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The Relation between Iron and Vitamin B12 Status with Coronary Artery Disease

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To investigate the association of iron and vitamin B12 status with coronary artery disease in Gaza city.
Study Design: A Case control study
Place and Duration of Study: Samples were collected from the cardiac unit at Al-Shifa hospital, Gaza Strip.
Methodology: Case-control study was conducted on a sample of 31 patients with coronary artery disease (CAD) and 27 apparently healthy controls aged between 30-60 years. Interviewed questionnaire was conducted among the study population. Vitamin B12, serum ferritin, serum iron, lipid profile parameters, and high sensitivity C reactive protein were performed. An approval was acquired from Helsinki ethical committee to perform this study. All data were analyzed by SPSS.
Results: The results showed that the mean level of serum iron in cases (71.6 ± 24.7 µg/dl) was lower compared to that of controls (87.3 ± 28.4 µg/dl) and the difference was statistically significant (*P*=.028). Moreover, transferrin saturation percentage in cases (24.0 ± 8.9%) was lower compared to controls (29.0 ± 9.9%) and the difference was statistically significant (*P*=.045). In addition, the

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mean levels of serum vitamin B12 in cases (238.8 ± 51.4 pg/dl) was lower compared to controls (337.3± 108.4 pg/dl) and was statistically significant (*P*<0.001). The Pearson correlation test showed that there was a significant positive correlation between the level of serum iron with the level of vitamin B12 among the participants (r = 0.28, *P*=.032).

Conclusion: The mean differences of transferrin saturation, serum ferritin, and vitamin B12 between cases and controls were statistically significant. The mean levels of serum vitamin B12 in cases was lower compared to controls and was statistically significant.

Keywords: Coronary artery disease; CAD; serum iron; vitamin B12; Gaza City.

ABBREVIATIONS

AUC : Area under the curve
BMI : Body mass index
CAD : Coronary artery disease
CVD : Cardiovascular disease
ECG : Electrocardiogram
FBG : Fasting blood glucose
HDL : High density lipoprotein
Hhcy : Hyperhomocysteinemia
hs-CRP : High sensitivity C reactive protein
LDL : Low density lipoprotein
ROC : Receiving operating curve
Tf : Transferrin
TGs : Triglycerides
TSAT : Transferrin saturation
χ^2 *: Chi-square.*

1. INTRODUCTION

Cardiovascular diseases (CVDs) form the most common cause of death globally, and is considered as an important life or death matter in all their forms. An estimated 17.9 million people died from CVDs in 2019, representing 32% of all global deaths [1]. CVD is still the leading cause of deaths in Palestine in a way that about 24.7% of total deaths were attributable to CVD in 2020 [2]. CAD is the most common cause of heart disease. The main cause is atherosclerosis in the coronary arteries leading to blood flow restriction to the heart [3].

Different risk factors have been associated with CVDs, some of these factors are modifiable such as sedentary lifestyle and smoking cigarettes, whereas others cannot be modified such as genetic composition. Furthermore, there are multiple risk factors for CVDs from the environment, including secondhand smoke, thirdhand smoke and other environmental pollutants such as air and noise pollution. The emerging risk factors for CADs include: inflammation and infection, high blood levels of homocysteine, atherogenic lipoprotein, fibrinogen, high triglycerides (TGs), iron overload and vitamin B deficiency in particular vitamin B6, B12, and folic acid [4-6].

Iron is particularly important for many physiological processes. It plays a key role in the maintenance of different cellular functions and mediates various metabolic processes. However, careful homeostasis is important for the human body [7]. Both iron deficiency and iron overload have been associated with increased cardiovascular morbidity and mortality. The evidence is strongest for heart failure: Hemochromatosis leads to cardiomyopathy. Iron deficiency has been associated with poor prognosis in heart failure patients even independently of anemia. Randomized controlled trials have demonstrated the beneficial effects of intravenous ferric carboxymaltose therapy in patients with heart failure with reduced ejection fraction [8,9]. The roles of iron deficiency and anemia in other areas of chronic CVDs, such as CAD require further investigation. Preliminary evidence suggests that iron deficiency and CAD have a detrimental association, and iron administration by any route can confer benefit [10].

A large number of studies have confirmed that hyper-homocysteinemia (HHcy) has been associated with endothelial dysfunction of atherosclerotic CAD owing to oxidative stress, endoplasmic reticulum stress, and involved inflammation [11-13]. Folic acid and vitamin B12 play an important role in regulating the metabolic process of Hcy [14]. A recent systematic review has shown that folic acid deficiency or/and vitamin B12 deficiency would result in Hhcy [15]. Vitamin B12 deficiency and HHcy are related to cardiovascular risk factors in patients with CAD [16].

Previous research studied the relation of homocysteine as a risk factor of CVD patients in Gaza Strip but they didn't attribute vitamin B12 and Iron status with CAD [17]. The present study aimed to investigate the association of iron and

vitamin B12 status in patients with CAD in Gaza city and compare them with those of control subjects. According to our knowledge, this study will be the first in Gaza on CAD patients that assesses the relationship between iron body status and vitamin B12 in patients with CAD.

2. MATERIALS AND METHODS

2.1 Study Design

The study was a retrospective case-control.

2.2 Study Population

The target population of this study consisted of patients presenting with CAD (case group) and apparently healthy adults (control group).

2.3 Sample Size and Sampling

A non-probability the study included 31 male cases (CAD) aged between 42-60 years registered in the cardiac unit at Al-Shifa hospital. 27 apparently healthy males without CAD history were randomly selected from the general population. Cases and controls were matched for age and health condition.

2.4 Eligibility Criteria

2.4.1 Inclusion criteria

Adult males aged between 30-60 years admitted to the cardiac unit at Al-Shifa hospital in Gaza city. The CAD cases were diagnosed at hospital, based on symptoms and Electrocardiogram (ECG) changes.

2.4.2 Exclusion criteria

To eliminate potential confounding factors, the following individuals were excluded from the study:

- Participants <30 years and >60 years.
- Patients having any acute or chronic illness (severe kidney disease requiring dialysis, thalassemia, hemochromatosis or malignancy).
- Participants who took supplements for iron and vitamin B12 for the last 5 months.

2.5 Data and Specimen Collection

A meeting interview was used to fill out a structural questionnaire designated for cases and controls to meet the study needs. The researcher interviewed all participants face to face. The researcher also explained the unclear questions to the participants during the interview. Most of the questions were dichotomous. The questionnaire included questions on personal information (age, height, and weight), socioeconomic character and medical history data.

Venous blood samples (5 ml) after twelve hours of fasting overnight were collected from 31 CAD patients and 27 healthy controls. The blood samples were placed into plain tubes allowing the blood to clot. Samples were centrifuged at 3000 rpm for 10 minutes to obtain serum for biochemical analysis. Biochemical analysis was performed using commercially available kits and involved the determination of different analytes including: serum iron, UIBC, total cholesterol, TGs, HDL, FBG and hs-CRP. Ferritin and Vitamin B12 were determined by using ELISA kits.

2.6 Statistical Analysis

Statistical Package for the Social Science (SPSS, version 22) was used for data processing and analysis. Data were normally distributed, as determined using Kolmogorox-Smirnov test. Description of quantitative variables were presented as the following: Normally distributed data were expressed as mean ± SD; description of qualitative variables was in the form of numbers (No.) and percent (%); comparison between quantitative variables was carried out by student T-test of two independent samples. Results were expressed in the form of P-values; comparison between qualitative variables was carried out by Chi-Square test (χ^2). Fisher exact test was used instead of Chi- square test when one expected cell or more were ≤ 5; binary correlation was carried out by Spearman correlation test.

Results were expressed in the form of correlation coefficient (R) and P-values. The following points are the accepted guidelines for interpreting the correlation coefficient: 0 indicates no linear relationship; +1 indicates a perfect positive linear relationship.

Receiver Operating Characteristic (ROC) curves were drawn for detection of reliability of markers as a diagnostic tool and their best cutoff values were calculated. area under the curve (AUC) was considered if > 0.60.

3. RESULTS

3.1 General Characteristics of the Study Population

The participants in the study were 58 persons from Gaza (31 cases "Patients with CAD" & 27 controls). Table 1 represents the general characteristics of the study population. The mean age of cases was 55.1 ± 5.9 years and 51.1 ± 11.1 years for controls (*P*=.09). The mean BMI of cases was 27.5 ± 4.5 while that of controls was 29.8 ± 9.2, the difference was not statistically significant. The percentage of cases and controls with university degree or higher was 45.1% & 59.3% and those with secondary certificate were 35.5% & 22.2% while those with primary school certificate or illiterate were 19.4% & 18.5%, respectively. There was no significant difference between cases and controls in educational level (*P*=.69). The percentage of cases and controls with monthly income less than 1000 NIS was 83.9% & 37.5%, 1000-2000 NIS was 12.9% & 42.5% and > 2000 NIS was 3.2% & 20.0%, respectively. The difference in monthly income was statistically significant between cases and controls (*P*<.001). 58.1% of the cases were smokers and 25.8% were ex-smokers, while most of the controls (77.8%) were not smokers and 11.1% were ex-smokers (*P*<.001).

3.2 Clinical Characteristics of the Study Population

Table 2 shows that the percentage of past family history of CAD was 48.4% in cases and 14.8% in controls (*P*=.007). 38.7% of the cases have hyperlipidemia, compared to 11.1% for the controls (*P*=.017). Regarding the family history of hyperlipidemia, 29.0% of the cases have family members with hyperlipidemia, compared to 0.0% for the controls (*P*=.002). On the other hand, 58.1% of the cases have hypertension, while 22.2% of the controls have hypertension (*P*=0.006).

3.3 Different Biochemical Parameters among the Participants

Table 3 shows that the mean level of serum iron in the cases (71.6 ± 24.7 µg/dl) was lower compared to that of controls (87.3 ± 28.4 µg/dl) and the difference was statistically significant (*P*=.028). Moreover, transferrin saturation percentage in cases (24.0 ± 8.9%) was lower compared to controls (29.0 ± 9.9%) and the difference was statistically significant (*P*=.045). Furthermore, there was a statistically significant difference in the levels of serum ferritin between cases (130.5 ± 64.4 ng/ml) and controls (76.0 ± 33.6 ng\ml) (*P*<.001). Additionally, the mean levels of serum vitamin B12 in male cases (238.8 ± 51.4 pg/dl) was lower compared to male controls (337.3 ± 108.4 pg/dl) and was statistically significant (*P*<.001). On the other hand, the mean levels of hs-CRP in cases (9.7 ± 10.5 mg/l) were higher compared to controls (3.7 ± 3.6 mg/l) and was statistically significant (*P*=.005). Moreover, there was a statistically significant difference in the levels of FBG between cases (119.2 ± 62.1 mg/dl) and controls (92.7 ± 18.9 mg/dl) (*P*=.030).

3.4 Lipid Profile Levels among Male Participants

Table 4 represents that the difference in the means of cholesterol, HDL and LDL was significantly different between cases and controls (*P*=.036, .013 & .008), respectively. The cholesterol (176.5 ± 24.6 mg/dl) & LDL (93.7 ± 25.7 mg/dl) mean levels in cases were lower compared to those of controls (195.9 ± 40.6 mg/dl) & (118.7 ± 40.3 mg/dl), respectively. On the other hand, there was no statistically significant difference in the levels of TGs between cases (161.9 ± 72.6 mg/dl) and controls (152.7 ± 46.7 mg/dl) (*P*=.575). Additionally, the mean of serum HDL in cases (50.5 ± 2.7 mg/dl) was higher compared to that of controls (48.4 ± 3.5 mg/dl) and was statistically significant (*P*=.013).

3.5 Correlation between iron profile, vitamin B12, hs-CRP and different biochemical parameters among the participants

Table 5 shows that there was a weak positive correlation between the level of serum iron with the level of vitamin B12 among the participants (r = 0.28, *P*=.032). Also, there was a weak positive correlation between the level of vitamin B12 with the levels of transferrin saturation (r = 0.29, *P*=.029), Cholesterol (r = 0.27, *P*=.043) and LDL (r = 0.29, *P*=.027) among the participants.

Additionally, there was a moderately strong negative correlation between the level of hs-CRP with the levels of serum iron (r = -0.48, *P*<.001) and transferrin Saturation (r = -0.45, P<0.001) among the participants. Also, there was a moderately strong positive correlation between the level of hs-CRP with the levels of serum

ferritin (r = 0.46, *P*<.001) and FBG (r = 0.59, *P*<.001) among the participants.

3.6 Receiving operating curve of serum concentration of iron, vitamin B12 and ferritin for identification of patients destined to develop CAD compared to control

The AUC for serum vitamin B12 was significantly different from 0.5 (AUC representing no discrimination, *P*<.001). The mean and 95% confidence interval of the AUC was 0.790 (0.668-0.912), and the cut-off value was 284.5 pg/dl for vitamin B12, representing a specificity of 84% and a sensitivity of 30%. (Fig 1; Table 6).

The AUCs for serum ferritin (0.756 (0.632-0.879); cut- off 92.6 ng/ml), was also significantly different (*P*<0.001) from the AUC of 0.5 (Fig. 2; Table 6). While the AUC for serum iron (0.648 (0.505-0.790); cut- off 86.5 µg/dl) was insignificantly different (*P*=0.054) from the AUC of 0.5 (Fig. 1; Table 6).

The cut-off values established by the ROC analyses were used to define low vitamin B12, low serum iron, and high serum ferritin.

4. DISCUSSION

Coronary artery disease is continued to be the first cause of death in the world and also in Palestine. CAD is a multi-factorial disease, resulting from the conjunction of genetical and environmental factors. The present study investigated the associations between iron and vitamin B12 status with CAD in Gaza city.

In our study, the mean levels of serum iron and transferrin saturation in patients with CAD was significantly lower compared to that of controls. In accordance with the present results, Kervinen et al. suggested an association between low serum iron level and coronary risk. They stated that the association is not independent, but is related to the fact that chronic infections and inflammation are accompanied with low serum iron [18]. In addition, other studies demonstrated an inverse association of serum iron or transferrin saturation and CAD [19,20]. On the other hand, our results were inconsistent with Pourmoghaddas et al. who found that there is no statistically significant difference in serum iron levels and mean difference of transferrin saturation between cases with CAD and controls [21].

The results of the present study showed that the concentration of ferritin as an indicator of iron status was significantly higher in patients with CAD in comparison with controls (*P*<.001). Our finding was consistent with Pourmoghaddas et al. who indicated that high iron store, as assessed by serum ferritin, was associated with the increased risk of CAD [21]. The iron-heart disease hypothesis rests on the supposition that high body iron burdens are a risk factor for increased oxidative stress, and oxidative stress is a risk factor for chronic diseases such as heart disease. In a recent study among patients with CVD, the presence of CVD was associated with higher mean of serum ferritin [22].

Additionally, a recent systematic review suggested that there is a negative association of transferrin levels and CAD with high transferrin saturations being associated with a lower risk of CAD. There was also a negative association of serum iron and CAD. While, there was no significant association between the other markers of iron status and CAD [23].

As indicated in the present study, there was a significant decrease in the mean levels of vitamin B12 among cases compared to controls (*P*<.001). This means that the lower level of vitamin B12 may be linked to CAD. Consistent with our findings, studies done by Kamble et al., and Sadeghian et al. reported a significant decrease in vitamin B12 in CAD patients when compared with healthy controls [24,25]. Inconsistent to our finding, Vanuzzo D et al., and Pancharuniti et al. observed that the serum level of vitamin B12 were not significantly different between patients and controls [26, 27].

On the other hand, the results show that there was a significant negative correlation (*P*<.001) between the level of hs-CRP with the level of serum iron and transferrin saturation among the participants. Our results are in agreement with Ponikowska et al. study who showed that low transferrin saturation among males was associated with high serum hs-CRP, linear relationship [28].Our results are also in agreement with Ekblom et al. who found that hs-CRP has a significant negative correlation with plasma iron and transferrin iron saturation among males and females [29]. In contrast, the results don't agree with the result of Eftekhari et al. who reported that there was a signficant positive correlation between hs-CRP and serum iron among males [22].

Table 1. General characteristics of the study population

Characteristics		Categories		*P*-value
		Cases n (31)	Controls n (27)	
Age (years)	Mean ± SD (min-max)	55.1 ± 5.9 (42-60)	51.1 ± 11.1(38-60)	0.09
Weight (kg)		84.7 ± 12.0(65-110)	85.1 ± 20.1(60-118)	0.93
Height (cm)		176.0 ± 9.0 (160-196)	166.5 ± 30.9 (150-188)	0.11
BMI (Kg/m^2)		27.5 ± 4.5 (18.8-38.1)	29.8 ± 9.2 (18.9-52.4)	0.22
Educational Level	n (%)			0.69
Illiterate & Primary Education		6 (19.4)	5 (18.5)	
Secondary		11 (35.5)	6 (22.2)	
University or higher		14 (45.1)	16 (59.3)	
Monthly Income (USD)				< 0.001
<300		26 (83.9)	11 (37.5)	
300-600		4 (12.9)	12 (42.5)	
>600		1 (3.2)	4 (20.0)	
Smoking				< 0.001
Smoker		18 (58.1)	3 (11.1)	
non-smoker		5 (16.1)	21 (77.8)	
Ex-smoker		8 (25.8)	3 (11.1)	

Table 2. Clinical characteristics of the study population

Variables		Categories		*P*-value
		Cases (31) n (%)	Controls (27) n (%)	
Family History of CAD	Yes	15 (48.4)	4 (14.8)	0.007
	No	16 (51.6)	23 (85.2)	
	Total	31 (100.0)	27 (100.0)	
Hyperlipidemia	Yes	12 (38.7)	3 (11.1)	0.017
	No	19 (61.3)	24 (88.9)	
	Total	31 (100.0)	27 (100.0)	
Family history of hyperlipidemia	Yes	9 (29.0)	0 (0.0)	0.002
	No	22 (71.0)	27 (100.0)	
	Total	31 (100.0)	27 (100.0)	
Hypertension	Yes	18 (58.1)	6 (22.2)	0.006
	No	13 (41.9)	21 (77.8)	
	Total	31 (100.0)	27 (100.0)	

CAD: Coronary artery disease

Table 3. The mean of different biochemical parameters among participants

Variables	Cases (31) Mean ± SD	Controls (27) Mean ± SD	*P*-value
Serum iron (µg/dl) (Min-Max)	71.6 ± 24.7 (14.8 - 117.0)	87.3 ± 28.4 (38.0 -152.0)	0.028
TSAT (%) (Min-Max)	24.0 ± 8.9 (3.7-39.1)	29.0 ± 9.9 (10.0-46.0)	0.045
Serum ferritin (ng/ml) (Min-Max)	130.5 ± 64.4(21.6-285.0)	76.0 ± 33.6 (12.0-143.0)	<0.001
Vitamin B12 (pg/dl) (Min-Max)	238.8 ± 51.4(150.3-328.9)	337.3 ± 108.4 (133.0-610.0)	<0.001
hs-CRP (mg/L) (Min-Max)	9.7 ± 10.5(0.5-33.0)	3.7 ± 3.6 (0.8-17.1)	0.005
FBG (mg/dL) (Min-Max)	119.2 ± 62.1(71.0-329.0)	92.7 ± 18.9 (75.0-172.0)	0.030

FBG: fasting blood glucose; hs-CRP: high sensitivity C reactive protein; TSAT: transferrin saturation

Table 4. The mean levels of lipid profile among male participants

Variables	Cases (31)	Controls (27)	*P*-value
	Mean ± SD	Mean ± SD	
Cholesterol (mg/dl) (Min-Max)	176.5 ± 24.6 (145.0-240.0)	195.9 ± 40.6 (128.0-274.0)	0.036
TGs(mg/dl) (Min-Max)	161.9 ± 72.6 (88.0-470.0)	152.7 ± 46.7 (84.0-250.0)	0.575
HDL (mg/dl) (Min-Max)	50.5 ± 2.7 (46.0-55.0)	48.4 ± 3.5 (40.0-54.0)	0.013
LDL (mg/dl) (Min-Max)	93.7 ± 25.7 (48.0-162.0)	118.7 ± 40.3 (56.8-200.0)	0.008

HDL: High density lipoprotein; LDL: Low density lipoprotein; TGs: Triglycerides

Table 5. Correlation between iron profile, vitamin B12, hs-CRP and different biochemical parameters among the participants

Variables	Serum iron		Vitamin B12		hs-CRP	
	r	*P*-value	r	*P*-value	r	*P*-value
Serum iron	-	-	0.28	0.032	-0.48	<0.001
Tf Saturation	0.98	<0.001	0.29	0.029	-0.45	<0.001
Serum ferritin	-0.26	0.048	-0.26	0.053	0.46	<0.001
Vitamin B12	0.28	0.032	-	-	-0.25	0.062
hs-CRP	-0.48	<0.001	-0.25	0.062	-	-
Cholesterol	0.22	0.098	0.27	0.043	-0.09	0.521
TGs	0.04	0.755	0.01	0.960	-0.07	0.601
HDL	-0.20	0.131	-0.16	0.227	0.01	0.916
LDL	0.23	0.077	0.29	0.027	-0.08	0.573
FBG	-0.17	0.214	-0.08	0.567	0.59	<0.001

FBS: Fasting blood glucose; HDL: High density lipoprotein; hs-CRP: High-sensitivity C-Reactive Protein; LDL: Low density lipoprotein; Tf: Transferrin; TGs: Triglycerides

Table 6. Receiving operating curve (ROC) curve of serum concentration of iron, vitamin B12 and ferritin for identification of patients destined to develop CAD compared to control

Variables	Cut-off value	Sensitivity %	Specificity %	AUC	95% CI	*P*-value
Serum iron (µg/dl)	86.5	74.2	44.0	0.648	0.505-0.790	0.054
Vitamin B12 (pg/dl)	284.5	84.0	30.0	0.790	0.668-0.912	0.001
Serum Ferritin (ng/ml)	92.6	64.5	22.2	0.756	0.632-0.879	0.001

AUC; area under the curve

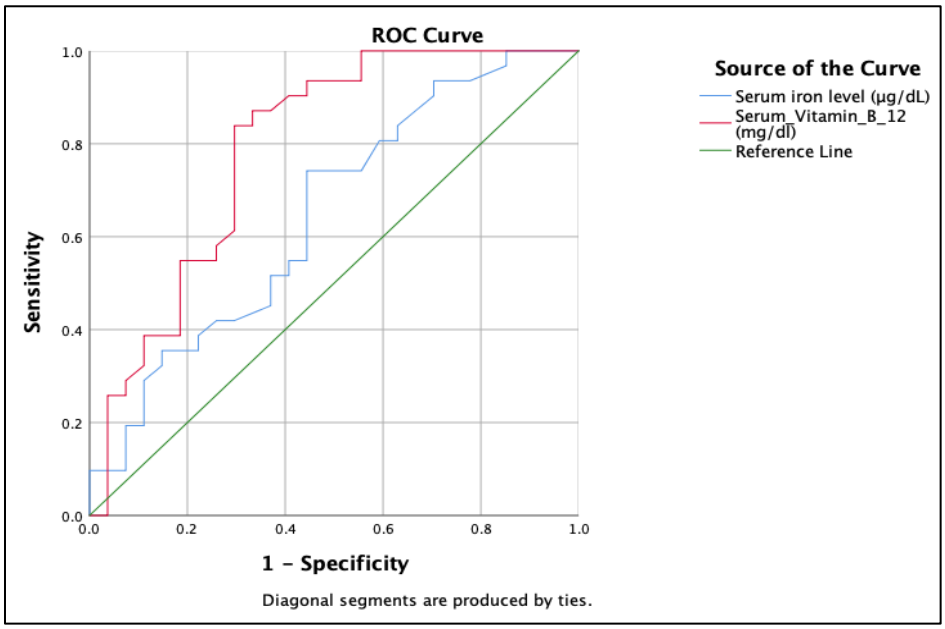

Fig. 1. ROC curves of serum iron, and vitamin B12 applied in predicting CAD. Serum iron level

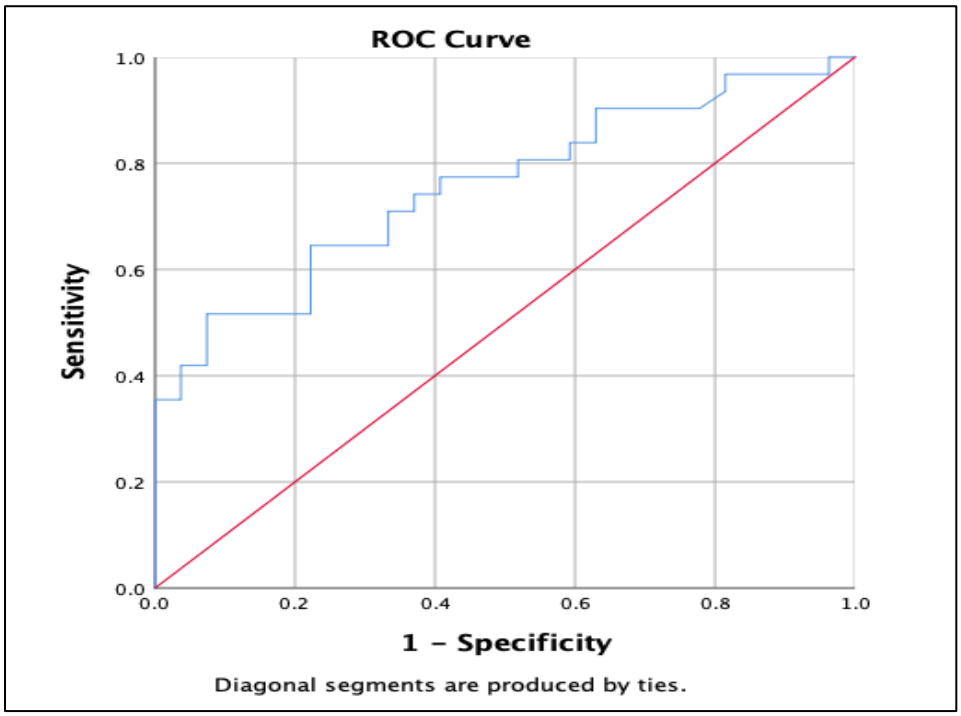

Fig. 2. ROC curves of serum ferritin applied in predicting CAD

Furthermore, there was a significant positive correlation (*P*< .001) between the level of hs-CRP with the levels of Ferritin among the participants. The result agrees with Eftekhari et al. study who reported that when the serum ferritin concentration was used as an independent variable, participants with higher level of ferritin had a higher concentration of CRP [22].

In the present study, ROC curve analysis indicated that the optimum cut off value in patients with CAD versus non-CAD for vitamin B12 was ≤284.5 pg/dl (84% sensitivity and 30% specificity). In addition, the results showed that the serum level of Ferritin ≥92.6 ng/ml, had moderate values (AUC= 0.756) when applied in predicting CAD with 64.5% sensitivity and 22.2% specificity.

5. CONCLUSIONS

The debate is still ongoing on 'whether serum iron and vitamin B12 can act as an independent marker for cardiovascular disease, or it simply results from the synergistic effects of other known cardiovascular risk factors. The major finding of this study is that the mean differences of serum iron, transferrin saturation, serum ferritin, and vitamin B12 between cases and controls were statistically significant. The mean levels of serum vitamin B12 in cases was lower compared to controls and was statistically significant. The decreased levels of vitamin B12 may be associated with higher risk of CAD. Thus, it is urgent to develop appropriate treatment guidelines for vitamin B12 deficiency.

6. LIMITATIONS

The limitations of the present study included: patients were enrolled from Al-Shifa hospital only; therefore, the sample size was small and localized only to a specific region. Hence, any future studies revolving around the same topic should include a greater number of hospitals to better generalize the data. In addition to this, sample collection was relatively difficult due to the objection of many patients to participate. Furthermore, our study did not highlight the different categories of CAD in patients. Finally, lack of resources including budget and facilities limited time because of the nature of researcher work.

7. RECOMMENDATIONS

The following recommendations are suggested: launching of health education programs on smoking, obesity, and diabetes mellitus are recommended to decrease the risk of CAD; further research should be carried out to understand the role of iron in the pathogenesis mechanism of CAD with a larger sample size to elucidate the preventive and therapeutic approaches for proper management of CAD; sample should be drawn serially at definite intervals in high-risk patients and tested for lipid profile and serum ferritin levels and the roles of regular administration of vitamin B12 supplementation in cardiac patients needs to be confirmed in additional studies.

CONSENT

Informed consent was taken from all participants who accepted to participate in the study after well explanation of the procedures and objectives and considerations beyond the study.

ETHICAL APPROVAL

An approval to perform the study was taken from the Palestinian Ethical Committee (Helsinki Ethics Committee) (PHRC/HC/388/18).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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