Association of Serum Ferritin with Metabolic Syndrome in Type II Diabetes from Medical City Hospital in Iraq

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ABSTRACT:

BACKGROUND:

Metabolic syndrome is a constellation of risk factors of metabolic origin that are accompanied by increased risk of cardiovascular disease and type II diabetes. These risk factors are atherogenic dyslipidemia, elevated blood pressure, elevated plasma glucose, a prothrombotic state, and a proinflammatory state. The two major underlying the risk factors of metabolic syndrome are obesity and insulin resistance; exacerbating factors are physical inactivity, advancing age, and endocrine and genetics . The condition is progressive, beginning with borderline risk factors that eventually progress to categorical risk factors. In many patients, metabolic syndrome culminates in type II diabetes, which further increases risk for cardiovascular disease. Hyperferritinemia has been linked with a wide spectrum of pathologies, including diabetes, cardiovascular disease, neurodegenerative disorders, and metabolic syndrome.

OBJECTIVE:

The association between serum ferritin and metabolic syndrome components (hypertension, dyslipidemia, body mass index) in cohort of Iraqi patients diagnosed with type II diabetes mellitus.

PATIENTS AND METHODS:

This a case-control study that was conducted at the teaching laboratories of the Medical City hospital . The study included 60 patients with type II diabetes mellitus and 25 healthy controls matching in age and gender . Height , body weight, waist circumference along with systolic and diastolic blood pressures were measured .The obtained serum samples were used to measure: serum ferritin, total cholesterol, HDL-cholesterol, LDL-cholesterol , TG, fasting serum glucose (FSG), hemoglobin and glycated hemoglobin A1c(Hb A1c).

RESULTS:

The results of the study showed that there were significant differences between patients and controls in relation to the following parameters :

- Serum ferritin , FSG , Hb A1c , total cholesterol , TG and LDL were significantly higher in patients with type II diabetes mellitus and have metabolic syndrome as compared to the control group. However HDL was Significantly lower in HDL when compared with control group.
- There were no significant differences in hemoglobin levels in comparison to the control group. The correlation between serum ferritin levels and the other parameters of the patients sample were as follows:
- A significant positive association with systolic blood pressure (SBP)(r= 0.260) (p= 0.044),with diastolic blood pressure (DBP)(r= 0.382)(p= 0.0025),with waist circumference(WC) (r= 0.269) (p= 0.037) , with body mass index(BMI) (r=0.289)(p=0.023),with fasting serum glucose (r = 0.27)(p = 0.035), with Hb A1c (r= 0.264) (p= 0.041),with total cholesterol TC)(r= 0.268) (p= 0.038), with triglyceride (TG)(r= 0.279)(p= 0.030), with LDL (r= 0.022)(p= 0.045) But no association with HDL (r= 0.184)(p= 0.153).

CONCLUSION:

The study showed that serum ferritin level could be used as a screening tool for hypertension, diabetes mellitus , atherosclerosis ,cardiovascular diseases and metabolic syndrome.

KEYWORDS: serum ferritin , metabolic syndrome , DM typeII

INTRODUCTION:

Metabolic syndrome (sometimes also known as syndrome X or insulin resistance syndrome) has been recognized since the late 1980s. In 1988, it was Reaven who used the term syndrome X to refer to the tendency of glucose intolerance, hypertension, low high density lipoprotein (HDL-Ch) cholesterol, raised

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triglycerides, and hyperinsulinemia when they exist in the same individual [1].The International Diabetes Federation had a new explanation of the metabolic syndrome which is a group of high risk factors: diabetes mellitus, high fasting plasma glucose, high blood pressure[2] . therefore the definition of metabolic syndrome was developed by the World Health Organization [3] as shown in table 1[4] .

To date, metabolic syndrome is not completely understood , Obesity mainly central obesity and insulin resistant are thought driving factors of metabolic syndrome and its consequent increase the risk for type II diabetes mellitus and cardiovascular disease[5].

Table 1: Definition of metabolic syndrome [4]

Clinical and biochemical features	WHO	NCEP ATP III 2001	IDF 2005
Insulin resistance	Impaired glucose tolerance, impaired fasting glucose, T2DM, or lowered insulin sensitivity plus any two of the following	Any three of the following	
Obesity	Abdominal obesity (waist-to-hip ratio N0.9 in men or N0.85 in women, or BMI N 30 kg/m2)	WC N102 cm in men, N88 cm in women	BMI N30 kg/m2 or WC with ethnicity-specific values, a plus any two of the following
Plasma glucose concentration	Impaired glucose tolerance, impaired fasting glucose, or T2DM	FPG ≥110 mg/dL	FPG ≥100 mg/dL
Hypertension	BP ≥140/90 mm Hg	BP ≥130/85 mm Hg	BP ≥130/85 mm Hgor on antihypertensive Medication
Triglycerides (TG)	TG ≥150 mg/dL	TG ≥150 mg/dL	TG ≥150 mg/dL or on treatment
HDL-cholesterol (HDLC)	HDLC b40 mg/dL in men and b50 mg/dL in women	HDLC b40 mg/dL in men and b50 mg/dL in women	HDLC b40 mg/dL in men and b50 mg/dL in women, or on treatment
Other	Urinary albumin excretion ≥20 µg/min, or ACR ≥30 mg/g		

Ferritin; a key protein regulating iron homeostasis, is a widely used parameter to evaluate the levels of iron stores in the body (6). In addition, ferritin has a role in disorder of energy metabolism(7). Depending on observation in type II diabetes mellitus it could be a complication in patients had hereditary hemochromatosis (had high ferritin level) so many studies done for searching for any association between high levels of serum ferritin and diabetes [8] .

Excessive accumulation of iron in the body has been proposed as a risk factor for a wide spectrum of diseases including cardiovascular diseases, liver dysfunction, peripheral arterial disease, and neurodegenerative diseases, among others. Iron overload notice by high serum ferritin [9] , but not the only cause for its high level as its elevated in other condition especially those associated with inflammatory state.

In recent study, there was association between serum ferritin and metabolic syndrome components (obesity ,Type II diabetes mellitus, dyslipidemia and hypertension)[١٠]. The underlying pathophysiology of the relationship between high serum ferritin level and metabolic syndrome is not yet completely understand. One possible mechanism is that the iron overload (manifesting high serum ferritin level) possibly related to insulin resistant which may be the underlying pathophysiology to development type II diabetes mellitus and metabolic syndrome [١٠] . High levels of serum ferritin are associated with dyslipidemia as cause high lipid peroxidation. Iron is a strong pro-oxidant and can cause cellular damage by producing reactive oxygen species (ROS) in various body tissue. Elevated ferritin levels augment pro-inflammatory cytokines that may mediate the association of ferritin with dyslipidemia [١٠]

AIM OF THE STUDY:

The investigate the association between serum ferritin and metabolic syndrome component (hypertension, dyslipidemia and body mass index) in type II diabetic Iraqi patients.

SUBJECTS, MATERIALS & METHODS:

This study was conducted at the Baghdad Medical City Complex . Sample collection was conducted during the period from (January to May 2018). Seventy patients were included in this study. The following tests were done for the all patients and controls FSG, Hb A1c, Hb, Serum Ferritin and lipid profile, used the Dimension® Rxl Max® Clinical Chemistry System(FBS, Hb A1c, lipid profile), IMMULITE® 2000 XPi system (serum ferritin) The ADVIA 2120 Hematology System (HB)

Statistical analysis

The statistical analysis in this study were done using Microsoft Excel Worksheet (version 2016). Calculating the mean ±SD and t-test for the patients and control parameters . In addition to calculating the degree of correlation between serum ferritin and other parameters of the patient by measuring the r-value and p-value which ≤0.05 consider significant and > ٠,٠٥ consider not significant

RESULTS:

The diabetic patients were chosen as they are already on treatment for diabetes mellitus which was confirmed by fasting blood sugar and hemoglobin A1C. Metabolic Syndrome was defined according to the International Diabetes Federation IDF definition for Asia [14] . In this study, Metabolic Syndrome was diagnosed according to the presence of abdominal obesity (WC ≥90cm in men or ≥80cm in women) and the fulfillment of ≥ 2/4 of the following criteria: an SBP ≥130mm Hg, a DBP ≥85mmHg, or treatment with antihypertensive medications; a fasting glucose ≥100mg/dL or a previous diagnosis of T2DM; an HDL-C<40mg/dL in men or <50mg/ dL in women; or a TG level ≥150mg/dL[١١].

The table (2) represents the males and females distribution which were nearly equal in both groups , with a male to female ratio in (1:0.9) patient (1:1) control (1:0.9) respectively , the age of patients was (53.7±9.07)years and age range between (35-65)years while the age of control was (47.2±9.25)years and age range between(35-65)years, with no significant differences.

Table 2: Clinical characteristics of the study population

Group	Male no.	female no.	Total	Male to female ratio	Mean age+ SD year	age range year
Patients	30	30	60	1:1	53.73±9.07	35-65
Controls	13	12	25	1:0.9	47.2±9.25	35-65
Total	43	42	85	1:0.9		

The table 2 shows the incidence of type II diabetes mellitus in the patient group was among the age group (40-60) years. The control group were 25 subjects selected at age between (40-60) this study shows the mean ±SD for serum ferritin level of the patients (210.4 mg/dl ± 39.3) found to be significantly high when compared with control group (80.9 mg /dl ±31.3) the level of significant ($P<0.05$) as shown in the figures (1).

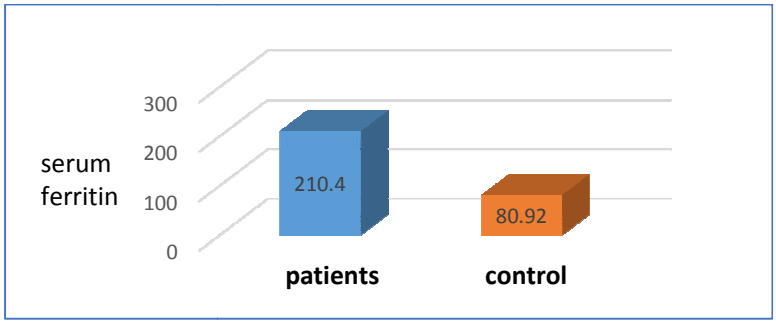

Figure 1: The mean level of serum Ferritin in patients as compared to control

The mean ±SD for hemoglobin level of the patients (13.57 mg/dl ± 1.04) found to be no significantly different when compared with control group(12.68 mg/dl ±1.3) as $p \geq 0.05$show in figure (2) .

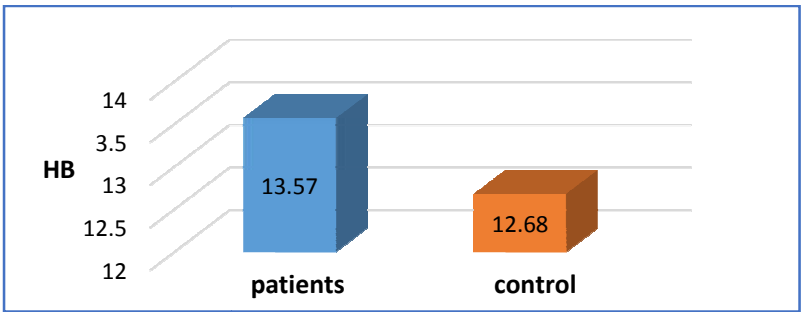

Figure 2: The mean of level of Hb in patients as compared to control

The mean ±SD for fasting blood sugar of the patients (130.8mg/dl ± 16.5) mg/dl found to be significantly different when compared with control group (91.04 mg/dl ± 7.26) as $p \leq 0.05$ as shown in figure (3) .

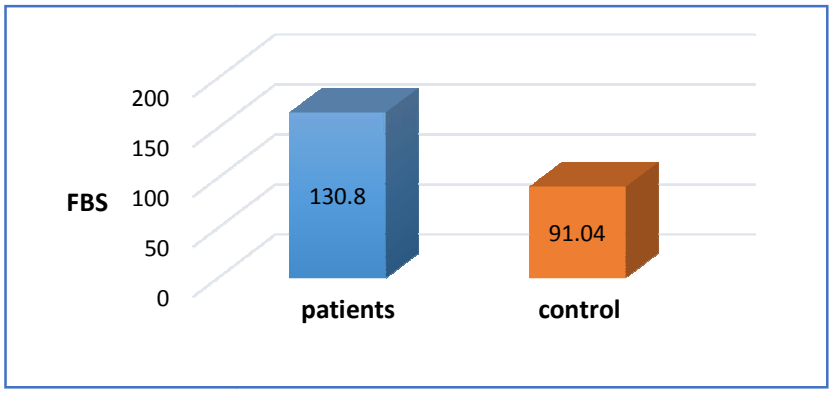

Figure 3: The mean level of FBS in patients as compared to control

The mean ±SD for Glycated Hemoglobin A1c measurement of the patients (7.9 ± 1.04) % found to be significantly increase when compared with control group (5.24 ± 0.66) % as $p \leq 0.05$ as shown in figure (4) .

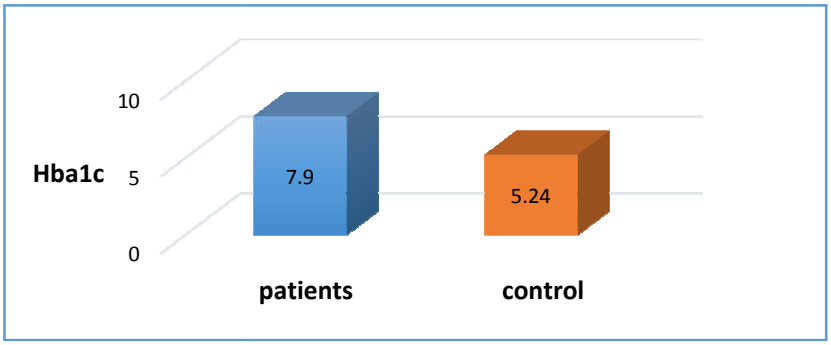

Figure 4: The mean of Hb A1c in patients as compared to control

The mean ±SD for total cholesterol level of the patients (198.9 ± 30.07) mg/dl found to be significantly high when compared with control group (147.79 ± 19.81) mg/dl as ($P \leq 0.05$) as shown in figure (5)

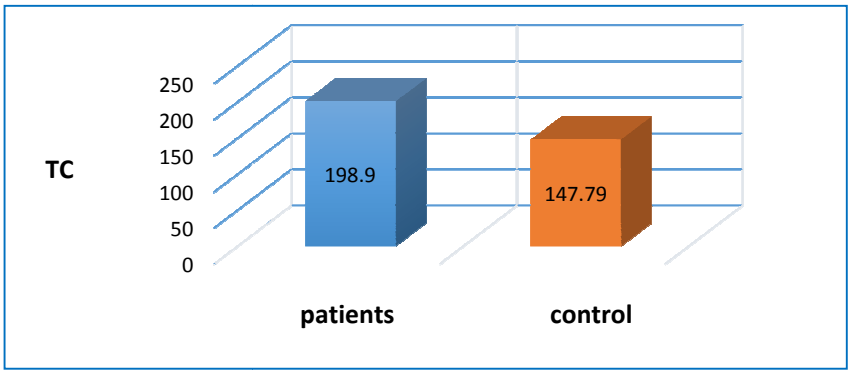

Figure 5: The mean of Total Cholesterol in patients as compared to control

The mean ±SD for Triglyceride level of the patients (177.35 ±45.0) mg/dl found to be significantly different (higher) when compared with control group (84.4 ± 21.3) mg/dl as ($P \leq 0.05$) as shown in figure (6).

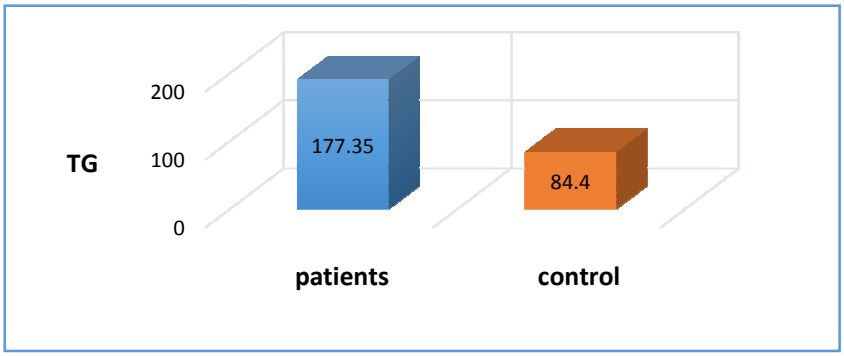

Figure 6: The mean of Triglyceride in patients as compared to control

The mean ±SD for HDL cholesterol level of the patients (39.26 ± 10.6) mg/dl found to be significantly low when compared with control group (47.92 ± 7.75) mg/dl as (P≤0.05)as shown in figure (7) .

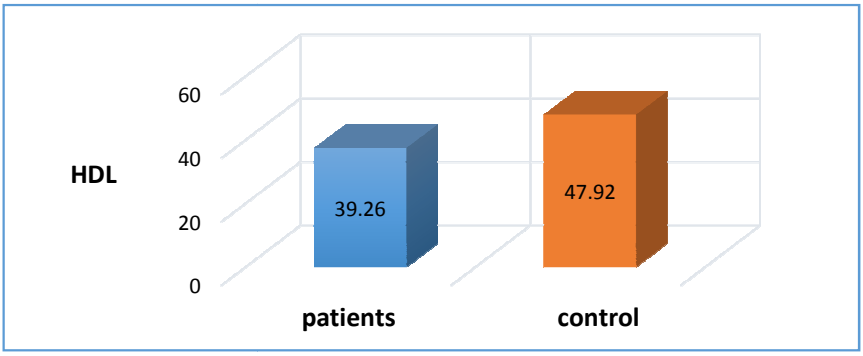

Figure 7: The mean of HDL in patients as compared to control

The mean ±SD for LDL cholesterol levelof the patients (133.06 ± 30.07) mg/dl found to be significantly high when compared with control group (83.48 ± 13.7) mg/dl as(P≤ 0.05) as shown in figure (8) .

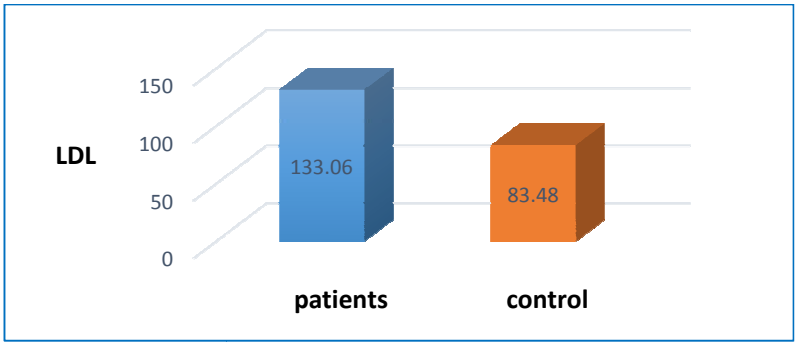

Figure 8: The mean of serum LDL in patients as compared to control

Correlation Between Serum Ferritin and Patients Parameters:

The correlation between serum ferritin and the parameters of the patient's sample is illustrated in table (3). It showed in table (3) the association of serum ferritin with other parameter as a significant correlation with systolic blood pressure (SBP) (r=0.260) (p=0.044), a significant association with diastolic blood pressure (DBP) (r=0.382) (p=0.0025), a significant association with waist circumference (WC) (r=0.269) (p=0.037), a significant association with body mass index (BMI) (r=0.289) (p=0.023), a significant association with fasting blood sugar (r = 0.27) (p = 0.035), a significant association with Hb A1c (r=0.264) (p=0.041) a significant association with total cholesterol (TC) (r=0.268) (p=0.038), a significant association with triglyceride (TG) (r=0.279) (p=0.030), a significant association with LDL (r=0.022) (p=0.045) but no association with HDL (r= 0.184) (p= 0.153).

Table (3): Mean ±SD ,R-value and P-value for parameter of the sample:

Parameters	Mean±SD	r-value	P-value
SBP	123.9±6.1	0.260	0.044*
DBP	79.16±7.12	0.382	0.0025*
WC	132.15 ±13.8	0.269	0.037*
BMI	28.9±3.8	0.289	0.023*
hemoglobin	13.7±1.04	0.280	0.029*
FBS	99.4±7.12	0.27	0.035*
Hba1c	7.9±1.04	0.264	0.041*
TC	198.9 ± 30.07	0.268	0.038*
TG	177.35 ± 45.01	0.279	0.030*
HDL	39.26 ± 10.6	0.184	0.153
LDL	133.06 ± 30.07	0.022	0.045*

*p-value ≤ 0.05 which is significant

DISCUSSION:

Metabolic Syndrome was diagnosed according to the presence of abdominal obesity (WC ≥90cm in men or ≥80cm in women) and the fulfillment of ≥ 2/4 of the following criteria: an SBP ≥130mm Hg, a DBP ≥85mmHg, or treatment with antihypertensive medications; a fasting glucose ≥100mg/dL or a previous diagnosis of T2DM; an HDL-C<40mg/dL in men or <50mg/ dL in women; or a TG level ≥150mg/dL [١١] .

The study examined the association between serum ferritin with metabolic syndrome and its components , the age of sample was between 35-65 years old with nearly equal ratio between male and female in patients and control groups.

The study sample consisted 60 patients (30 one of them was male and 30 one was female) while the control group contained 25 apparently healthy subjects (13 one of them was male and 12 was female) . The age of the sample was between 35-65 years old. There was significant difference between the result of patient and control groups with an increase in the level of parameter out the reference range in patient group due to increased insulin resistant and increase inflammation that augment the dyslipidemia as in the study Chang Hee Jung study –korean study [١٢] that show significant difference between patients and healthy subjects.

In patients' parameters, the correlation between serum ferritin and other parameters was as follows: There was a significant association between serum ferritin, systolic blood pressure (r=0. 0.260)(p= 0.044) and diastolic blood pressure (r=0.382)(p=0.0025); this is similar to the results reported by IJsbrand T. Klip [١٣],Netherlands study in 2016 where an increase higher serum ferritin levels where more common amongst patients with hypertension .Meanwhile, Young Suk Shim and others [١٤], a Korean study in 2017, reported that higher serum ferritin levels cause an increased risk of 36% for Metabolic Syndrome in women. So the relationship between serum ferritin and BP is controversial. These differences may be associated with the underlying relationship between ferritin and Blood pressure. One possible explanation for the impact of ferritin on BP is that the relationship between of them may be mediated by insulin resistance, as opposed to ferritin exerting a direct influence on blood pressure [12] .

There is a significant association with waist circumference (WC)(r=0.269) (p=0.037), and body mass index(BMI)(r=0.016)(p=0.9) a result similar to that reported by Young Suk Shim and others [14] , the Korean study in 2017,as show there is association between serum ferritin and BMI and WC, other study IJsbrand T. Klip [13] , Netherlands study in 2016[16], show that

increasing ferritin level, individuals were generally older, more often male, and more likely to have CV risk factors (e.g. diabetes or hypertension).

There is a significant association between hemoglobin(r=0.280) (p=0.029) and serum ferritin levels; the same result was found by IJsbrand T. Klip [13] , Netherlands study in 2016, show that increasing ferritin level associated with hemoglobin other markers of iron homeostasis . Also Young Suk Shim and others [14], the Korean study in 2017,as show there is association between serum ferritin and hemoglobin level, as serum ferritin represent the body state of iron store .

There is significant association with fasting blood sugar(r=0.27) (p=0.035) and significant association with HbA1c (r=264)(p=0.041) and this similar to the IJsbrand T. Klip[13] ,Netherlands study in 2016 , show that increasing ferritin level associated with diabetes Also Young Suk Shim and others [14], the Korean study in 2017, as show there is association between serum ferritin and fasting blood sugar, the exact underlying mechanism of the association between the elevated serum ferritin concentrations and incident type II diabetes is not known, but possible explanation is that iron deposition in the liver can result in hepatic insulin resistance and increase production of hepatic glucose ,other possible mechanism could be due to an elevation in oxidative stress through the increased formation of hydroxyl radicals catalyzed by iron, which may lead to systemic insulin resistance and hyperglycemia.

In addition, iron excess probably contributes initially to insulin resistance and subsequently to decreased insulin secretion [12] .

There is a significant association with lipid profile total cholesterol (TC) (r=0.268) (p=0.038), significant correlation with triglyceride (TG) (r=0.279) (p=0.030), positive correlation with LDL (r=0.022) (p=0.045) but negative correlation with HDL (r= 184) (p= 0.153). and this also similar to the study of Young Suk Shim and others [14], the Korean study in 2017, as show there is association between serum ferritin and lipid profile except HDL show reverse association, While IJsbrand T. Klip [13], Netherlands study in 2016, show that increasing ferritin level associated with major component of lipid profile (TC,TG,LDL,HDL).

The possible underlying mechanism is due higher circulating ferritin level cause higher lipid peroxidation that cause cellular damage by producing reactive oxygen species (ROS) in various body tissue other mechanism is that serum ferritin augment pro-inflammatory cytokines that may mediate the association of ferritin with dyslipidemia [15] .

The limitations of this study could be summarized in three points;

- First, the small number of subjects
- Second multivitamin or iron intake amounts were not assessed in this study. It could not rule out the possibility that the results were influenced by vitamins or iron supplement intake.
- Third iron overloud could be secondary to undiagnosed hematological disorder

CONCLUSIONS:

The study showed that serum ferritin could be used as screening for: Hypertension , Diabetes mellitus, Atherosclerosis, Cardiovascular diseases and Metabolic syndrome

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