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Serum ferritin level and associated factors among uncontrolled adult type II diabetic follow-up patients: comparative based cross-sectional study

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Abstract

Background Uncontrolled type 2 diabetes mellitus (UT2DM) and its associated consequences nowadays have been a global health crisis, especially for adults. Iron has the property to oxidize and reduce reversibly, which is necessary for metabolic processes and excess accumulation of iron indicated by serum ferritin levels could have a significant impact on the pathophysiology of T2DM via generation of reactive oxygen species (ROS). However, no conclusive evidence existed about the association of serum ferritin with the state of glycemic control status. Therefore, this study aimed to evaluate serum ferritin levels and associated factors in uncontrolled T2DM patients and compare them with those of controlled T2DM and non-diabetic control groups.

Methods A hospital-based comparative cross-sectional study was conducted among conveniently selected 156 study participants, who were categorized into three equal groups of uncontrolled T2DM, controlled T2DM, and non-diabetic control groups from October 2 to December 29, 2023 at St. Paul's Hospital Millennium Medical College. A pre-tested structured questionnaire was used to collect socio-demographic and diabetes-related information. The laboratory tests were done using an automated chemistry analyzer and IBM-SPSS statistical software (version-27) was utilized for data entry and analysis with a significance level of $p < 0.05$.

Result The mean serum ferritin level was noticeably higher in uncontrolled T2DM patients as compared to controlled T2DM and control groups ($p < 0.001$). It was significantly correlated with HbA1c [$r = 0.457$, $p < 0.001$], fasting blood sugar (FBs) [$r = 0.386$, $p < 0.001$], serum iron [$r = 0.430$, $p < 0.001$], and systolic blood pressure (SBP) [$r = 0.195$, $p = 0.047$] in T2DM patients. A multivariate logistic regression model revealed that a rise in HbA1c (AOR = 3.67, 95% CI(1.50–8.98), serum iron (AOR = 1.02, 95% CI(1.01–1.04), male gender (AOR = 0.16, 95% CI(0.05–0.57) and being on oral hypoglycemic agent (OHA) monotherapy (AOR = 0.26, 95% CI(0.07–0.95) were key associated factors for the elevated serum ferritin among T2DM patients.

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Conclusion The present study demonstrated that T2DM patients had elevated serum ferritin levels which might be related to the existence of long-term hyperglycaemia and that serum ferritin had a significant positive association with HbA1c and FBs, implying that it could be used as an additional biomarker to predict uncontrolled T2DM patients.

Keywords T2DM, Ferritin, HbA1c, Glycemic control

Background

Uncontrolled Type 2 Diabetes Mellitus (UT2DM) has become a global health crisis contributing to 4.2 million deaths, particularly in adults aged 20–79 years as seen in the International Diabetic Federation (IDF) reports [1]. It causes various complications by damaging nerves and blood vessels as well as many other diabetic consequences if left untreated [2]. Of all the diagnosed cases of diabetes, about 90% are T2DM which is characterized by a failure of insulin secretion or action [3, 4]. One of the main causes of diabetes and its complications is oxidative stress and the conditions are linked to body iron stores [5].

The increasing rate of obesity in Africa potentially leads to a risk of iron overload in addition to T2DM by altering the normal metabolic process [6]. Hyperglycaemia results in increased glycated haemoglobin A1c (HbA1c) in red blood cells (RBC) [7] and causes releasing of free iron from the RBC during the glycation process that tends to initiate redox reactions to generate free radicals such as reactive oxygen species (ROS) which damage pancreatic β-cell [8], intensify inflammatory response, and accelerate oxidative damage of biomolecules [9]. Although iron and glucose metabolism are tightly regulated by hepcidin and insulin hormones respectively [10], a bi-directional link exists and the deregulation of iron homeostasis impacts on the clinical course of T2DM [11, 12]. Ferritin is a key protein maintaining iron homeostasis [13] and is a useful biomarker for iron storage in the body [14].

Uncontrolled T2DM is a serious health concern that should be prevented, especially in low and middle-income countries like Ethiopia [15]. HbA1c is a gold standard test that provides long-term glycemic control over the past two or three months rather than daily fluctuation in blood glucose levels [16]. The American Diabetes Association (ADA) and Canadian Diabetes Association Clinical Practice Guidelines Expert Committee recommend glycaemic goals of HbA1c≤7% for adult diabetic patients in order to reduce its complications [17, 18]. Various studies in Ethiopia have revealed a high proportion of uncontrolled T2DM patients and comorbidities related to the condition [19, 20].

Although the deregulation of micronutrients like iron and marker of iron storage (ferritin) were reported to be linked with the pathophysiology of T2DM [5, 21], no conclusive evidence exists about the association of serum ferritin with the state of glycaemic control and studies in this regard were inconsistent. Some indicating a null association [22, 23], while others showed significant positive [24, 25] or negative associations [26].

Therefore, this study aimed to evaluate serum ferritin levels and associated factors in uncontrolled T2DM patients and compare them with those of controlled T2DM and non-diabetic control groups. Studies in this area were limited, especially in Ethiopia. Besides, the investigation could lead to a better understanding of the relationship between serum ferritin and glycaemic indicators of T2DM such as fasting blood sugar (FBs) and HbA1c as well as might improve the treatment response of uncontrolled T2DM patients transitioning to the controlled T2DM category.

Methods

Study area, design, and periods

A hospital-based comparative cross-sectional study was conducted for three months from October 2 to December 29, 2023 among T2DM patients, who had follow-up appointments at St. Paul's Hospital Millennium Medical College (SPHMMC), Addis Ababa, Ethiopia. It is one of the biggest teaching and public referral hospitals, offering healthcare services and student training programs. Besides, the hospital had endocrine clinics for outpatient follow-up chronic illness patients and the majority of them were diabetics, who were primarily monitored by endocrinologists and a team of nurses working in the clinic.

Study populations and the selection criteria

Adult T2DM patients from 18 to 65 years of age, who had at least one-year follow-up appointment and started anti-diabetic medication at the outpatient diabetic clinic of SPHMMC were selected and sub-grouped based on the ADA (2022) [17] and Canadian Diabetes Association Clinical Practice Guidelines Expert Committee (2018) [18] criteria as having either uncontrolled diabetes with HbA1c>7% or controlled diabetes with HbA1c≤7% were included as cases. Besides, age-sex-matched non-diabetic healthy control groups were selected from the same population as cases in the hospital from the care-givers who did not have the conditions based on their history, FBs (70–100 mg/dl), and HbA1c (<5.7%) levels as per the ADA criteria [27].

Participants who were pregnant, lactating, heavy drinkers, active smokers, had an acute infection within a week, had a known history of cancer or anemia, had blood transfusion or donation or iron supplements within the

previous three months, and had been diagnosed with other types of diabetes were excluded based on their medical history and physical examinations as summarized in Fig. 1.

Description of study variables

Serum ferritin level was a dependent variable while socio-demographic factors like age, sex, and educational levels; clinical factors like body mass index (BMI), Blood Pressure (BP), glycemic control status, and duration of diabetes mellitus, as well as biochemical factors like serum iron, HbA1c, and FBs levels, were regarded as an independent variable.

Sample size and sampling technique

The sample size was determined using a comparative-based study design for quantitative data by taking the 95% confidence interval and 80% power of the study using the formula $n=2SD^2(Z_{\alpha/2}+Z_{\beta})^2/d^2$ [28]. Where; n is the minimal sample size for each group, SD is the standard deviation from previous studies, $Z_{\alpha/2}$ is 1.96 from the Z table at 95% CI & 5% type 1 error), Z_{β} is 0.84 from the Z table with 80% power of the study and 20% type II errors, and d is Effect size which is the difference in mean values. As per the authors' knowledge, no published study was conducted in Ethiopia on serum ferritin levels among uncontrolled and controlled T2DM patients. Thus, data from an Indian study was taken, which showed the mean serum ferritin levels in uncontrolled and controlled diabetes patients were 269.8 and 73.30 ng/ml respectively with a standard deviation of 347.1 [29]. Therefore, $n=2(347.1)^2\times(1.96+0.84)^2/(269.8-73.30)^2=48.92=49$. However, it was increased by 5% to eliminate potential outliers to make it up to 52 subjects per group, and 156 total study subjects were enrolled.

Measurement and data collection

Data collection procedures

After participants provided written informed consent, data was collected via face-to-face interviews, direct measurements, and reviewing medical records by professional data collectors in cooperation with outpatient department nurses and laboratory personnel under close supervision of the principal investigator. Participants' anthropometric data (height and weight) were measured to calculate body mass index (BMI) and categorized as Obesity (≥30 kg/m^2), overweight (25–29.9 kg/m^2), Normal (18.5–24.9 kg/m^2) and underweight (<18.5 kg/m^2) based on the World Health Organisation (WHO) guideline [30]. Besides, blood pressure readings were taken after a 5-minute rest using an automatic digital sphygmomanometer apparatus that recorded the systolic and diastolic blood pressures and it was classified according to the Seventh Report of the Joint National Committee (JNC7) blood pressure classification criteria as normal (<120mmHg), pre-hypertension (120–139 mmHg) and hypertension (≥140mmHg) for systolic blood pressure

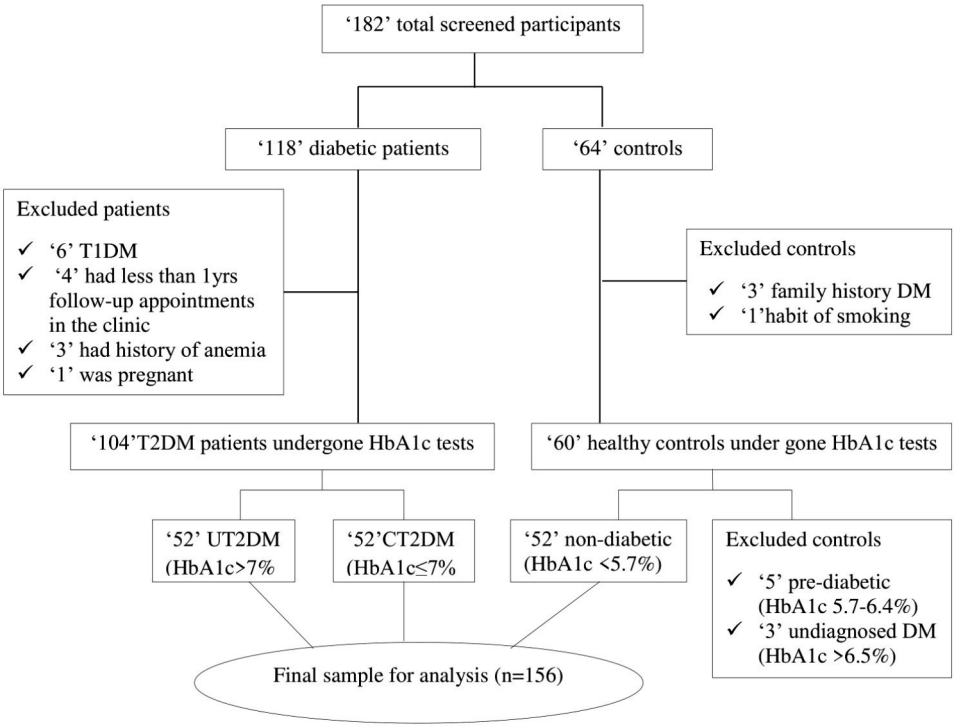

Fig. 1 Flowchart showing the schematic presentation of selection of study participants at SPHMMC, Addis Ababa, Ethiopia, 2024

(SBP) and <80 mmHg, 80–89 mmHg and ≥90 mmHg for diastolic blood pressure (DBP) [31].

Laboratory sample collection, analysis, and test principles

Participants were oriented to have overnight fasting for about 8–10 h before sample collection. About 3 ml of venous blood was collected in Ethylenediaminetetraacetic acid (EDTA) tubes and 5 ml in Serum Separator Tube (SST) via venipuncture with an evacuated tube method under aseptic precautions, by a competent laboratory technologist. The EDTA tube was used for HbA1c determination using the Cobas c501module of the analyzer with a principle of turbidimetric inhibition immunoassay (TINIA) that standardized against the International Federation of Clinical Chemistry (IFCC) reference method and traceable to the Diabetes Control and Complications Trial (DCCT)/National Glycohemoglobin Standardization Program (NGSP) % HbA1c, while the SST tube was allowed for about 20–30 min at room temperature until coagulated and centrifuged for 5 min at 3000 RPM to separate serum from whole blood. FBs, ferritin, and iron were determined using a principle of glucose hexokinase (HK) of the c501, electrochemiluminescent immunoassay (ECLIA) of the e601, and colorimetric assay techniques of the c501 modules of the Roche diagnostic technology respectively.

Reference range and clinical implications of the laboratory tests

The reference ranges for HbA1c and FBs were based on the ADA criteria as healthy groups (HbA1c<5.7% and FBs 70-99 mg/dl), pre-diabetes (HbA1c 5.7–6.4% and FBs 100-125 mg/dl), diabetes mellitus (HbA1c≥6.5% and FBs≥126 mg/dl) [27]. Furthermore, T2DM patients were categorized into controlled (HbA1c≤7%) and uncontrolled (HbA1c>7%) diabetes [17, 18]. The WHO guidelines classify serum ferritin levels as iron deficiency (<15ng/ml), sufficiency (15-200ng/ml), and excess (>200ng/ml) for males and iron deficiency (<15ng/ml), sufficiency (15-150ng/ml), and excess (>150ng/ml) for females, with low risk of iron overload (≤200 ng/ml) and increased risk (>200 ng/ml) [32]. Adults' reference range of serum iron is 59–158 ug/dL for males and 37–145 ug/dL for females [33].

Data quality assurance

Before the actual data collection took place, the pre-test was done. To reduce misleading answers, the purpose of the investigation was informed to the study participants and sufficient time was taken to collect the data. To assure the reliability of test results, the standard operating procedure (SOP) format of each analyte was followed throughout the process. The performance verification of the clinical chemistry analyzer was checked daily by using standard controls. Generally, quality assurance was maintained throughout the pre-analytical, analytical, and post-analytical phases.

Data analysis and interpretation

The IBM-SPSS statistical software package (version 27) was used for data entry and analysis. The data distribution was checked with the help of the Shapiro-Wilk test of normality. Normally distributed data was done via parametric tests and descriptive statistics like frequency, percentage, mean and standard deviation (SD) were computed. One-way analysis of variant (ANOVA) and the corresponding post-hock test was used to evaluate (mean±SD) of the continuous biochemical and clinical parameters. Similarly, bivariate correlations of those parameters with the levels of serum ferritin were computed via Pearson correlation coefficient (r). Furthermore, bivariate and multivariate logistic regression was done to calculate the crude odds ratio (COR) and adjusted odds ratio (AOR) for estimating factors associated with serum ferritin levels in T2DM patients using a 95% confidence interval (CI). Besides, P-values less than 0.05 were considered statistically significant.

Operational definitions

- **Good glycaemic control –** adult non-pregnant diabetic patients whose HbA1c ≤ 7% based on the ADA guideline [17].
- **Poor glycaemic control –** adult non-pregnant diabetic patients whose HbA1c > 7% based on the ADA guideline [17].
- **Uncontrolled diabetes –** diabetic patients who were unable to achieve the target glycemic control status for the past three months and had poor glycemic control at the time of data collection (HbA1c > 7%) as per ADA criteria of glycemic targets [34].
- **Controlled diabetes –** diabetic patients who had optimal glycemic control status for the past three months and had good glycemic control at the time of data collection (HbA1c ≤ 7%) as per ADA criteria of glycemic targets [34].
- **Adult diabetic patients –** diabetic patients who had an age group from 18 to 65 years based on WHO (2019) guidelines [35].

Result

Descriptive features of the study participants

In this study, a total of 156 study subjects were enrolled and sub-grouped into three equal groups based on glycemic control status. Of the total (156) participants, 72(46%) were males. Female participants outnumbered males in each group, accounting 27(52%), 29(56%) and

28(54%) in the uncontrolled T2DM, controlled T2DM and control groups respectively. Most of the respondents in uncontrolled and controlled T2DM patients had a BMI between 25 and 29.9 kg/m^2 while the control groups were in the 18.5–24.9 kg/m^2 range. There were no blood pressure records of ≥140/90 mmHg in the control group. Approximately two-thirds (65.4%) of T2DM patients were on an oral OHA while 34.6% were injectable insulin users (Table 1).

Table 1 Descriptive characteristics of study participants at SPHMMC, Addis Ababa, Ethiopia, 2024 (*N* = 156)

Variables	Category	Study groups			Total
		Uncontrolled T2DM (*n*=52)	Controlled T2DM(*n*=52)	Control groups(*n*=52)	
		N (%)	N (%)	N (%)	N (%)
Sex	Male	25(48)	23(44)	24(46)	72(46)
	Female	27(52)	29(56)	28(54)	84(54)
Age (yrs)	18-33	7(13.5)	8 (15.4)	9(17.3)	24(15.4)
	34-49	21(40.4)	23(44.2)	22(42.3)	66(42.3)
	50-65	24(46.1)	21(40.4)	21(40.4)	66(42.3)
Educational levels	No formal	7(13.5)	4(7.7)	3(5.7)	14(8.9)
	Primary	12(23.1)	17(32.7)	9(17.3)	38(24.4)
	Secondary	20(38.5)	18(34.6)	20(38.5)	58(37.2)
	Higher	13(25)	13(25)	20(38.5)	46(29.5)
BMI(kg/m^2)	<18.5	1(1.9)	5(9.6)	6(11.5)	12(7.7)
	18.5-24.9	16(30.8)	21(40.4)	33(63.5)	70(44.9)
	25-29.9	25(48.1)	24(46.2)	13(25)	62(39.7)
	≥ 30	10(19.2)	2(3.8)	-	12(7.7)
SBP (mmHg)	<120	6(11.6)	15(28.8)	24(46.1)	45(28.8)
	120-139	23(44.2)	25(48.1)	28(53.9)	76(48.7)
	≥ 140	23(44.2)	12(23.1)	-	35(22.5)
DBP (mmHg)	<80	16(30.8)	18(34.6)	30(57.7)	64(41)
	80-89	19(36.5)	24(46.2)	22(42.3)	65(41.6)
	≥90	17(32.7)	10(19.2)	-	27(17.4)
Duration on DM (yrs)	<5	7(13.5)	13(25)	-	20(19.2)
	5-10	14(26.9)	26(50)	-	40(38.5)
	>10	31(59.6)	13(25)	-	44(42.3)
Treatment option	OHA	32(61.5)	36(69.2)	-	68(65.4)
	Insulin	20(38.5)	16(30.8)	-	36(34.6)

No formal education- have no classroom-based education; Primary school- from grades 1–8; secondary school- from grades 9–12; higher level education- college or university; OHA- oral hypoglycemic agent; DM-diabetes mellitus

Comparison of the biochemical and clinical parameters in different study groups

A one-way ANOVA results revealed that the mean differences in the age of participants in Uncontrolled T2DM, controlled T2DM, and control groups were not statistically significant ($F_{2, 153}$=0.277, P=0.759). The corresponding post-hock test results for serum ferritin showed that the mean difference between uncontrolled and controlled T2DM patients was significant (p<0.001). However, the mean difference in DBP was not significant (p=0.665). Additionally, the mean difference of serum iron between the controlled T2DM and the non-diabetic control group was not significant (p=0.055). Except for the age of participants, the mean difference of all the tested variables between the uncontrolled T2DM and non-diabetic control groups was statistically significant (p<0.001), as summarized in Table 2.

The distribution of the data set and the five-number summary of minimum, lower quartile (Q_1), median, upper quartile (Q_3), and maximum values of serum ferritin levels among the three different study groups were plotted in (Fig. 2). The maximum value of serum ferritin level was higher in uncontrolled T2DM as compared tocontrolled T2DM and control groups. Similarly, the median serum ferritin levels decreased from uncontrolled T2DM to control groups from left to right. The control groups showed a narrower interquartile range (IQR) compared to uncontrolled and controlled T2DM patients, which showed more consistent data sets seen in the control groups than diabetic groups. However, the minimum values of serum ferritin levels were recorded among the controlled T2DM patients, as shown in Fig. 2.

The mean differences in age, BMI, SBP, DBP, HbA1c, FBs, serum ferritin, and serum iron in T2DM patients with different pharmacological treatment options were analyzed. Accordingly, our study indicated that serum ferritin was increased in OHA users than in patients having injectable insulin as a therapeutic option and the difference was statistically significant (p=0.048). Similarly, DBP was increased among OHA users as compared to injectable insulin users and the difference was significant (p=0.034). However, the mean difference of duration on diabetes mellitus was decreased in OHA users than in injectable insulin users and the difference was statistically significant (p=0.047), as shown in Table 3.

Relation of serum ferritin level with biochemical and clinical parameters

Our study demonstrated that there was a significant positive correlation of serum ferritin levels with HbA1c, FBs, serum iron and SBP (r=0.457, p<0.001; r=0.386, p<0.001, r=0.430, p<0.001 and r=0.195, p=0.047, respectively) in T2DM patients. However, there were no

Table 2 Comparison of serum ferritin and other tested parameters among study subjects with different glycemic control status at SPHMMC, Addis Ababa, Ethiopia, 2024 ($n=52$ per group)

Study groups	ANOVA results		Post hoc analysis	
	Variables	F (*p*-value)	Paired groups	*P*-value
	Age (yrs)			
UT2DM	47.54 ± 9.44	0.277(0.759)	UT2DM vs. CT2DM	0.79
CT2DM	46.31 ± 9.36		CT2DM vs. CG	0.993
CG	46.35 ± 9.97		CG vs. UT2DM	0.802
	BMI (kg/m^2)			
UT2DM	26.43 ± 3.53		UT2DM vs. CT2DM	0.023
CT2DM	24.67 ± 3.51	19.443(<0.001)	CT2DM vs. CG	0.001
CG	22.31 ± 3.06		CG vs. UT2DM	<0.001
	SBP (mmHg)			
UT2DM	136.85 ± 14.04		UT2DM vs. CT2DM	0.045
CT2DM	130.67 ± 11.30	33.171(<0.001)	CT2DM vs. CG	<0.001
CG	119.77 ± 5.17		CG vs. UT2DM	<0.001
	DBP (mmHg)			
UT2DM	85.19 ± 8.70		UT2DM vs. CT2DM	0.665
CT2DM	83.24 ± 7.70	15.318(<0.001)	CT2DM vs. CG	<0.001
CG	77.62 ± 5.16		CG vs. UT2DM	<0.001
	Duration on DM (yrs)			
UT2DM	12.21 ± 6.25		UT2DM vs. CT2DM	<0.001
CT2DM	8.35 ± 3.81	-	CT2DM vs. CG	-
CG	-		CG vs. UT2DM	-
	HbA1c (%)			
UT2DM	9.31 ± 1.47		UT2DM vs. CT2DM	<0.001
CT2DM	6.64 ± 0.27	262.205(<0.001)	CT2DM vs. CG	<0.001
CG	5.44 ± 0.23		CG vs. UT2DM	<0.001
	FBs (mg/dl)			
UT2DM	201.03 ± 43.38		UT2DM vs. CT2DM	<0.001
CT2DM	113.03 ± 19.09	230.063(<0.001)	CT2DM vs. CG	<0.001
CG	89.81 ± 9.37		CG vs. UT2DM	<0.001
	Serum ferritin (ng/ml)			
UT2DM	243.05 ± 91.77		UT2DM vs. CT2DM	<0.001
CT2DM	169.30 ± 89.98	40.114(<0.001)	CT2DM vs. CG	<0.001
CG	109.60 ± 29.33		CG vs. UT2DM	<0.001
	Serum iron (ug/dl)			
UT2DM	140.17 ± 37.26		UT2DM vs. CT2DM	0.002
CT2DM	117.90 ± 31.48	16.726(<0.001)	CT2DM vs. CG	0.055
CG	102.75 ± 30.42		CG vs. UT2DM	<0.001

UT2DM- Uncontrolled T2DM; CT2DM-Controlled T2DM; CG-Control groups; SD-Standard deviation; $f_{2\backslash153=}$ F and the p-value < 0.05 level (2-tailed) showed the existence of a significant difference between the groups. All the variables were expressed in (Mean ± SD) form

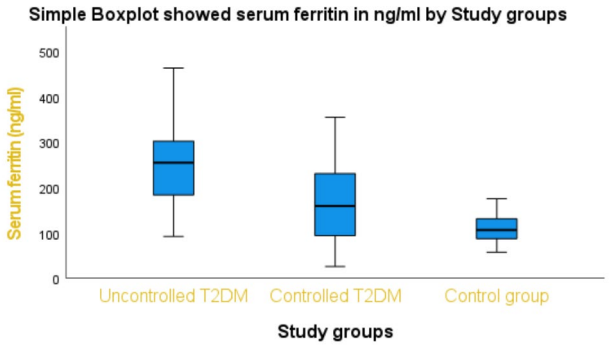

Fig. 2 The box and whisker plot summarized the distribution of serum ferritin levels among different study groups at SPHMMC, Addis Ababa, Ethiopia, 2024

Table 3 Comparison of serum ferritin levels and other tested parameters among OHA and injectable insulin users of T2DM patients at SPHMMC, Addis Ababa, Ethiopia, 2024 ($n=104$)

Tested parameters	Diabetes treatment option		*p*-value
	OHA	Injectable insulin	
Age (Mean ± SD) yrs	47.13 ± 9.76	46.53 ± 8.73	0.756
BMI (Mean ± SD) kg/m^2	25.59 ± 3.91	25.46 ± 3.03	0.882
SBP (Mean ± SD) mmHg	134.44 ± 13.56	132.47 ± 12.13	0.467
DBP (Mean ± SD) mmHg	85.60 ± 8.77	82.03 ± 6.55	0.034
Duration of DM (Mean ± SD) yrs	9.50 ± 4.91	11.75 ± 6.30	0.047
HbA1c (Mean ± SD) %	8.01 ± 1.79	7.90 ± 1.55	0.749
FBs (Mean ± SD) mg/dl	159.27 ± 58.87	152.81 ± 48.63	0.551
Serum ferritin (Mean ± SD) ng/ml	218.38 ± 107.93	183.12 ± 70.53	0.048
Serum iron (Mean ± SD) ug/dl	133.72 ± 38.06	120.19 ± 30.66	0.069

OHA = oral hypoglycemic agents; p-value is significant at < 0.05 levels (2-tailed)

significant correlations found in the non-diabetic control group, as shown in Table 4.

The study found a linear relationship between serum ferritin levels and glycaemic indicators (HbA1c, FBs) in T2DM patients. The correlation was significantly positive, with an uphill pattern, indicating that serum ferritin rises as HbA1c and FBs increased with a Pearson correlation (r) of 0.386 and 0.457 respectively, as shown in Fig. 3 parts A and B. Likewise, a significant positive correlation also existed in uncontrolled T2DM patients ($r=0.363$, $p=0.008$), as demonstrated in Fig. 3 part C.

Factors associated with an increase in serum ferritin level among T2DM patients

The bivariate analysis was done to identify the candidate variables for multivariate logistic regression based on the Wald test from logistic regression and a p-value cut of < 0.25 at least one within the group [36]. As such, tested variables like age group, sex, BMI, SBP, DBP, duration of

Table 4 Correlation of serum ferritin with some biochemical and clinical parameters among patients with T2DM and non-diabetic control groups at SPHMMC, Addis Ababa, Ethiopia, 2024

Tested parameters	Study groups			
	T2DM patients (*n*=104)		Control groups (*n*=52)	
	r	*p*-value	*r*	*p*-value
Age (yrs)	-0.035	0.722	-0.042	0.766
BMI(kg/m^2)	0.182	0.065	0.214	0.127
SBP (mmHg)	0.195	0.047*	-0.005	0.971
DBP (mmHg)	0.177	0.072	-0.082	0.564
Duration on DM (yrs)	0.092	0.355	-	-
HbA1c (%)	0.457	<0.001**	-0.066	0.643
FBs (mg/dl)	0.386	<0.001**	-0.056	0.693
Serum iron (ug/dl)	0.430	<0.001**	-0.023	0.871

r=Pearson correlation coefficient; **=p-value is significant at 0.01 level (2-tailed; *= p-value significant at 0.05 level (2-tailed) and all the tested parameters were expressed in terms of (Mean±SD)

diabetes, treatment option, HbA1c, FBs and serum iron were all associated with an increase in serum ferritin level in T2DM patients and exported into a multivariate logistic regression model.

The result of this study showed that T2DM patients who were taking injectable insulin as a treatment option were 0.26 times less likely to have increased serum ferritin levels as compared to only OHA users (AOR=0.26, 95% CI(0.07–0.95), p=0.042). A 1% increase in HbA1c of T2DM patients was 3.67 ng/ml times more likely to increase serum ferritin level (AOR=3.67, 95% CI (1.50–8.98), p=0.004). This study also illustrated that a rise in serum iron was positively associated with elevation of serum ferritin in T2DM patients (AOR=1.02, 95% CI (1.01–1.04), p=0.017). Similarly, female T2DM patients were 0.16 times less likely to increase serum ferritin level as compared to males (AOR=0.16, 95% CI (0.05–0.57), p=0.004), as shown in Table 5.

Discussion

The study evaluated the relationship of serum ferritin levels and related factors according to the participants' state of glycemic control status. The overall results of the present study showed that the mean level of serum ferritin was high in uncontrolled T2DM patients as compared to controlled T2DM and control groups. A significant positive correlation of serum ferritin with HbA1c, FBs, serum iron and SBP was found among T2DM patients. However, no significant correlation was found among the control groups. Insulin injection users had significantly

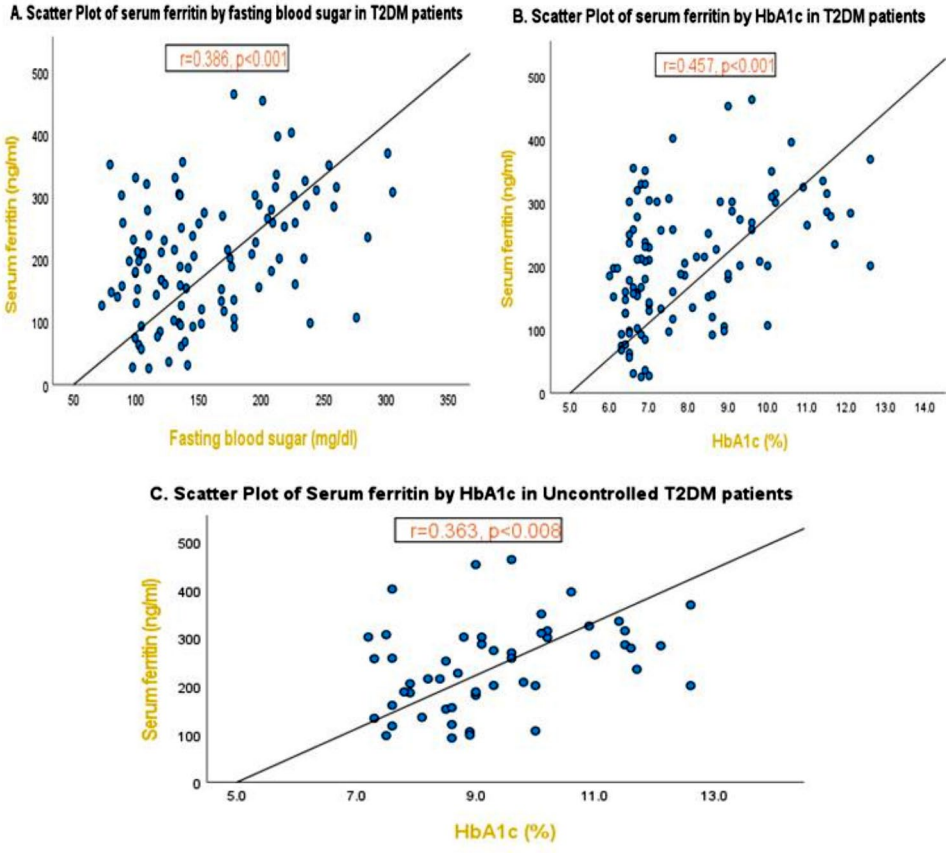

Fig. 3 Scatter plot showing the relationship of serum ferritin with glycaemic indicators in T2DM patients at SPHMMC, Addis Ababa, Ethiopia, 2024

Table 5 Bivariate and multivariate logistic regression showing factors associated with elevated serum ferritin levels among T2DM patients at SPHMMC, Addis Ababa, Ethiopia, 2024 ($n=104$)

Tested parameters	Category	Serum ferritin >200 ng/ml		Bivariate analysis		Multivariate analysis	
		Yes (*n*=54)	No (*n*=50)	COR(95% CI)	*P*	AOR(95% CI)	*P*
Age (yrs)[a]	18-33	10	5	1			
	34-49	23	21	0.55(0.16-1.87)	0.336	0.43(0.06-2.94)	0.389
	50-65	21	24	0.44(0.13-1.49)	0.185	0.19(0.02-1.50)	0.115
Sex[a]	Male	33	15	1			
	Female	21	35	0.27(0.12-0.62)	0.002	0.16(0.05-0.57)	0.004
Educational levels[b]	No formal	5	6	1			
	Primary	15	14	1.29(0.32-5.18)	0.724		
	Secondary	22	16	1.65(0.43-6.37)	0.467		
	Higher	12	14	1.03(0.25-4.24)	0.969		
BMI(kg/m^2)[a]	<18.5	3	3	1			
	18.5-24.9	13	24	0.54(0.09-3.08)	0.489	0.12(0.01-1.46)	0.097
	25-29.9	28	21	1.33(0.24-7.28)	0.740	0.44(0.04-4.42)	0.485
	≥30	10	2	5.0(0.55-45.39)	0.153	2.27(0.09-57.2)	0.618
SBP(mmHg)[a]	<120	8	13	1			
	120-139	24	24	1.63(0.57-4.63)	0.363	1.48(0.33-6.73)	0.610
	≥140	22	13	2.75(0.90-8.40)	0.076	1.56(0.25-9.81)	0.637
DBP(mmHg)[a]	<80	15	19	1			
	80-89	21	22	1.21(0.49-2.98)	0.680	0.50(0.12-2.23)	0.365
	≥90	18	9	2.53(0.89-7.23)	0.082	0.48(0.08-2.89)	0.425
Duration on DM (yrs)[a]	<5	12	8	1			
	5-10	17	23	0.49(0.17-1.47)	0.204	0.80(0.16-4.06)	0.788
	>10	25	19	0.88(0.30-2.57)	0.811	0.35(0.05-2.30)	0.276
Mode of therapy [a]	OHA	41	27	1			
	Insulin	13	23	0.37(0.16-0.86)	0.020	0.26(0.07-0.95)	0.042
HbA1c (%)[a]	M±SD	8.8 ±1.9	7.1± 1.0	2.12(1.50-3.01)	<0.001	3.67(1.50-8.98)	0.004
FBs (mg/dl)[a]	M±SD	176.4±59.2	136.1±42.4	1.02(1.01-1.03)	<0.001	0.99(0.97-1.01)	0.233
Serum iron (ug/dl)[a]	M±SD	142.8±33.9	114.2±32.6	1.03(1.01-1.04)	<0.001	1.02(1.01-1.04)	0.017

1-Indicates the reference group; COR=crude odds ratio; AOR=adjusted odds ratio; CI=confidence interval; M=mean; SD=Standard Deviation; p-value significant at 0.05 level (2-tailed); [a]=variables exported to multivariate logistic regression; [b]=variables not exported to multivariate logistic regression model

decreased ferritin levels compared to those who had been on OHA. A rise in HbA1c and serum iron, male gender, and having only OHA were the key associated factors for the elevation of serum ferritin in T2DM patients.

According to our research, the mean serum ferritin level was significantly increased in uncontrolled T2DM patients as compared to controlled T2DM and non-diabetic control groups. The finding of this study was different from a study done in Saudi Arabia that described serum ferritin had no link with glycaemic indicators and diabetic complications [22] as well as contrasted with a study conducted in Ethiopia showing a significant decrease in serum ferritin levels among T2DM patients as compared to non-diabetic control groups [26]. Even though the exact reasons remained unknown, the variation in dietary intake and follow-up care might have a greater influence on the discrepancies in serum ferritin levels [37]. Conversely, our study was consistent with a studies done in India [38] and Turkey [39], which showed noticeable hyperferritinemia among uncontrolled T2DM patients when compared to controlled T2DM patients. This could be due to hyperferritinemia affecting pancreatic β-cells through oxidative stress, impairing the liver's capacity to extract hepatic insulin, interfering with insulin's ability to reduce hepatic glucose synthesis [40], and potentially leading to diabetic complications via interaction with vascular endothelial growth factor (VEGF) [41].

This study demonstrated the existence of a significant positive correlation of serum ferritin with HbA1c, FBs, serum iron and SBP in T2DM patients. The current finding was contrasted with a study done in Iran [23] and Iraq [42] that showed a null correlation. However, our finding was consistent with studies conducted by Shubham J, et al. [25], Rajeev C, et al. [43] and Li S, et al. [44], who found a significant correlation of serum ferritin with glucose control, serum iron and SBP/DBP respectively. This might be due to hyperglycaemia causing a non-enzymatic irreversible interaction of glucose with hemoglobin in RBC [7] and free iron is released during the glycation process which tends to initiate redox reactions

to generate free radicals like ROS, which damage pancreatic β-cell [8] and intensifies the inflammatory response as well as oxidative damage to biomolecules which results in elevated serum ferritin levels [9].

The multivariate logistic registration model of the present study suggested that increased average HbA1c by 1% in T2DM patients had 3.67ng/ml times more likely to increase serum ferritin levels and an increase in serum iron was also positively associated with elevation of serum ferritin level. This finding was in line with a study done by Sarin S, et al. that showed for every 1ng/ml increase in serum ferritin levels, patients' average HbA1c raised by 0.01% [45]. Moreover, this study showed a positive likelihood association of serum ferritin with glycemic control status and was consistent with earlier similar studies [46–48]. This might be due to the biochemical properties of ferritin and the pathophysiology of T2DM which is attributed to the close connection of serum ferritin with glycemic control status [49–51].

The WHO and IDF guidelines recommend metformin as the first-line pharmacological treatment option for T2DM, followed by sulfonylureas and other hypoglycaemic agents before insulin therapy starts [52]. Our study found that OHA users had significantly higher serum ferritin levels than injectable insulin users ($p=0.048$), which was consistent with previous Ethiopian study [26]. The multivariate logistic regression of the current study also illustrates that insulin injection users were 0.26 times less likely to increase ferritin levels as compared to only OHA users. Even though we didn't know the exact mechanism for such a difference, possibly insulin injection made a rapid stimulation of iron uptake by fat cells and hepatocytes [53].

In this study, OHA users had a significantly higher mean DBP record compared to insulin injection users ($p=0.032$). This might be due to insulin stimulating the production of nitric oxide (NO) in endothelium which induces vasodilation by relaxing the inner muscle of the blood vessels and regulates sodium homeostasis by enhancing sodium reabsorption in the kidney. Thereby, contributing to the regulation of blood pressure [54]. Conversely, OHA users had a considerably shorter duration of diabetes ($p=0.047$) compared to those using injectable insulin, this difference might be due to management guidelines of T2DM patients [52]. In our study, female T2DM patients were 0.16 times less likely to increase serum ferritin levels as compared to males. Our finding was consistent with other studies which showed that being male could be a risk factor for iron overload [55, 56]. This might be due to the nature of females that may lose iron during the menstrual period [57].

This study also suggested the presence of a positive correlation between serum ferritin and BMI even though the association was not significant ($r=0.182$, $p=0.065$), which is in line with a study done by Aregbesola A, et al. showed that higher BMI was associated with elevated levels of serum ferritin [58]. Even if we didn't know the exact mechanism, scientific studies showed that males stored more fat in their bellies than females [59]. Therefore, a variation in body composition and fat deposition among sexes may contribute to gender-specific serum ferritin disparities.

Although diabetes mellitus affects both sexes, epidemiological studies showed that the prevalence of diabetes mellitus was increased in males as compared to females. Worldwide, an estimated 17.7 million more men than women have diabetes mellitus [60]. Even though we didn't know the exact mechanisms, body iron stores might be one of the risk factors for such differences [5].

Strengths and limitations of the study

The major strengths of the current study were the use of a fully automated clinical chemistry analyzer for investigating each laboratory test and as per the authors' knowledge, this was the first Ethiopian study investigating serum ferritin levels and associated factors among patients with uncontrolled T2DM and compared them to those with controlled T2DM and non-diabetic controls. However, the investigation was constrained by a cross-sectional study unlike a longitudinal design, which did not show a well-established relationship between serum ferritin levels and state of glycaemic control. Furthermore, it was conducted only in T2DM patients undergoing follow-up appointments at outpatient clinics, which might not be reflective of the overall diabetes community.

Conclusion and recommendation

The study found that uncontrolled T2DM patients had elevated serum ferritin levels with a significant positive correlation of biochemical indicators like HbA1c, FBs, and iron levels. Factors such as increased HbA1c, raised serum iron, male gender, and having only OHA were all associated with increased ferritin levels in T2DM patients. Thereby, elevated serum ferritin might indicate long-term hyperglycemia in T2DM patients, suggesting a potential therapeutic target for iron excess. Future research should use longitudinal design with the addition of hepcidin tests, and incorporation of adolescents and children with T1DM for the representativeness.

Abbreviations

ADA	American Diabetic Association
BMI	Body Mass Index
DBP	Diastolic blood pressure
FBS	Fasting Blood Sugar
HbA1c	Hemoglobin A1c
IDF	International Diabetic Federation
OHA	Oral Hypoglycemic Agent
RBC	Red blood cell
ROS	Reactive Oxygen Species
SBP	Systolic blood pressure

SOP	Standard operating procedure
SPHMMC	St. Paul's Hospital Millennium Medical College
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
WHO	World Health Organization

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Author contributions
AB was the principal investigator who participated in the conceptualization of the study, drafted the manuscript, performed the data analysis, and participated in data collection and laboratory tests; MW, GD, SK, AE and MA were advised throughout the process and participated in editing and reviewing the manuscript; GTA, AA, AG and BG were participated in data collection; AB, AB, GG and MT were participated in data analysis and interpretation. Each author reviewed and gave their approval to the final draft.

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Data availability
The datasets used or analyzed during the current study are available from the corresponding author on reasonable requests.

Declarations

Ethics approval and consent to participate
The ethical clearance for the study was obtained from the Departmental Research and Ethics Review Committee (DRERC) of the Department of Medical Laboratory Science, College of Health Science of Addis Ababa University with a Ref. no. MLS/045/23 and the study was conducted in accordance with the principles of the Declaration of Helsinki. Furthermore, an official permission letter was granted from the Endocrinology unit of St. Paul's Hospital Millennium Medical College (SPHMMC) and the study participants well-understood the purpose of the study and the information obtained in the course investigation was kept confidential. Finally, each study participant underwent a consent process to confirm their willingness to participate in the study through a written informed consent perior to data collection.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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