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AKADÉMIAI KIADÓ

Dietary iron intake aggravates dyslipidaemia by elevating ferritin levels in patients with insulin resistance and cardiovascular diseases: A cross-sectional study

B. Bayram[1*] and P.F. Türker[2]

[1] Department of Nutrition and Dietetics, Faculty of Health Sciences, Hasan Kalyoncu University, 27010, Gaziantep, Türkiye

[2] Department of Nutrition and Dietetics, Faculty of Health Sciences, Başkent University, 06790, Ankara, Türkiye

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ABSTRACT

Dietary iron intake causes the elevation of ferritin levels, and higher iron intake might improve insulin resistance and cardiovascular diseases. The aim of this study was to determine the relationship between dietary iron intake and serum ferritin levels, insulin resistance, and nutritional status in patients with cardiovascular disease. Health information of individuals were obtained with a questionnaire form. There were a total of 103 patients, 59 male (57.3%) and 44 female (42.7%). Patients also filled a questionnaire on dietary habits, a 3-day food record. There was a statistically significant difference between ferritin quartiles and total cholesterol, HDL-C, non-HDL-C, LDL-C/HDL-C ratio, and TG/HDL-C ratio ($P < 0.05$). Study data show that dietary iron intake was associated with the elevation of serum ferritin levels ($P < 0.05$) and this difference was significant in Q1 and Q4 groups in post-hoc analysis. There was a negative correlation between serum ferritin levels and total cholesterol and HDL-C in patients with insulin resistance ($r = -0.384$, $P < 0.05$; $r = -0.520$, $P < 0.05$). In conclusion we found a strong association between serum ferritin levels and inflammation, causing an oxidative stress, atherosclerosis, and bringing along cardiometabolic diseases such as cardiovascular diseases and type 2 DM.

* Corresponding author. E-mail: buse.kiratli@hku.edu.tr, busekiratli@gmail.com

KEYWORDS

ferritin, cardiometabolic diseases, insulin resistance, dietary iron, cardiovascular diseases

1. INTRODUCTION

Cardiovascular disease and its comorbidities change the mechanism of human metabolism and cause further progression of the disease. Chronic diseases, such as obesity and diabetes mellitus, result in metabolic changes, affecting body fat composition and insulin sensitivity. According to American Heart Association (AHA) (Virani et al., 2021), high fasting blood glucose and high body mass index (BMI) are the first and subsequent leading factors in cardiovascular disease formation.

The development of cardiovascular and coronary heart diseases stem from endothelial dysfunction, resulting in the formation of inflammation. Free iron in circulation takes part as a catalyser in the formation of free radicals, lipid peroxidation, and atherosclerosis (Holay et al., 2012). Intracellular iron concentrations act as an essential part of cell signalling dependent on reactive oxygen species (ROS). However, this role also accounts for producing toxic ROS. Fenton reaction, which takes place in the mitochondria, and hydroperoxides and peroxyl radicals, formed in membrane phospholipids as a result of lipid peroxidation in which Fe^{+2} and Fe^{+3} occur, play a huge role in ferroptosis pathophysiology (Cornelissen et al., 2019). Ferritin is an acute-phase protein that indicates inflammation, particularly when correlated with oxidative stress and metabolic syndrome. Ferritin levels are associated with the oxidative process of the body, suggesting that ferritin plays a huge role in cardiovascular diseases, insulin resistance, and hyperinsulinemia, as well as decreased insulin activity (Kang et al., 2012).

According to the reports issued by the European Society of Cardiology (ESC), 1/3 of patients with acute coronary syndrome have anaemia. Decreased serum iron and haemoglobin levels exacerbate tissue ischemia and increased C-reactive protein (CRP) levels in these patients (Kaiafa et al., 2015). CRP triggers those mechanisms by increasing the expression of plasminogen activator inhibitor-1 (PAI-1), causing atherothrombosis in vascular endothelium (Kaiafa et al., 2015). Ferritin and CRP are two reciprocal acute phase reactants. Levels of CRP and ferritin are correlated with metabolic syndrome and acute myocardial infarction (Ramesh et al., 2018). It has been postulated by the Turkish TEKHARF cohort study that CRP, an acute-phase reactant, is correlated with cardiovascular diseases and metabolic syndrome (Onat et al., 2017).

Insulin resistance causes lipodystrophy, leading to increased production of very low-density lipoproteins (VLDL), hypertriglyceridaemia, and increased fatty acid flow to the liver. Hyperlipidaemia is an indirect result of insulin resistance. With the effect of hyperinsulinaemia, dyslipidaemia is a condition in which levels of VLDL-C are higher and of high-density lipoprotein (HDL-C) are lower; increased VLDL levels induce the synthesis of PAI-1, causing the pathology of atherosclerosis (Ginsberg, 2000).

These results suggest that cardiovascular diseases and insulin resistance are non-communicable chronic diseases that need to be taken precautions against and to be detected before the onset of disease based on the effect of diet and serum ferritin level, an acute phase reactant. This study aims to investigate the correlation between dietary iron intake, serum ferritin levels, and insulin resistance in patients diagnosed with cardiovascular disease.

2. MATERIALS AND METHODS

2.1. Ethics statement

This study was approved by Başkent University Institutional Review Board and Ethics Committee (Project no: KA19/215) and Gaziantep Provincial Health Directorate (Pharmaceuticals and Medical Devices Administration of Turkey) by file no 65587614-774.99.

2.2. Study design

This was a cross-sectional, observational study conducted from August to October 2019 at the Department of Endocrinology and Metabolism in Gaziantep Dr. Ersin Arslan Training and Research Hospital (Turkey). The study was carried out in accordance with the Declaration of Helsinki. Every participant was willing to enrol in this study and signed the informed consent form.

There was a total of 103 patients, 59 male (57.3%) and 44 female (42.7%). The sample size justification of the study was calculated using G-Power data program, and it was found 93.40% by a 95% CI. Patients who enrolled in this study were diagnosed with cardiovascular disease and insulin resistance or type 2 diabetes mellitus. Exclusion criteria for patients were:

1. Age <20 years and >64 years,
2. Pregnant and breastfeeding females,
3. Individuals diagnosed with cancer; chronic liver and chronic kidney diseases; iron deficiency anaemia.

Patients also filled out a questionnaire with 36 questions including socio-demographic characteristics, general information, dietary habits; a 3-day food record (2 weekdays and 1 weekend day). Dietary iron intake was calculated via 3-day food record; with heme and non-heme iron together.

2.3. Biochemical parameters of patients

Patient files were also used to gather the patients' biochemical parameters, which were fasting plasma glucose, postprandial plasma glucose, fasting insulin, haemoglobin, haematocrit, blood urea nitrogen (BUN), total cholesterol (mg dL^{-1}), HDL-C (mg dL^{-1}), LDL-C (mg dL^{-1}), VLDL-C (mg dL^{-1}), non-HDL-C (mg dL^{-1}), triglycerides (mg dL^{-1}), serum iron (μg dL^{-1}), total iron binding capacity (TIBC) (μg dL^{-1}), ferritin (μg L^{-1}), HOMA-IR, HbA1c (%), CRP (mg dL^{-1}), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), alanine aminotransferase (ALT) (U L^{-1}), aspartate aminotransferase (AST) (U L^{-1}), total protein (g dL^{-1}), creatinine (mg dL^{-1}), uric acid (mg dL^{-1}). HOMA-IR, LDL-C/HDL-C, total cholesterol/HDL-C, and triglycerides/HDL-C ratios were also calculated. Biochemical parameters of serums were assessed using a photometric and ion-selective electrode (ISE) determinations principle Roche Cobas c 501 (Roche Diagnostics GmbH, Germany) autoanalyser machine; hormones such as ferritin and fasting insulin were analysed by an electrochemiluminescence (ECL) based Roche Cobas e 601 (Roche Diagnostics GmbH, Germany) immunoassay analysis machine. All serum samples were collected with gel collection tubes.

2.4. Statistical analysis

All data were analysed using IBM SPSS Statistics 23.0 (Statistical Package for Social Sciences) package program (IBM Corp., 2015). Individuals' dietary assessments were analysed using Ebispro for Windows, Stuttgart, Germany; Turkish Version (BeBiS 8.1) computer package program (Ebispro für Windows, 2017). Insulin resistance was calculated by HOMA-IR equation. *P*-value less than 0.05 (≤5%) was considered statistically significant, with the confidence interval of 95% CI. The power of the study was calculated using G-Power data program, and it was found 93.40% by a 95% CI. The data distribution was evaluated using Kolmogorov–Smirnov test, and the abnormal data were normalised by logarithm. Results were expressed as mean ± SD and categorical variables were expressed as a percentage. Differences between two groups were analysed using Independent Samples *t*-test when the values were parametric; for non-parametric results, differences were analysed using Mann-Whitney U test. Serum ferritin values were sorted from small to large and divided into four quartiles of 25% by Post-hoc Tukey's test, and when serum ferritin was <65.0 $\mu g\,L^{-1}$, it was classified into Q1 (quartile 1), 65.0–154.6 $\mu g\,L^{-1}$ was classified into Q2, 154.6–290.6 $\mu g\,L^{-1}$ was classified into Q3, and >290.6 $\mu g\,L^{-1}$ was classified into Q4. Differences between quartiles were calculated using One-Way ANOVA for parametric values and Kruskal–Wallis test for non-parametric values. Post-Hoc tests were used for finding out which groups were significant. Evaluation for cross tables was analysed by both Pearson Chi-square test and Fisher's Exact Chi-square test. Correlations between the values were analysed using Pearson correlation coefficient for parametric values and Spearman correlation coefficient was used for non-parametric values. Statistically significant groups were given as α-ρ groups through the tables as symbols and shown with bold characters.

3. RESULTS AND DISCUSSION

This is a cross-sectional, observational single study that was conducted with the participation of 103 individuals, 59 male and 44 female participants. Male participants had higher educational levels and lower cardiovascular disease duration than female participants. Age was 52.9 ± 10.1 for males and 51.6 ± 11.7 for females; the average age was 52.3 ± 10.8 years.

Table 1 shows lipid profile of patients classified into groups of serum ferritin levels. In male participants, there was a statistically significant difference in serum total cholesterol levels in $Q2^{(\alpha)}$ group (177.1 ± 39.7 mg dL^{-1}, $P < 0.001$) and Q2 values were higher than total cholesterol levels among all groups; the result was analysed using a post-hoc test. HDL-C levels were found the lowest in $Q4^{(\alpha)}$ group (24.7 ± 7.7 mg dL^{-1}, $P < 0.001$) among all quartile groups of male participants. In female participants, there was statistically significant difference between α-ρ groups in total cholesterol (mg dL^{-1}) and HDL-C (mg dL^{-1}) levels, which were higher in α groups (198.9 ± 37.5 mg dL^{-1} for total cholesterol, 45.9 ± 16.4 mg dL^{-1} for HDL-C, $P < 0.001$) analysed using post-hoc test. There was statistically significant difference in LDL-C/HDL-C ratio ($P < 0.001$) in female participants, but quartiles were not different among all groups in post-hoc test.

Table 2 shows the blood glucose parameters of patients in ferritin quartile groups. There was statistically significant difference in HOMA-IR in male participants among all groups; however, there were no different quartile groups in post-hoc analysis ($P < 0.001$).

Table 1. The lipid profile of patients in ferritin quartiles according to gender

	Ferritin quartiles (μg L^{-1})				
Men	Q1 (n:25) $\bar{x} \pm SS$ (n:5)	Q2 (n:26) $\bar{x} \pm SS$ (n:19)	Q3 (n:26) $\bar{x} \pm SS$ (n:18)	Q4 (n:26) $\bar{x} \pm SS$ (n:17)	*P*
Triglycerides (mg dL^{-1})	84.2 (99.0)	182.5 (69.1)	127.4 (80.7)	128.9 (102.3)	0.309
Total cholesterol (mg dL^{-1})	164.9 ± 55.4	**177.1 ± 39.7$^{\alpha}$**	142.0 ± 40.1	138.5 ± 34.8	**0.020**
HDL-C (mg dL^{-1})	36.1 (9.5)	38.4 (17.8)	33.6 (9.4)	**27.2 (6.8)$^{\alpha}$**	**0.000**
LDL-C (mg dL^{-1})	88.7 ± 30.8	98.0 ± 30.5	89.0 ± 53.9	109.1 ± 146.6	0.703
VLDL-C (mg dL^{-1})	16.8 (20.0)	36.5 (15.2)	25.3 (16.2)	25.2 (20.5)	0.366
Non-HDL-C (mg dL^{-1})	122.4 ± 60.6	136.9 ± 34.2	111.3 ± 38.8	112.2 ± 37.7	0.136
LDL-C/HDL-C	2.3 (0.1)	2.4 (1.3)	2.3 (1.9)	2.7 (1.4)	0.362
TC/HDL-C	3.6 (0.4)	4.5 (1.6)	4.1 (1.7)	4.8 (1.8)	0.119
TG/HDL-C	2.4 (1.0)	4.1 (3.4)	4.3 (3.2)	5.0 (6.0)	0.058
Women	(n:20)	(n:7)	(n:8)	(n:9)	
Triglycerides (mg dL^{-1})	216.9 (172.5)	205.2 (100.5)	196.5 (256.4)	244.9 (146.5)	0.588
Total cholesterol (mg dL^{-1})	**198.9 ± 37.5$^{\alpha}$**	156.3 ± 19.4	178.6 ± 71.9	**145.2 ± 31.9$^{\rho}$**	**0.014**
HDL-C (mg dL^{-1})	**47.0 (18.8)$^{\alpha}$**	41.4 (17.7)	29.9 (20.2)	**23.3 (18.0)$^{\rho}$**	**0.005**
LDL-C (mg dL^{-1})	101.2 ± 38.1	81.5 ± 16.1	98.7 ± 41.1	74.9 ± 26.4	0.477
VLDL-C (mg dL^{-1})	39.5 (28.3)	41.1 (20.1)	39.3 (51.3)	35.6 (33.0)	0.861
Non-HDL-C (mg dL^{-1})	154.3 ± 41.4	117.4 ± 21.0	147.3 ± 61.5	119.3 ± 29.1	0.088
LDL-C/HDL-C	2.1 (1.2)	2.4 (1.0)	3.4 (1.0)	2.4 (2.0)	0.043
TC/HDL-C	4.3 (2.5)	4.1 (1.9)	5.9 (1.2)	5.2 (5.5)	0.108
TG/HDL-C	4.5 (7.5)	6.5 (5.0)	9.5 (8.9)	10.1 (7.8)	0.186

Kruskal-Wallis test; One-way ANOVA test; LDL-C/HDL-C: LDL-cholesterol/HDL-cholesterol ratio; TC/HDL-C: total cholesterol to HDL-cholesterol ratio; TG/HDL-C: triglyceride to HDL-cholesterol ratio; Nonparametric values are given as Median (IQR).
$^{\alpha}$: Statistically significant difference among other quartiles.
$^{\alpha\text{-}\rho}$: Statistically significant difference among α-ρ groups.

Table 3 indicates the dietary intake of the patients in ferritin quartiles. As can be seen in the table, there was statistically significant difference between ferritin quartiles and dietary proteins (g), dietary cholesterol (mg), and dietary vitamin C (mg), zinc (mg), and iron (mg) intakes ($P < 0.05$). The difference between Q1 and Q4 quartiles in proteins (g), cholesterol (mg), zinc (mg), and iron (mg) intakes was also statistically significant in post-hoc analysis (between α-ρ groups). A statistically significant difference was also found between Q3 and Q4 groups in dietary vitamin C intake (mg) in post-hoc analysis ($P < 0.05$).

Table 4 indicates the correlation between energy and nutrient intake and serum ferritin levels in presence of IR in patients. There was a positive relationship between magnesium intake ($r = 0.247$, $P < 0.05$) in IR group. A positive relationship was found between saturated fatty acid intake ($r = 0.378$, $P < 0.05$) and zinc in serum ferritin levels ($r = 0.388$, $P < 0.05$) in non-IR group. In total, there was a positive relationship between serum ferritin levels and cholesterol ($r = 0.196$, $P < 0.05$), saturated fatty acid intake ($r = 0.289$, $P < 0.05$), magnesium intake ($r = 0.195$, $P < 0.05$), and zinc intake ($r = 0.261$, $P < 0.05$).

In the Turkish TEKHARF study, of the highest CRP levels, hazard ratio (HR) for cardiovascular diseases are 1.62 for men, and 2.59 for women (Onat et al., 2017). In MESA study, every

Table 2. The blood glucose parameters of patients in quartiles of ferritin according to gender

	Ferritin quartiles (μg L^{-1})				
	Q1 (n:25) $\bar{x} \pm SS$	Q2 (n:26) $\bar{x} \pm SS$	Q3 (n:26) $\bar{x} \pm SS$	Q4 (n:26) $\bar{x} \pm SS$	*P*
Men	*(n:5)*	*(n:19)*	*(n:18)*	*(n:17)*	
Fasting plasma glucose (mg dL^{-1})	152.7 ± 57.0	167.1 ± 2.3	183.6 ± 76.7	214.8 ± 86.2	0.196
Postprandial plasma glucose (mg dL^{-1})	184.4 ± 59.3	179.6 ± 92.7	196.4 ± 93.5	229.9 ± 95.6	0.235
Fasting insulin (μU mL^{-1})	23.8 ± 36.8	6.9 ± 4.6	10.7 ± 6.2	14.5 ± 13.6	0.224
HOMA-IR	7.3 ± 9.5	2.9 ± 2.4	5.1 ± 3.8	9.3 ± 8.5	**0.015**
HbA1c (%)	8.3 ± 1.7	8.2 ± 2.9	9.0 ± 2.4	10.3 ± 2.2	0.103
Women	*(n:20)*	*(n:7)*	*(n:8)*	*(n:9)*	
Fasting plasma glucose (mg dL^{-1})	179.2 ± 78.1	245.2 ± 73.7	213.9 ± 92.2	226.3 ± 83.2	0.193
Postprandial plasma glucose (mg dL^{-1})	216.3 ± 75.8	227.0 ± 58.2	181.4 ± 70.7	234.6 ± 61.4	0.310
Fasting insulin (μU mL^{-1})	12.9 ± 10.9	13.2 ± 8.0	5.5 ± 2.8	10.9 ± 9.8	0.157
HOMA-IR	6.6 ± 6.4	7.8 ± 4.5	3.9 ± 3.0	8.6 ± 7.9	0.369
HbA1c (%)	9.8 ± 2.8	10.8 ± 2.4	10.9 ± 1.8	10.4 ± 2.7	0.703

One-way ANOVA test.

Table 3. The dietary intake of patients in quartiles of ferritin

	Ferritin quartiles (μg L^{-1})				
	Q1 (n:25) $\bar{x} \pm SD$	Q2 (n:26) $\bar{x} \pm SD$	Q3 (n:26) $\bar{x} \pm SD$	Q4 (n:26) $\bar{x} \pm SD$	*P*
Energy (kcal)	2,221.7 ± 665.1	2,347.8 ± 544.5	2,499.5 ± 792.8	2,486.2 ± 646.7	0.412
Proteins (g)	**86.3 ± 22.3$^{\rho}$**	95.0 ± 26.7	97.7 ± 32.4	**106.6 ± 25.5 $^{\alpha}$**	**0.042**
Fats (g)	101.5 ± 35.0	104.1 ± 37.4	107.2 ± 33.4	113.0 ± 37.2	0.677
Cholesterol (mg)	**305.3 ± 133.2 $^{\rho}$**	395.5 ± 210.7	344.8 ± 127.0	**519.2 ± 489.3 $^{\alpha}$**	**0.045**
Saturated fatty acids (E%)	13.0 ± 3.5	14.8 ± 6.7	14.7 ± 3.7	16.1 ± 3.6	0.122
Monounsaturated fatty acids (E%)	13.1 ± 3.5	13.6 ± 4.1	13.8 ± 3.1	14.7 ± 3.2	0.446
Polyunsaturated fatty acids (E%)	5.1 ± 2.0	5.1 ± 1.7	5.0 ± 2.1	5.0 ± 1.7	0.813
Carbohydrates (g)	232.2 ± 79.9	249.9 ± 88.0	276.9 ± 119.5	253.7 ± 82.7	0.536
Dietary fibre (g)	24.8 ± 5.5	24.6 ± 7.2	28.7 ± 10.4	26.0 ± 6.6	0.319
Vitamin C (mg)	101.5 (44.4)	96.4 (59.5)	**118.4 (45.5)$^{\rho}$**	**84.4 (40.8) $^{\alpha}$**	**0.004** ^{f}
Zinc (mg)	**11.6 ± 3.2 $^{\rho}$**	12.8 ± 3.4	13.4 ± 4.7	**14.8 ± 4.1 $^{\alpha}$**	**0.046**
Iron (mg)	**11.5 ± 2.3 $^{\rho}$**	11.6 ± 3.0	12.3 ± 4.1	**13.5 ± 4.8 $^{\alpha}$**	**0.050**

^{f}: Kruskal-Wallis test.

$^{\alpha\text{-}\rho}$: Statistically significant difference among α-ρ groups. E%: percentage of energy intake.

Table 4. The correlation between energy and nutrient intakes and serum ferritin levels in presence of insulin resistance (IR)

	Serum ferritin (μg L^{-1})					
	With IR (n:68)		Without IR (n:35)		Total (n:103)	
	r	*P*	*r*	*P*	*r*	*P*
Energy (kcal)	0.181	0.140	0.114	0.516	0.157	0.113
Proteins (E%)	0.186	0.129	0.047	0.789	0.147	0.139
Fats (E%)	−0.062[h]	0.617	0.079[h]	0.651	−0.016[h]	0.872
Cholesterol (mg)	0.122	0.322	0.312	0.068	0.196	**0.048**
Saturated fatty acids (g)	0.248	**0.041**	0.378	**0.025**	0.289	**0.003**
Carbohydrates (E%)	0.031	0.799	−0.087	0.618	0.000	0.998
Dietary fibre (g)	0.083	0.501	0.031	0.861	0.065	0.516
Vitamin B_{12} (mcg)	0.130[h]	0.292	0.278[h]	0.105	0.185[h]	0.061
Calcium (mg)	0.194	0.113	0.073	0.678	0.155	0.118
Magnesium (mg)	0.247	**0.042**	0.137	0.432	0.195	**0.049**
Iron intake (mg)	0.114	0.356	0.183	0.292	0.138	0.166
Zinc (mg)	0.190	0.121	0.388	**0.021**	0.261	**0.008**
Potassium (mg)	0.144	0.240	−0.102	0.559	0.046	0.645
Folate (mcg)	0.174	0.156	0.030	0.865	0.122	0.220

[h]: Spearman correlation; E%: percentage of energy intake.

1.16 unit increase in CRP levels increased the incidence of chronic heart failure by 1.41 times in exclusion of other risk factors (Bahrami et al., 2008). In NHANES 2014, mean of systolic blood pressure was found 131.2 mmHg and the mean of diastolic blood pressure was found 68.6 mmHg in hyperglycaemic patients, and these were similar to our study (Bancks et al., 2019). In patients with blood pressure higher than 130/85 mmHg, hazard ratio for chronic heart failure was found 2.66 in MESA study (Bahrami et al., 2008). However, blood pressure values obtained in the current study were found similar to the findings of a study on the patients with CVD (cardiovascular disease) in Luxemburg (Alkerwi et al., 2019).

Jackson Heart Study found statistically significant results with serum ferritin and HDL-C, LDL-C, and total cholesterol levels, and the findings of this study are also consistent with our results. Modelling shows an increase in ferritin quartiles, resulting in increased risk of cardiovascular diseases and stroke (Egbuche et al., 2017). In the Singapore Chinese Health Study, ALT, HDL-C, and hs-CRP levels significantly higher within increased ferritin levels and positively associated with type 2 DM (Wang et al., 2017). Serum ferritin levels are associated with hs-CRP and metabolic syndrome (Ramesh et al., 2018), in ARIC cohort study, models were made on non-anaemic individuals and adjusted factors were age, gender, and race; hazard ratio (HR) for women with high serum ferritin (women >200 ng mL^{-1}, men >300 ng mL^{-1}) was found 2.15 (Silvestre et al., 2017). In a study, odds ratio (OR) for myocardia risk factors such as high serum ferritin levels (>200 μg L^{-1}) and myocardia infarct (MI) were found 5.72; type 2 diabetes and MI were found 7.64 (Holay et al., 2012). In another study, high serum ferritin levels were found associated with ALT, AST, haemoglobin, TIBC, serum iron, and direct bilirubin, and this relationship was found to be caused by inflammatory characteristics by ferritin, and hyperferritinaemia caused NASH and high ferritin levels caused the secretion of inflammatory

cytokines such as TNFα, IL-1ß, NFκB and led to oxidative stress, resulting in the onset of NASH pathogenesis, steatosis, and lipotoxicity (Kowdley et al., 2012). Quebec Cardiovascular Study found LDL-C/HDL-C and TC/HDL-C ratio higher in patients who were obese, hyperinsulinaemic and hypertriglyceridaemic, and reported that it could be used as a cardiovascular risk factor (Lemieux et al., 2001). Our study appears to be similar to their studies in terms of serum ferritin levels and higher serum lipid levels. This could be an inflammatory and oxidative process. Serum ferritin is an acute phase protein that shows inflammation since the patients had cardiovascular disease. This is also eligible for low HDL-C levels in both genders; the lowest HDL-C levels were found in Q4 group in both genders but it was not found in total cholesterol levels. In women, LDL-C/HDL-C ratio was found to be significantly different between quartiles, although it was not supported by post-hoc analysis; Q4 groups had higher ratio. Total cholesterol was expected to be higher in Q4, but no such result was obtained; the reasons for this could be a decrease of HDL-C in Q4 groups, and LDL-C and VLDL-C showed no change.

Our study hypothesised that dietary intake of iron would cause the elevation of serum ferritin levels and that would lead to oxidative stress and oxidation processes. We found in our study that dietary iron intake along with dietary protein, cholesterol, and zinc intakes were higher in Q4 and that was statistically significant ($P < 0.05$). In KNHANES study, they assorted postmenopausal female participants into 4 ferritin quartiles and found that protein intake and vitamin C intake were lower in Q4 (Ju and Ha, 2016). MESA study suggests that decrease in DASH diet score results in an increase in heart failure incidence. Vitamin C prevents LDL oxidation on sub-endothelia on CVD and preserves the reduction state of vitamin E and enhances the synthesis of NO- leads increasing in anti-oxidant capacity as well as preventing the cell apoptosis pathway of smooth muscle cells, inhibiting the damage of inflammatory cytokines (Honarbakhsh and Schachter, 2009). The data obtained by Seven Countries Study shows that intakes of saturated and dietary cholesterol were higher and intakes of vitamin C was lower in insulin resistance and type 2 DM groups, where there was no change in protein intake in normoglycemic groups (Feskens et al., 1995). In a study associating dietary pattern with cardiovascular incidents with factor analysis was found that a higher diet in sugar-sweetened beverages, red meats, cheese, and pastry increased the CVD incidence in 20 and cardiovascular mortality in 40 years (Menotti et al., 2012). Zinc, magnesium, and calcium have protective effects against cardiovascular disease and metabolic syndrome and increase HDL-C levels. Low intake of potassium is associated with a high incidence of metabolic syndrome. In the current study, higher serum ferritin levels are associated with higher dietary iron, protein, cholesterol, and zinc intake and lower intake of vitamin C. This could result from the fact that there is a higher intake of red meat and dairy and lower intake of fruits and vegetables in Gaziantep city (Türkiye Cumhuriyeti Sağlık Bakanlığı, 2017). As suggested by our study, not only dietary iron intake but also higher protein intake (86.34 g in Q1, 106.63 in Q4) and cholesterol intake (305.38 in Q1, 519.26 in Q4) both with low vitamin C intake (84.4 mg in Q4) could have led to an increase in serum ferritin and inflammatory cytokines levels. As the anti-inflammatory nutrient intakes were lower in those patients, inflammatory nutrient indices were higher.

The data obtained by KNHANES 2007–2008 revealed that serum ferritin levels positively correlated with fasting blood glucose, triglyceride, HOMA-IR levels and negatively correlated with HDL-C levels in both man and woman. The reason for this is that ROSs cause oxidative stress leading to ß cell dysfunction, insulin dysfunction, and insulin resistance, consequently

hyperinsulinaemia and oxidative stress caused by ROS production. Insulin resistance, serum ferritin levels, metabolic syndrome, and their relationship with CRP is prominent. CRP and serum ferritin levels, which are indicators of inflammation, were found positively related with insulin resistance and metabolic syndrome (Kang et al., 2012). A retrospective cohort study (Wright et al., 2020) showed risk factors for both type 2 DM and CVD, patients with type 2 DM and higher risk factors, 3 and more, were more correlated with cardiovascular disease incidents, HR for 2.27 for 5 risk factors and 1.80 for 4 risk factors. These data with our findings show that not only serum ferritin is leading to cardiovascular disease formation, but for patients with higher HOMA-IR levels and intact insulin resistance it is progresses the disease further.

On the other hand, a study in the USA revealed an opposite correlation between serum ferritin and TIBC levels (Kowdley et al., 2012). A study in Scottish adults showed that higher serum ferritin was associated with type 2 DM, CVD, and cerebrovascular diseases; fully adjusted modelling showed 1.59, 1.07, 1.36 HR, respectively (Suárez-Ortegón et al., 2022). These data show that serum ferritin is correlated mostly with type 2 DM and its complications, possibly relying on the insulin resistance mechanism. The data obtained from other countries show a strong relationship between serum ferritin levels and hyperlipidaemic blood lipid profile, although it should be considered that dietary intakes and dietary patterns may differ in various countries and variations could produce heterogeneous results. However, these data show a remarkable relationship between serum ferritin levels and hyperlipidaemic blood lipid profile in patients whose serum ferritin levels are 154.61 $\mu g\,L^{-1}$ and higher. Our study data supports these results, as this relationship was found in Q4 (>290.60 $\mu g\,L^{-1}$) among all quartiles, meaning we could consider the presence of this relationship under higher serum ferritin levels. However, confounding factors are still remaining, as there are some studies claiming that same serum ferritin levels are associated with lower cardiovascular risks, the underlying mechanism is not still certain.

4. CONCLUSIONS

In conclusion, we found a strong association between serum ferritin levels and inflammation; they are responsible for causing an oxidative stress, atherosclerosis and bringing along cardiometabolic diseases such as cardiovascular diseases and type 2 DM. Limitations for our study were the small sample size, so in the future more cohort studies with bigger sample size will be needed, most patients were receiving insulin treatment and using oral antidiabetics as drugs, dietary records were not correctly reported by patients, and this study design was only observational. Further studies should discuss a detailed dietary iron intake and serum iron levels, together with an anthropometric measurement such as BIA, and a detailed dietary record based on a dietary intervention study design.

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