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The Link Between Alpha-Klotho Level and Iron Status Among Children with Iron Deficiency Anemia.

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ABSTRACT: **Background:** Iron deficiency anemia (IDA) is the most common nutritional deficiency worldwide, particularly affecting children during critical periods of growth and skeletal development. Alpha-Klotho (α-Klotho) is an essential regulator of mineral metabolism and bone health, acting as a co-receptor for fibroblast growth factor 23 (FGF23). However, the relationship between iron status and Klotho expression in pediatric populations remains poorly understood.

Objective: This study aimed to assess serum α-Klotho levels in children with IDA and examine their association with iron status and fracture history.

Methods: A cross-sectional study was conducted on 77 children aged 9–15 years (39 with IDA and 38 controls). Clinical assessment, anthropometric measurements, complete blood count, iron profile (serum iron, ferritin, total iron-binding capacity, transferrin saturation), and serum α-Klotho levels were performed. Fracture history was recorded as a surrogate marker of bone health.

Results: Children with IDA had significantly lower serum α-Klotho levels compared to controls (median 2.4 vs. 3.7 ng/mL, $p = 0.018$). Within the IDA group, Klotho correlated positively with serum iron ($\varrho = 0.447$, $p = 0.004$) and ferritin ($\varrho = 0.349$, $p = 0.036$), and inversely with age ($\varrho = -0.322$, $p = 0.045$). Multiple regression analysis identified IDA ($B = -1.655$, $p = 0.015$) and ferritin ($B = 0.040$, $p = 0.013$) as independent predictors of Klotho levels. Children with fracture history had significantly lower Klotho levels (median 2.2 vs. 3.4, $p = 0.009$), with ROC analysis showing moderate discriminatory ability (AUC = 0.701).

Conclusion: IDA is independently associated with reduced serum α-Klotho levels in children, with ferritin emerging as the strongest predictor. These findings suggest that iron deficiency may impair Klotho-mediated mineral metabolism during critical periods of skeletal growth, supporting early detection and treatment of IDA for optimal bone health.

INTRODUCTION

Iron deficiency anemia (IDA) is the most prevalent nutritional deficiency, affecting approximately 40% of children worldwide, with the highest burden in low- and middle-income countries (Safiri et al., 2021). School-aged children and adolescents represent a particularly vulnerable group due to increased iron requirements from rapid growth, blood volume expansion, and pubertal

development (Cohen & Powers, 2024; Donker et al., 2021). In Egypt, anemia prevalence among school-aged children ranges from 26% to 38%, with iron deficiency identified as the major underlying cause (Abdel-Aaty et al., 2015; El-Shafie et al., 2020).

Beyond hematological complications, emerging evidence indicates that iron plays a critical role in bone health. Iron acts as a cofactor for enzymes involved in collagen synthesis and osteoblast function, and experimental studies have demonstrated that iron deficiency impairs bone formation and increases bone resorption (Katsumata et al., 2009; von Brackel & Oheim, 2024). Childhood and adolescence represent critical periods for bone mineral accrual, with approximately 90% of peak bone mass achieved by early adolescence (Weaver et al., 2016).

Alpha-Klotho (α-Klotho) is a transmembrane protein initially identified as an anti-aging factor, with critical roles in mineral metabolism and bone health (Kuro-o et al., 1997). It functions as an obligate co-receptor for fibroblast growth factor 23 (FGF23), regulating phosphate homeostasis and vitamin D metabolism (Quarles, 2012). Reduced α-Klotho levels have been associated with osteoporosis, impaired bone mineral density, and increased fracture risk in adult populations (Arroyo et al., 2023; Kaludjerovic et al., 2017). However, the relationship between iron status and Klotho expression in pediatric populations has not been adequately investigated.

This study aimed to evaluate serum α-Klotho levels in children with IDA and examine their association with iron status and fracture history, exploring the potential role of Klotho as a biomarker linking iron deficiency to altered bone mineral metabolism during childhood.

METHODS

This analytical cross-sectional study was conducted at the outpatient clinic of the Pediatric Department, October 6 University Hospital, Giza, Egypt, over a 6-month period. Children aged 9–15 years diagnosed with IDA attending the outpatient clinic during the study period were enrolled. Participants were classified into two groups: an IDA group and a control group.

Inclusion Criteria for IDA Group:

- Hemoglobin concentration below age- and sex-specific WHO reference ranges
- Serum ferritin < 15 ng/mL
- Microcytic hypochromic indices (MCV < 80 fL, MCH < 27 pg)

Control Group:

Normal hemoglobin and iron profile (ferritin ≥ 15 ng/mL)

Exclusion Criteria: Chronic diseases affecting bone health (e.g., chronic kidney disease, endocrine disorders), medications influencing bone mineral density (e.g., corticosteroids), thalassemia or other hemoglobinopathies, recent blood transfusion (within 3 months), acute infections or febrile illness (within 2 weeks).

Data Collection

A structured data sheet was collected including demographic data (age, sex), medical history (chronic diseases, medication use, iron supplementation), clinical manifestations (pallor, fatigue, headache, lack of concentration, poor appetite, pica, nail changes), and fracture history (site and number of fractures). Anthropometric measurements included weight, height, and body mass index (BMI).

Laboratory Investigations

Venous blood samples (5 mL) were collected. Complete blood count was performed using an automated hematology analyzer. Iron profile (serum iron, ferritin) was measured using an automated chemistry analyzer (Cobas c311). Serum α-Klotho was measured using a sandwich enzyme-linked immunosorbent assay (ELISA) kit (Human Klotho ELISA Kit, IBL, Japan), with a detection range of 0.05–20 ng/mL and sensitivity of 0.027 ng/mL.

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Sample Size and Statistical Analysis

Sample size was calculated to detect a moderate correlation of r = 0.33 between α-Klotho and iron parameters (An et al., 2023). Using Fisher's z-transformation with α = 0.05 (two-tailed) and 80% power, 70 participants were required; 77 were enrolled (39 cases, 38 controls).

Statistical analyses were performed using SPSS version 26.0. Non-parametric tests were used for group comparisons (Mann-Whitney U test) and correlations (Spearman's rho). Multiple linear regression was performed to identify independent predictors of α-Klotho. Receiver operating characteristic (ROC) analysis determined the discriminatory ability of α-Klotho for predicting fracture history. A two-tailed p-value < 0.05 was considered statistically significant.

Ethical Considerations

The study protocol was approved by the Institutional Review Board of October 6 University (O6U-ERC-0090). Written informed consent was obtained from parents or legal guardians, and verbal assent from children aged ≥ 12 years.

RESULTS

There were 77 participants (39 IDA, 38 controls) in our research with no significant differences between groups regarding age, gender, height, weight, or BMI (Table 1).

Table 1: Demographic characteristics of the study population

Variable	IDA (n=39)	Control (n=38)	p-value
Age (years), mean ± SD	12.1 ± 2.0	11.1 ± 1.8	0.32
Female, n (%)	27 (69.2%)	20 (52.6%)	0.135
Male, n (%)	12 (30.8%)	18 (47.4%)	
BMI, median (IQR)	19.27 (17.01–24.35)	19.3 (16.22–21.68)	0.427
BMI: Body Mass Index; IQR: Inter-quartile Range, IDA: Iron Deficiency Anemia			

Clinical manifestations were significantly more prevalent in the IDA group: headache (94.9% vs. 50.0%, p < 0.001), lack of concentration (89.7% vs. 47.4%, p < 0.001), pallor (66.7% vs. 39.5%, p = 0.017), tiredness (64.1% vs. 44.7%, p = 0.088), and poor appetite (71.8% vs. 47.4%, p = 0.028).

Regarding fracture history, children with IDA had a higher prevalence compared to controls (35.9% vs. 13.2%, p = 0.052). Notably, all cases of multiple fractures (4 children, 10.3%) occurred exclusively in the IDA group. The forearm (radius/ulna) was the most injured site (10.4% overall).

The IDA group demonstrated classic microcytic hypochromic anemia with significantly lower hemoglobin (median 10.8 vs. 12.85 g/dL, p = 0.006), MCV (72.3 vs. 84.2 fL, p = 0.004), and MCH (24.2 vs. 27.5 pg, p = 0.026). Table 2 shows that children with IDA had significantly lower serum iron (median 51 vs. 60 µg/dL, p = 0.021) and ferritin (median 10.1 vs. 40 ng/mL, p < 0.001), alongside significantly higher TIBC (median 425 vs. 318 µg/dL, p < 0.001) and lower transferrin saturation (median 12.0% vs. 18.9%, p < 0.001) compared to controls, confirming the classic pattern of iron-deficient erythropoiesis.

Table 2: Iron profile parameters among the study population

Variable		Total (N = 77)	IDA (N = 39)	Control (N = 38)	P-value[1]
Serum Iron (µg/dL)	**Mean± SD**	55.5 ± 28.2	52.9 ± 24.2	58.2 ± 31.9	0.021
	Median (IQR)	55 (37–70)	51 (34–70)	60 (38–70)	
Ferritin (ng/mL)	**Mean± SD**	30.5 ± 26.9	10.8 ± 2.7	49.6 ± 26.4	**<0.001*****
	Median (IQR)	25 (10–40)	10.1 (9.7–13.8)	40 (34–56)	
TIBC (µg/dL)	**Mean± SD**	370 ± 60	420 ± 40	320 ± 30	**<0.001*****
	Median (IQR)	372 (320–440)	425 (400–455)	318 (295–340)	
Transferrin Saturation (%)	**Mean± SD**	16.0 ± 5.0	12.5 ± 4.0	19.5 ± 5.0	**<0.001*****
	Median (IQR)	15.4	12.0	18.9	

		(11.0–19.0)	(10.5–14.5)	(16.5–22.0)	

IQR: Interquartile Range; SD: Standard Deviation; IDA: Iron Deficiency Anemia; [1]Mann-Whitney U Test; TIBC: Total Iron Binding Capacity; * <0.05: Statistically significant; ** <0.01: Highly statistically significant; *** <0.001: Very highly statistically significant.

Regarding children with IDA, α-Klotho levels had significantly lower serum level compared to controls (Table 3). This difference was more pronounced in females (median 2.2 vs. 4.1, p = 0.011) than males (median 2.8 vs. 3.4, p = 0.082).

Table 3: Serum alpha-Klotho levels in the study population

Variable	Median (IQR)	p-value
Overall (N=77)	3.5 (2.2–5.2)	—
IDA (n=39)	2.4 (2.0–3.9)	**0.018***
Control (n=38)	3.7 (2.2–5.1)	
Fracture history (n=19)	2.2 (1.9–3.0)	**0.009****
No fracture (n=58)	3.4 (2.4–4.5)	

**IQR: Interquartile range; *p < 0.05; *p < 0.01*

ROC analysis demonstrated that serum Klotho has moderate discriminatory ability for fracture history (AUC = 0.701, 95% CI: 0.563–0.838, p = 0.009). (Figure 1) The optimal cutoff was ≤ 2.6 ng/mL, yielding a sensitivity of 72.4% and specificity of 68.4%.

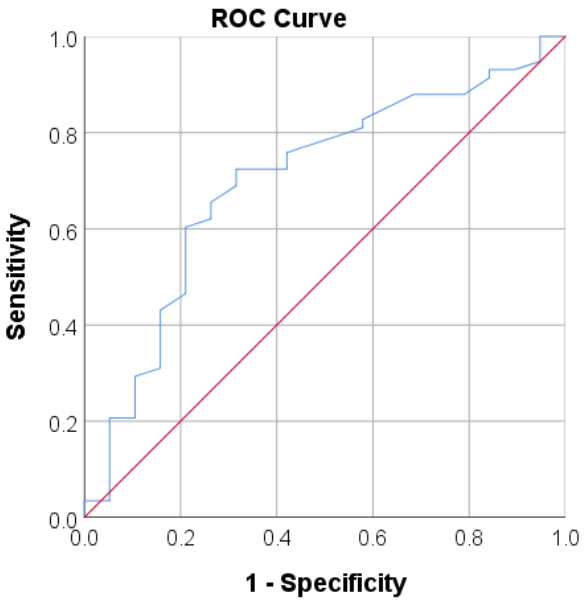


Figure 1 Receiver Operating Characteristic (ROC) Curve for Fracture Prediction

Within the IDA group, Klotho showed significant positive correlations with serum iron (Figure 2A) and ferritin (Figure 2B), and an inverse correlation with age (ϱ = -0.322, p = 0.045) (Table 4).

Table 4: Correlations between serum Klotho and laboratory parameters in the IDA group

Variable	Correlation Coefficient (ϱ)	p-value
Age	-0.322	**0.045***
Serum iron	0.447	**0.004****
Ferritin	0.349	**0.036***
Hemoglobin	0.325	**0.043***
***ϱ: Spearman's rho; *p < 0.05; *p < 0.01**		

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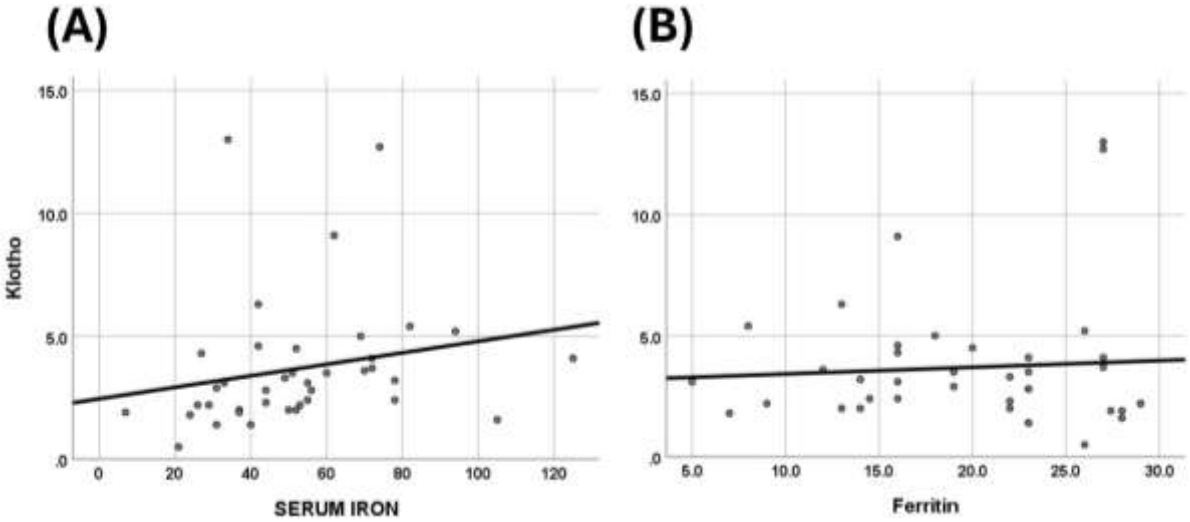


Figure 2 Correlation between Serum α-Klotho and Iron Status (A: Klotho and Serum iron ϱ = 0.447; B: Klotho and Ferritin ϱ = 0.349)

After adjustment for age, gender, and BMI, IDA remained independently associated with lower Klotho levels (B = -1.655, p = 0.015). Serum ferritin emerged as a significant independent positive predictor of Klotho (B = 0.040, p = 0.013), while age was a negative predictor (B = -0.515, p = 0.042). On the other hand, gender and BMI were statistically insignificant negative predictors (B = -1.108, p = 120), (B = -0.061, p = 0.471), respectively (Table 5).

Table 5: Multiple linear regression analysis of predictors of serum Klotho levels

Predictor	B	SE	β	p-value	95% CI
IDA (Ref: Control)	-1.655	0.681	-0.226	**0.015***	[-3.02, -0.29]
Ferritin	0.040	0.015	0.281	**0.013***	[0.010, 0.070]
Gender (Ref: Female)	-1.108	0.703	-0.196	0.120	[-2.51, 0.29]
Age	-0.515	0.221	-0.351	**0.042***	[-0.956, -0.074]
BMI	-0.061	0.084	-0.110	0.471	[-0.23, 0.11]
***IDA: Iron Deficiency Anemia, BMI: Body Mass Index, B: Unstandardized coefficient; SE: Standard error; β: Standardized coefficient; CI: Confidence interval; BMI: Body Mass Index;* *p < 0.05**					

DISCUSSION

IDA is considered the most common nutritional disorder worldwide, that affects pediatric population especially during growth and skeletal development (Powers et al., 2026). Iron imbalance affects bone homeostasis by disrupting the function of osteoblast and osteoclast, this leads to a decrease in bone mineral density and an increase in the risk of fracture (Ledesma-Colunga et al., 2021; Rauner, 2025).

Klotho is a transmembrane protein expressed mainly in the kidney, choroid plexus, and parathyroid glands, existing as both a membrane-bound FGF23 co-receptor and a soluble circulating hormone. It regulates phosphate and vitamin D metabolism, and the soluble form influences osteoblast and osteoclast activity, bone mineralization, and oxidative stress. Circulating α-Klotho declines with age and is associated with bone mineral density and fracture risk (Arroyo et al., 2023; Kuro-o et al., 1997; Quarles, 2012).

Our study demonstrated a female predominance (61%) which was in accordance with a study done by (Lee et al., 2025). This difference between males and females could be related to the increased iron requirements during the pubertal growth spurt, as well as menstrual blood loss in adolescent girls (Baruah & Gautam, 2023)

Headache was the most prevalent symptom overall (84.4%) which was significantly more common in the IDA group which aligns with the findings of (Lopez et al., 2016) in which headache was reported in 63%. Also, tiredness was more common in

IDA group. IDA leads to decreased oxygen delivery to tissues due to reduced hemoglobin levels. When compared with age-matched peers, children with IDA may show reduced physical activity and decreased tolerance to exercise (Bereznitskiy et al., 2021).

Lack of concentration was significantly more common in the IDA group (89.7% vs. 47.4%, $p < 0.001$), IDA in children is associated with behavioral and neurocognitive changes due to the critical role of iron in brain development, neurotransmitter synthesis, and myelination (Beard & Connor, 2003; Lozoff et al., 2006).

The finding that children with IDA had a notably higher prevalence of fracture history compared to the control group (35.9% vs. 13.2%, $p = 0.052$) with a near-significant trend. A study by (Wagner et al., 2026) showed that IDA may directly affect bone formation and increase fracture risk. They found reduced expressions of genes involved in collagen production and bone formation in osteoblasts and osteocytes, with collagen 1A1 (Col1a1), collagen 11A1 (Col11a1), and Osterix (Sp7) showing the strongest downregulation.

(Rauner, 2025) demonstrating that iron deficiency impairs both osteoblast and osteoclast function by depriving these cells of iron necessary for efficient energy metabolism and metabolic processes, ultimately resulting in decreased bone mineral density and increased fracture risk. (Jung et al., 2017) reported a positive association between hemoglobin and serum ferritin levels and bone mineral content suggesting that iron-replete states are protective for bone health during this critical period of skeletal development. Furthermore, (Zheng et al., 2026) found a nonlinear association between serum ferritin and bone turnover markers. Bone resorption markers were significantly higher at low ferritin levels, suggesting that low iron stores may be associated with increased bone resorption

The observation of reduced α-Klotho in children with IDA aligns with findings from adult population-based studies (An et al., 2023) demonstrated that anemic individuals had significantly lower serum α-Klotho levels compared to non-anemic participants, independent of age, sex, renal function, and inflammatory markers.

The biological plausibility of this association is supported by the known regulatory relationship between iron metabolism and the FGF23–Klotho axis. Iron deficiency stimulates FGF23 transcription in osteocytes, and in normal physiology, increased FGF23 production is coupled with increased cleavage to maintain phosphate homeostasis (Wolf & White, 2014). However, when this coupling is disrupted, elevated intact FGF23 can suppress 1,25-dihydroxyvitamin D synthesis and promote phosphate wasting, potentially downregulating Klotho expression through feedback mechanisms (Edmonston & Wolf, 2020). (Braithwaite et al., 2021) provided clinical evidence for this pathway, demonstrating that antenatal iron supplementation reduced total FGF23 concentrations by 62.6% in mothers, confirming that iron deficiency drives FGF23 dysregulation.

Alpha-Klotho serum levels had significantly lower serum levels in children with fracture history. In addition, it has a moderate discriminatory ability for fracture history (AUC = 0.701, 95% CI: 0.563–0.838, $p = 0.009$) with a cutoff value ≤ 2.6 ng/mL. Alpha-Klotho plays a critical role in skeletal health by affecting mineral metabolism and activity of osteoblasts and osteoclasts. Any disruption in klotho expression may affect bone architecture and reduce bone strength (Komaba & Fukagawa, 2012; Zhang et al., 2025). Low serum alpha-klotho levels were associated with reduced bone mineral density, osteoporosis, and increased fracture risk, independent of age and renal function (Amaro-Gahete et al., 2019; Arroyo et al., 2023).

The significant positive correlations between Klotho and both serum iron ($\rho = 0.447$) and ferritin ($\rho = 0.349$) exclusively within the IDA group further support a direct regulatory relationship. The positive correlation with hemoglobin ($\rho = 0.325$) suggests that the severity of anemia parallels the degree of Klotho suppression. A study conducted by (An et al., 2023) who studied the association between anemia and serum α-Klotho levels in a large cohort of middle-aged and older adults.

The inverse correlation between Klotho and age in the IDA group ($\rho = -0.322$) is consistent with (Yamazaki et al., 2010) who first demonstrated that soluble α-Klotho levels in healthy children were significantly higher than in adults, and multivariate analysis confirmed age as an independent negative predictor of Klotho. The significant age-related decline observed specifically in the IDA group may indicate that iron deficiency enhances the normal age-related reduction in circulating Klotho, potentially through iron-mediated oxidative stress or alterations in FGF23 signaling (Correnti et al., 2026).

Several limitations should be acknowledged. The cross-sectional design precludes establishing causality, and the relatively small sample size, particularly in the fracture subgroup, limits generalizability. Bone mineral density was not directly measured, and fracture history relied on parental recall. Additionally, we did not measure FGF23 or vitamin D metabolites, which would have

provided further mechanistic insights. Despite these limitations, this study provides the first evidence linking iron deficiency to reduced Klotho levels in children, supporting the hypothesis that iron deficiency may impair Klotho-mediated mineral metabolism during critical periods of skeletal development. Future longitudinal studies incorporating bone mineral density measurements and FGF23 assessment are needed with a larger sample size.

CONCLUSIONS

This study demonstrates that IDA in children is independently associated with significantly reduced serum α-Klotho levels, with ferritin emerging as the strongest predictor of Klotho concentration. These findings suggest that iron deficiency may impair Klotho-mediated mineral metabolism and bone health during the critical period of skeletal growth. Early detection and treatment of iron deficiency may therefore be essential not only for correcting anemia but also for preserving optimal bone health.

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Data availability statement

The corresponding author can provide data of this study upon reasonable request, subject to ethical restrictions.

Authors contribution

Ahmed Saad El-Gayed worked on study design. Mohamed Elsaid contributed to data collection and clinical assessment. Ahmed Saad El-Gayed and Sarah Abdelrashid conducted data analysis and interpretation. The biochemical analysis and laboratory data interpretation were carried out by Maysa Hatem Rashed. Mohamed Elsaid wrote the manuscript. Sarah Abdelrashid revised the manuscript. The final version of the mqanuscript was reviewed and approved by all authors.

DECLARATIONS

Ethics approval and consent to participate

The study was conducted following approval from the Institutional Review Board of October 6 University (O6U-ERC-0090). Written informed consent was secured from parents or legal guardians, while children aged 12 years or older provided verbal assent.

Competing interests

The authors declare that they have no competing interests

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