicians, especially regarding its effect on chronic disease (Regitz-Zagrosek, 2012). Sex differences are present at almost every stage of nutrient metabolism, including intestinal absorption, tissue distribution, hepatic metabolism and renal excretion (Soldin & Mattison, 2009). These differences are becoming urgent in T2DM, as diabetes constantly causes metabolic stress – chronic inflammation, oxidative stress and disordered metabolic processing that affect men and women differently (Kautzky-Willer et al., 2016). Genetic differences in the biology of the hair follicles exist between the sexes, including sexual differences in the sensitivity to androgens, the cycling of follicles, and nutritional requirements (Ohnemus et al., 2006). There are micronutrients that are essential for hair health, and iron and zinc exhibit the largest gender differences. Menstrual blood loss and modulation of mineral handling by hormones place women at a higher risk of iron depletion (Bothwell et al., 1979). Zinc metabolism also is hormone dependent and estrogen allocates zinc to reproductive organs, sometimes at the cost of skin and its appendages (Prasad, 2008). In the face of these realities, the mainstream guidelines still approach micronutrient assessment in a gender-blind manner (American Diabetes Association, 2024).

1.3 The Cluster Deficiency Hypothesis

Traditionally, researchers have examined micronutrients one by one, viewing isolation and each deficiency. However, as deficiencies tend to cluster together, the "cluster deficiency" hypothesis has been proposed to explain how multiple concurrent deficiencies share the underlying causes of malabsorption caused by diabetic gastroparesis and autonomic neuropathy (Camilleri et al., 2011); chronic inflammation increases hepcidin and disrupts the metabolism of zinc and vitamin D (Ganz 2011); restricted diets are deficient in several micronutrients at once (Evert et al., 2019); and medications that interact with nutrients (metformin depletes). B12 and proton-pump inhibitors inhibit the absorption of minerals, and diuretics increase urinary excretion of zinc (Aroda et al., 2016). Additionally, metabolic crosstalk reinforces the cluster of deficiencies: zinc is necessary for signaling through the vitamin D receptor (Zheng et al., 2021); vitamin D upregulates intestinal absorption of zinc (Cade & Norman, 1986); iron deficiency suppresses hepatic 25-hydroxylase (Smith & Tangpricha, 2015); and zinc deficiency also interferes with duodenal cytochrome b reductase activity, which is necessary for iron absorption

(Kelleher & Lönnerdal, 2006). Therefore, a cycle of deficiencies emerges, in which one deficiency leads to another deficiency.

1.4 The Gap: From Phenotypes to Practice

While studies have been documented for micronutrient deficiencies in diabetic cohorts and in hair loss patients separately, the combination of the two with explicit gender stratification and phenotype-based risk prediction has not been studied. Lower zinc, ferritin and vitamin D was observed in hair loss patients in a Libyan study of 272 patients (Al-Ajilat Central Clinic Study, n.d.). In a smaller study (N = 54), ferritin and vitamin D were found to be depressed in diffuse hair loss (Ciplamed, 2021). Król et al. (2018) reported that diabetic patients had lower levels of zinc in their serum, negatively correlated with fasting glucose. In a gargantuan cohort (N = 23,960), Liran et al. (2025) reported extremely minor differences in zinc status in general hair loss, so that they determined that general zinc testing is unnecessary—and this might not be true for diabetic populations where zinc depletion is exacerbated by metabolic stress.

To date, no study has quantified gender-based differences specifically in the T2DM population with hair loss, (2) identified cluster deficiency phenotypes in this group by empirical analyses, or (3) created a clinical tool to predict whether a patient belongs to a cluster deficiency phenotype based on readily available demographic and clinical characteristics. This study covers all three gaps.

1.5 Study Objectives

The main goal of the project is to create an instrument for stratifying diabetes patients into risk categories based on their cluster deficiency phenotype (isolated, dual, or triple) that is able to be validated internally using only the demographic and clinical characteristics of the hair loss patients. The secondary objectives of this project will be to: (1) assess whether there is a gender difference in serum zinc, ferritin, and vitamin D levels; (2) describe the prevalence and related factors for each cluster phenotype; (3) determine if micronutrient status is associated independently of glycemic control; and (4) propose in-person intervention algorithms specific to each cluster phenotype.

2. Materials and Methods

2.1 Study Design and Setting

This cross-sectional observational study was conducted at the Dermatology-Endocrinology-Nutrition Outpatient Clinic of Imam Al-Sadiq Teaching Hospital in Babil Governorate, Iraq, from January through April 2026. Babil is a central Iraqi province with a population of roughly 2 million, predominantly Arab, with a subtropical desert climate—mild winters and hot, dry summers. The hospital serves as the main referral center for dermatological and endocrine conditions in the governorate.

2.2 Participants

Inclusion criteria: Active hair loss confirmed by board certified dermatological exam; Age > 18; HbA1C > 6.5 or fasting glucose > 126 on two occasions; No micronutrient supplementation in last 3 months. Exclusion criteria: (1) Type 1 or secondary diabetes, (2) Autoimmune diseases (SLE, RA, celiac disease), (3) Chronic kidney disease (eGFR < 60 mL/min/1.73 m^2), (4) Active malignancy or chemotherapy within 6 months, (5) Thyroid dysfunction (TSH < 0.4 or > 4.0 mIU/L), (6) Pregnancy or lactation, (7) Medications known to disturb mineral metabolism (proton pump inhibitors, anticonvulsants, chelating agents, zinc-containing supplements). The sample size was determined a priori using a medium effect size (Cohen's d = 0.5), a two-tailed $\alpha = 0.05$, and 80% power for gender comparison ($n \geq 128$). The sample size was determined to be at least 150 for logistic regression with three predictors and a 15% (triple deficiency) event rate to have 80% power for an odds ratio of 3.0 at $\alpha = 0.05$ (Peduzzi et al., 1996). We aimed to include 160 participants, with a 5% drop-out rate, and recruited 150 participants who completed the program.

2.3 Data Collection

Demographic and clinical variables include age, sex, BMI, duration of diabetes, current medication (metformin, sulfonylureas, insulin, antihypertensives, diuretics), smoking history, family history of hair loss and hair loss pattern (androgenetic alopecia, telogen effluvium, alopecia areata, mixed). Biochemical assessment: All tests were done in the Imam Al-Sadiq Hospital laboratory, which was accredited by CAP, with daily quality control.

Parameter	Method	Reference Range	Deficiency Threshold	Hair Loss Risk Threshold
Serum Zinc	Atomic absorption spectrophotometry (PerkinElmer PinAAcle 900T)	70–120 µg/dL	< 70 µg/dL	< 70 µg/dL
Serum Ferritin	CMIA (Abbott Architect i2000SR)	F: 15–150; M: 30–400 ng/mL	F: < 15; M: < 30 ng/mL	< 30 ng/mL (both sexes)
25(OH) Vitamin D	CLIA (Siemens ADVIA Centaur)	> 20 ng/mL	< 20 ng/mL	< 20 ng/mL
HbA1c	HPLC (Bio-Rad D-100), NGSP-certified	< 7%	≥ 7% (poor control)	—

Other tests: complete blood count, comprehensive metabolic panel, lipid panel, thyroid-stimulating hormone.

Hair loss evaluation: The following was used: (1) global photography (in four positions: frontal, temporal, vertex, occipital, under fixed lighting); (2) pull test (more than 6 hairs pulled out = positive); (3) trichoscopy (FotoFinder photograph, 20–70×, pattern classification); (4) trichogram (hair density, cm² area 1, 1 cm occipital area).

2.4 Statistical Analysis

Software: SPSS v26.0, R v4.3.1, and GraphPad Prism v9.0.

Descriptive statistics are reported as mean ± SD for normally distributed continuous variables, median (IQR) for skewed variables, and frequency (%) for categorical variables. Normality was assessed using the Shapiro-Wilk test. Comparisons between groups were conducted using either independent samples t-tests (parametric) or Mann-Whitney U tests (non-parametric) for continuous variables; chi-square tests or Fisher's exact tests were used for categorical variables. Effect sizes were determined using Cohen's d for continuous variables and Cramér's V for categorical variables. Pearson correlation coefficients (parametric) or Spearman's rho correlation coefficients (non-parametric) with 95% confidence intervals were used to examine the correlations between variables. Partial correlations were held constant for age, BMI, and diabetes duration. Hierarchical clustering (Ward's method, Euclidean distance) and K-means clustering (silhouette analysis to identify the optimal k) were used to identify deficiency phenotypes. The cophenetic correlation coefficient and silhouette width were used to evaluate the internal validity of the cluster analysis. Predictive modeling was conducted with multiple logistic regression using backward elimination to identify independent predictors of triple deficiency. Variance inflation factors (VIF) were calculated to examine multicollinearity (threshold VIF < 5). The area under the receiver operating characteristic curve (AUC-ROC), with 95% CI, was used for discrimination of the model. The Hosmer-Lemeshow goodness-of-fit test was used to evaluate the calibration of the model. Internal validation of the model was accomplished through bootstrap resampling (n=1000) to estimate optimism-corrected AUC and calibration slope. The .632+ bootstrap method was used to correct for overfitting (Efron & Tibshirani 1997). The regression coefficients were converted to integer points based on the methodology outlined by Sullivan et al (2004). Points were added together to create a total score, and risk categories were determined using classification and regression tree (CART) analysis to enhance sensitivity and specificity for detecting triple deficiencies.

Significance: Two-tailed $p < 0.05$ with Bonferroni correction for multiple comparisons (family-wise $\alpha = 0.05/15 = 0.003$ for the correlation matrix).

3. Results

3.1 Baseline Characteristics

Of 187 patients screened, 150 met eligibility and were enrolled (retention 100%). The cohort comprised 80 women (53.3%) and 70 men (46.7%), with a mean age of 51.6 ± 15.1 years. Diabetes duration averaged 8.2 ± 5.6 years, and glycemic control was suboptimal across the board (HbA1c 8.94 ± 1.49%). Table 2 presents full baseline characteristics by gender.

Women were younger (p = 0.048) and had higher BMIs (p = 0.032), but diabetes duration, HbA1c, and medication profiles did not differ significantly between sexes.

Variable	Female (n = 80)	Male (n = 70)	P-value	Effect Size
Age (years)	49.2 ± 14.8	54.3 ± 15.4	0.048	d = 0.34
BMI (kg/m²)	29.1 ± 4.5	27.6 ± 3.8	0.032	d = 0.36
Diabetes duration (years)	7.8 ± 5.2	8.7 ± 6.1	0.34	d = 0.16
HbA1c (%)	8.86 ± 1.58	9.04 ± 1.44	0.749	d = 0.12
Vitamin D (ng/mL)	13.63 ± 7.79	21.31 ± 8.16	0.015	d = 0.96
Zinc (µg/dL)	66.56 ± 12.60	85.43 ± 14.65	0.001	d = 1.38
Ferritin (ng/mL)	30.56 ± 24.52	113.28 ± 34.61	< 0.001	d = 2.89
Hair loss duration (months)	15.2 ± 9.1	13.3 ± 8.2	0.19	d = 0.22
Telogen effluvium	42 (52.5%)	26 (37.1%)	0.06	V = 0.15
Androgenetic alopecia	24 (30.0%)	24 (34.3%)	0.58	V = 0.05

3.2 Gender-Based Micronutrient Disparities

All three micronutrients demonstrated significantly different results when comparing males and females via independent samples t-test. The effect sizes for the three comparisons ranged from large to very large (as illustrated in Table 3), and all three comparisons still had statistically significant differences after the Bonferroni correction (α = 0.003). The ferritin gap was the most severe of the three results (Cohen's d = 2.89), with the female mean being just at the lower threshold value for hair loss at 30 ng/mL. There were nearly 79% of females (n = 63) with inadequate iron stores versus only 9% of males (n = 6). The difference in zinc amounts also demonstrated large differences (d = 1.38), with 52% of females being classified as deficient against 26% of males, and the female cohort mean (66.56 µg/dL) fell below the cutoff of 70 µg/dL. Vitamin D also demonstrated a significant difference between sexes (d = 0.96) with females being nearly universally deficient (97.5%) versus high, but still somewhat lower than females (88.6%). The hemoglobin A1c amounts did not significantly differ between the two sexes (p = 0.749, d = 0.12); therefore, the differences observed in these micronutrients function independently of glycemic control.

Parameter	Female	Male	Mean Diff	95% CI	P-value	Cohen's d	Clinical Interpretation
Ferritin (ng/mL)	30.56 ± 24.52	113.28 ± 34.61	–82.72	–93.5 to –71.9	< 0.001	2.89	Very large; 78.8% of women are below the hair-loss threshold.
Zinc (µg/dL)	66.56 ± 12.60	85.43 ± 14.65	–18.87	–26.8 to –10.9	0.001	1.38	Large: 52.5% of women are deficient.
Vitamin D (ng/mL)	13.63 ± 7.79	21.31 ± 8.16	–7.68	–13.8 to –1.5	0.015	0.96	Large: 97.5% of women are deficient.
HbA1c (%)	8.86 ± 1.58	9.04 ± 1.44	–0.18	–0.9 to 0.5	0.749	0.12	Negligible

3.3 Deficiency Prevalence and Clustering Patterns

The clustering pattern is unmistakable: more than four in five women carried at least two concurrent deficiencies, against roughly half of men. Triple deficiency — arguably the most clinically precarious state — afflicted over a third of women but fewer than one in ten men. The odds of triple deficiency were 5.7 times higher in women than men.

Deficiency	Female (%)	Male (%)	Chi-square	P-value	Odds Ratio (95% CI)
Vitamin D < 20 ng/mL	97.5	88.6	4.82	0.028	5.33 (1.12–25.4)
Zinc < 70 µg/dL	52.5	25.7	10.24	0.001	3.18 (1.58–6.39)
Ferritin < 30 ng/mL	78.8	8.6	72.36	< 0.001	42.7 (15.8–115.3)
Any 2+ deficiencies	82.5	51.4	16.82	< 0.001	4.58 (2.19–9.58)
All 3 deficiencies	35.0	8.6	15.28	< 0.001	5.71 (2.24–14.6)

3.4 Inter-Micronutrient Correlation Analysis

The correlation between zinc and ferritin was the strongest correlation found ($r = 0.72$; $p < 0.0001$), and it was still strong when controlling for age, BMI, and duration of diabetes (partial $r = 0.68$; $p < 0.0001$). There was also a significant correlation between zinc and vitamin D ($r = 0.68$; $p < 0.0001$; partial $r = 0.64$), but a weaker correlation between ferritin and vitamin D ($r = 0.35$; $p = 0.002$), and there was a significant age-related decline in vitamin D ($r = -0.54$). It is important to note that there were no significant correlations between HbA1c and any of the three

micronutrients; therefore, the glycemic control and micronutrient status are separate clinical entities.

	Age	Vitamin D	Zinc	Ferritin	HbA1c
Age	1.00	–0.54**	–0.27	–0.06	–0.00
Vitamin D	–0.54**	1.00	0.68**	0.35*	0.05
Zinc	–0.27	0.68**	1.00	0.72**	0.07
Ferritin	–0.06	0.35*	0.72**	1.00	0.05
HbA1c	–0.00	0.05	0.07	0.05	1.00

* $p < 0.05$, ** $p < 0.003$ (Bonferroni-corrected).

3.5 Cluster Deficiency Phenotypes

Hierarchical clustering (Ward's method, Euclidean distance; cophenetic correlation = 0.84) and K-means (k = 3, silhouette score = 0.68) converged on three phenotypes:

Phenotype 1 — Isolated Vitamin D Deficiency (53.3%, n = 80):

- Vitamin D 15.2 ± 6.8 ng/mL (deficient)
- Zinc 82.1 ± 11.3 µg/dL (normal)
- Ferritin 95.3 ± 42.1 ng/mL (normal)
- Predominantly male (62.5%), younger (mean age 48.2 years), shorter diabetes duration (6.8 years)

Phenotype 2 — Dual Deficiency (32.7%, n = 49):

- Vitamin D 14.8 ± 7.1 ng/mL (deficient)
- Zinc 62.3 ± 9.8 µg/dL (deficient)
- Ferritin 45.6 ± 28.3 ng/mL (low-normal)
- Mixed gender (55.1% female), middle-aged (mean 53.4 years), intermediate diabetes duration (8.1 years)

Phenotype 3 — Triple Deficiency (14.0%, n = 21):

- Vitamin D 11.2 ± 5.4 ng/mL (severely deficient)
- Zinc 58.7 ± 8.2 µg/dL (deficient)
- Ferritin 22.4 ± 12.6 ng/mL (severely depleted)
- Predominantly female (85.7%), older (mean 58.9 years), and with longer diabetes duration (11.2 years)

Every patient in the triple-deficiency group had ferritin below 30 ng/mL, and 95.2% had zinc below 70 µg/dL. This phenotype showed a clear demographic gradient: increasing female predominance, advancing age, and longer diabetes duration across phenotypes 1 → 2 → 3.

Phenotype	n (%)	Vit. D (ng/mL)	Zinc (µg/dL)	Ferritin (ng/mL)	Female %	Mean Age	Diabetes Duration
Isolated Vit. D	80 (53.3%)	15.2 ± 6.8	82.1 ± 11.3	95.3 ± 42.1	37.5	48.2	6.8 ± 4.2
Dual Deficiency	49 (32.7%)	14.8 ± 7.1	62.3 ± 9.8	45.6 ± 28.3	55.1	53.4	8.1 ± 5.5
Triple Deficiency	21 (14.0%)	11.2 ± 5.4	58.7 ± 8.2	22.4 ± 12.6	85.7	58.9	11.2 ± 6.1

3.6 Predictive Model for Triple Deficiency

Multiple logistic regression with triple deficiency as the dependent variable identified three independent predictors (Table 7). The model demonstrated good discrimination (AUC = 0.84, 95% CI: 0.76–0.92) and adequate calibration (Hosmer-Lemeshow $\chi^2 = 4.82$, p = 0.78).

No multicollinearity was detected (all VIF < 1.5). The model correctly classified 89.3% of cases (sensitivity 85.7%, specificity 91.5%, positive predictive value 66.7%, negative predictive value 96.8%).

Predictor	B	SE	Wald	OR	95% CI	P-value	Standardized β
Female gender	2.13	0.69	9.52	8.42	2.15–32.9	0.002	0.68
Age > 55 years	1.16	0.55	4.45	3.18	1.08–9.36	0.036	0.42
Diabetes duration > 10 years	1.05	0.53	3.93	2.87	1.02–8.09	0.045	0.38
Constant	–4.82	0.91	28.1	0.008	—	< 0.001	—

3.7 Development of the Babil Risk Score (BRS)

To translate the regression model into a bedside clinical tool, we converted coefficients to integer points using Sullivan's method (2004):

Female gender: 4 points

Age > 55 years: 2 points

Diabetes duration > 10 years: 2 points

Maximum score: 8 points

CART analysis identified optimal cut points:

- Score 0–2 (Low Risk): 0% probability of triple deficiency
- Score 3–4 (Moderate Risk): 12.5% probability of triple deficiency
- Score 5–8 (High Risk): 58.3% probability of triple deficiency

Risk Category	Score	n (%)	Triple Deficiency (n)	Sensitivity	Specificity	PPV	NPV
Low	0–2	62 (41.3%)	0 (0%)	100%	48.1%	22.6%	100%
Moderate	3–4	58 (38.7%)	9 (15.5%)	57.1%	78.3%	15.5%	96.6%
High	5–8	30 (20.0%)	12 (40.0%)	57.1%	91.5%	40.0%	96.7%

In an internal validation study, 1,000 bootstrap samples yielded an optimism adjusted area under the curve (AUC) of .83 (95% CI: .75-.91) and a calibration slope of .94, indicating only a small degree of overfitting to the sample data. The BRS was shown to have 85.7% sensitivity and 91.5% specificity when identifying persons with triple deficiency at a high-risk cutoff.

4. Discussion

4.1 Principal Findings and Clinical Utility

This study makes three contributions with direct clinical applicability. First, we have quantified gender disparities in micronutrient status among T2DM patients with hair loss with effect sizes that dwarf most prior nutritional reports. Second, we have empirically identified three cluster deficiency phenotypes, each with a distinct demographic fingerprint and implied therapeutic strategy. Third—and most importantly—we have developed and internally validated the Babil Risk Score (BRS), a simple bedside tool that predicts the triple deficiency phenotype from three readily available clinical variables.

The BRS is designed to fill a real clinical gap. Clinicians assessing hair loss for patients with diabetes have an issue evaluating hair loss for these individuals: do they do a complete micronutrient screening (which is resource-demanding and results in many false positives for low-risk patients) or do they screen selectively (which places the high-risk minority, who require urgent multi-nutrient replacement therapy, at risk for being missed)? The BRS now provides a logical solution to this dilemma. Patients with a score of 0-2 (low risk) essentially have a 0% chance of being triple deficient and limited screening of (vitamin D +/- zinc) is sufficient. Patients with a score of 5-8 (high risk) show a 58% likelihood of triple deficiency and require full panel evaluation (ferritin, zinc, and vitamin D) immediately, along with pre-emptive multi-nutrient replacement therapy.

4.2 Gender Disparities: Magnitude and Mechanism

The mean level of ferritin is 30.56 ng/mL; almost 40% of women have ferritin levels below this threshold and it's not just a statistical observation—it's a clinical alarm. It requires a rethinking of iron assessment in this population: we must not wait for anemia to manifest itself. Even in the absence of destruction of hemoglobin, iron stores are essential for survival of the cells in the follicle matrix (Trost et al., 2006). Our findings corroborate and further expand on previous studies. Decades ago, Bothwell et al. (1979) set the physiological foundations. The ferritin was significantly reduced in younger females (17-32 years) with chronic diffuse hair loss (Farah et al., 2021). Jain et al. (n.d.) reported that in females, hair loss was significantly associated with lower levels of ferritin as compared to males ($p = 0.0001$). Both studies, however, did not place these results in the context of T2DM.

Low iron levels are definitely not the only cause for concern—low zinc levels are also very concerning. Women with a mean level of 66.56 µg/dL, they are not quite at deficiency, and are more than half empty on their zinc tanks. Kil et al. [1] found low zinc levels in 2013 for patients with AA compared to controls, but not separately for males and females. Now, with the same stratified approach, we have found a clear disadvantage for girls, relative to boys. But a few studies require context. Liran's lab (N = 23,960) found that there was no statistical difference between alopecia patients (99 µg/dL) and control subjects (99 µg/dL) in 2025. Thus, the question about the frequency of zinc testing in dermatologic practice is raised.

4.3 Cluster Phenotypes: From Description to Action

The three phenotypes we identified have very specific clinical implications, which directly inform the BRS. The isolated vitamin D group (53.3%) is mainly young males with intact zinc and iron stores. They do not have systemic malabsorption or inflammatory depletion of vitamin D, and the issue is probably a behavioral or environmental one, either due to lack of sun or inadequate vitamin D intake. Here vitamin D replacement is the only thing that is needed. This phenotype is consistent with diabetic foot ulcer literature, as deficient in vitamin D is the most common nutritional finding (55.7% of patients), while zinc deficiency often occurs in conjunction with vitamin C deficiency (Pena et al., n.d.). The middle group is the dual-deficiency group (32.7%) – mixed gender, middle age, and borderline ferritin and vitamin D and zinc deficiency. The patients are at the beginning of the cascade of cluster deficiency—they are experiencing early malabsorption or nutritional deficiency. They require a combination of vitamin D and zinc replacement, and monitoring of ferritin levels should be done closely. The most vulnerable of all are the triple-deficiency group (14.0%). They are mostly older women, who have had long-term diabetes, and have used up all three mineral systems. This female predominance (85.7%) and the correlation with diabetes duration > 10 years suggests that the cause is cumulative metabolic damage. These patients require a very intensive multi-nutrient replacement, monitored closely (Wessells and Brown, 2012). The high zinc–ferritin ($r = 0.72$) and zinc–vitamin D ($r = 0.68$) correlation is not only statistical, but reflects the metabolic interdependencies mentioned above: Zinc-dependent function of VDR, VDR-induced zinc absorption, and the common inflammatory and absorptive insults of diabetes

(Bikle, 2014; Haussler et al., 2013). The bio-correlation demonstrates the need for cluster intervention over single nutrient intervention.

4.4 Independence from Glycemic Control: Implications for Practice

One of the most clinically relevant findings, in our opinion, is the lack of any HbA1c–micronutrient correlation. This implies that a patient may have an HbA1c value of 6.5% or 10.5%, but still have severe mineral deficiencies. That doesn't necessarily mean it is simply a question of tightening glucose control, as that is the only way to provide protection from the macrovascular and microvascular issues, but it is not enough to bring the zinc, iron, and vitamin D back to healthy hair cycling levels. For the clinician, it implies the need to adopt a two-track approach – first optimizing glycemic targets, and second, seeking to target specific nutritional repletion. This temporal mismatch is one factor that accounts for this independence: the glucose level captured by measuring HbA1c is a snapshot of glucose levels over 2–3 months, while micronutrient status reflects months to years of nutritional intake, absorption efficiency, and inflammatory burden (Chiu et al., 2004). In keeping with this, a study of diabetic foot ulcer patients was unable to detect any relationships between micronutrient deficiency and HbA1c, BMI, grip strength, diabetes duration or smoking status (Pena et al., n.d.), which suggests that mineral depletion in diabetes is not related to glycemic control, but to a different mechanism. This discovery has implications for the BRS as micronutrient status is not predicted by HbA1c, and therefore should not be used to be a triaging tool for nutritional screening. The BRS variables (gender, age, diabetes duration) are better predictors, precisely because they reflect chronic rather than short-term metabolic derangements.

4.5 The Babil Risk Score: Validation and Generalizability

The BRS showed strong internal validity. The bootstrap-corrected AUC of 0.83 with moderate optimism (calibration slope 0.94) indicates that the model is not overfitted to this dataset. The simplicity of the score—three binary variables summed up to an 0-8 scale—improves its usability at bedside. Because initial risk stratification does not require laboratory data, the score can be calculated during the first clinical appointment, before any blood is drawn.

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4.6 Phenotype-Specific Intervention Algorithm

Based on our findings, we propose a tiered, phenotype-matched intervention algorithm (Figure 1):

Step 1: Calculate BRS at the initial encounter.

- Female gender (4 points)
- Age > 55 years (2 points)
- Diabetes duration > 10 years (2 points)

Step 2: Direct screening and intervention by risk category

BRS Category	Probability of Triple Deficiency	Recommended Screening	Intervention
Low (0–2)	0%	Vitamin D ± Zinc	Vitamin D3 50,000 IU/week × 8 weeks if deficient
Moderate (3–4)	12.5%	Full panel (ferritin, zinc, Vit D)	Vitamin D3 + zinc gluconate 50 mg/day if dual deficiency is confirmed
High (5–8)	58.3%	Full panel + repeat in 3 months	Vitamin D3 + Zinc + Iron (ferrous sulfate 325 mg/day if ferritin < 30)

Step 3: Reassess at 3 months

- Target: Ferritin > 30 ng/mL, Zinc > 70 µg/dL, Vitamin D > 20 ng/mL
- If targets are not met: investigate malabsorption (celiac screening, gastric emptying study)

This algorithm becomes a clinical decision support system and directs allocation of resources and therapeutic intensity as a function of individual risk, moving the BRS from a research tool to a clinical tool.

4.7 Comparison with Previous Literature

We believe that our ferritin effect size (d = 2.89) is the highest gender gap found in the micronutrient literature. Previous research has identified decreased ferritin in women with hair loss; however, this has not been reported specifically in the context of T2DM. The cluster deficiency concept has been suggested in general nutrition (Wessells & Brown, 2012; Raiten et al., 2011), but not yet tested in diabetic hair diseases. This indicates that a single nutrient assessment approach is insufficient because 82.5% of women and 51.4% of men had multiple concurrent deficiencies. The BRS itself is new. There is no validated tool to predict micronutrient cluster deficiency in diabetic patients with hair loss while there is a risk score for diabetic complications (e.g., UKPDS risk engine for cardiovascular disease). The BRS bridges this gap, providing a practical link between research and practice.

5. Conclusion

This study clearly shows that there are gender differences in the micronutrient status of T2DM patients with hair loss, which are not only statistically significant, but clinically staggering. Males had significantly higher ferritin (Cohen's d = 2.89), zinc (d = 1.38), and vitamin D (d = 0.96) levels than females within the study. Three cluster deficient phenotypes were identified: isolated vitamin D deficiency (53.3%), dual deficiency (32.7%), or triple deficiency (14.0%) and provide practical scaffolding to take us beyond the one-size-fits-all approach to supplementation. Developed and internally validated in this study, the Babil Risk Score (BRS) is the first clinically applicable tool for predicting the triple deficiency phenotype based on three easily-obtained variables. The BRS showed a sensitivity of 85.7%, specificity of 91.5% and AUC of 0.83 (bootstrap corrected) making it an efficient triage tool for lower and higher risk patients to receive brief and in-depth screening, respectively, and for low-risk patients to receive multi-nutrient therapy in advance. The strong inter-micronutrient correlations and the remarkable glycemic independence point to a broad, gender-specific, and phenotype-specific nutritional approach. We feel that these results are a strong argument for moving to a new paradigm, from replacement of one nutrient to systems-based nutritional medicine in diabetic hair disorders, with validated risk stratification at the bedside.

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