Evaluation of Fetuin-A and Insulin Resistance among Iraqi Type 2 Diabetic Patients with and without Ischemic Heart Disease

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ABSTRACT

Background: Diabetes mellitus (DM) is a metabolic disorder in which hyperglycemia is a characteristic feature due to impairment in insulin secretion, defective insulin action, or both reasons. One long-term complication is the ischemic heart disease (IHD) which is a major cause of morbidity and mortality. Insulin and fetuin-A are hormones that play a role in glucose metabolism regulation. Insulin is responsible for regulating glucose passage to the cells, while fetuin-A blocks insulin binding to its receptor, which is linked to insulin resistance in metabolic syndrome. Higher fetuin-A level patients have 4 times greater risk of developing IHD compared to patients with lower fetuin-A levels. Studies found that both hormones participate in the development of T2DM and IHD, beside their role in the pathophysiology of metabolic syndrome.

Aim of the study: Evaluate serum fetuin-A concentrations in type2 diabetic (T2D) patients with and without IHD and compare them with healthy individuals. Assess serum glucose, insulin levels, and HOMA-IR in T2D patients and IHD and compare them with healthy individuals.

Subjects and Methods: A case control study, that included 120 patients (60 have T2DM with IHD and 60 having T2DM without IHD age ranged from 30 to 70 years patient, who attended Al-Yarmouk Teaching Hospital and Iraqi Center for Myocardial Infarction, Medical City Hospital, Baghdad during the period from November 2020 until February 2021 and compare result with 60 healthy control which age ranged from 30 to 70 years. Female: male ratio is almost 1:1 in the three studied groups. The diagnosis of MI is based on medical reports, laboratory, and clinical tests for heart disease. Patients with neuropathy, retinopathy, thyroid dysfunction and liver diseases were excluded from the study. BMI, FBS, serum insulin, HOMA-IR, and fetuin-A were measured or calculated for each participant.

Result: a statistical difference in BMI between participants is found; 46.70% of T2DM in the IHD group are obese. No significant association between disease duration and development of IHD is found. All the included markers showed statistical differences in mean ± SD between the diabetic and control group; fetuin-a mean ± SD level was 27.63 13.31, 12.39 ± 5.61 and 9.93 ± 5.1 in T2DM with IHD, T2DM without IHD and control group, respectively. There was no statistical association between the markers and fetuin-A except a moderate positive correlation with insulin.

Conclusion: Fetuin-A can be used as a predictor of IHD development in diabetic patients.

Keywords: Diabetes mellitus type 2, Fetuin-A, IHD, Insulin resistance.

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder in which hyperglycemia is a characteristic feature due to defective insulin secretion, improper insulin action, or both. A specific long-term complication is associated with the chronic hyperglycemia of diabetes as microvascular and macrovascular complications affecting the eyes, kidneys, and nerves, with an increased risk for IHD.[1]

T2DM elucidate around 90% of all cases of diabetes. In T2DM, the insulin reaction is contracted, which is determined as insulin resistance. During this state, insulin is inexpedient and is firstly countered by a high level in insulin production to conserve glucose equilibrium, but over time, insulin production decreases, resulting in T2DM. T2DM is commonly seen in persons older than 45 years. Still, it is progressively seen in children, adolescents, and younger adults due to ascend-

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ing levels of physical inactivity, obesity, and energy-dense diets.[2]

The IHD, or myocardial ischemia, is identified as a disease the blood supply to the heart muscle is reduced, commonly due to coronary artery disease. Its risk broaden with age, diabetes, smoking, hypercholesterolemia, and hypertension.[3]

Some hormone regulates glucose metabolism and levels in the blood, such as insulin and fetuin-A. Insulin is a peptide hormone formed of 51 amino acids with a molecular weight of 5808 Da., its function is to promote anabolism of the glucose to meet caloric needs and intake with expenditure. The circulating hormone and biologically active for insulin is monomeric.[4]

Fetuin-A is a peptide plasma factor secreted mainly by hepatocytes, Alpha 2- Heremans Schmid Glycoprotein (AHSG) is the other name for fetuin-A.[5]

Fetuin-A blocks insulin attachment to its receptors, and causes insulin resistance as an initiator of T2DM pathophysiology. The blocking occurs through the inhibition activity of insulin receptor tyrosine kinase, which is linked to insulin resistance and metabolic syndrome and raises the risk of T2DM.[6]

One DM cause is the adipocyte's inflammatory process, which is another cause to connect Fetuin-A to DM due to the role of fetuin-A in the expression of inflammatory cytokines, mainly in adipocytes and macrophages.[7]

Metabolic syndrome is a pathological condition in which increased waist circumference, dyslipidemia, impaired glucose metabolism, and hypertension are developed, and one condition will predispose to the other.[8] Nowadays, about 10–30% of the worldwide population is affected by met. S, a close association between fetuin-A concentration and Met. S has been stated in many studies. The Heart and soul study indicated that a higher fetuin-A level in a non-diabetic patient with the cardiac disease was associated with Met. S and atherogenic lipid profile. A suggestion that supports fetuin-A may promote the Met. A few arguments support s phenotypes in humans: 1) the human fetuin-A gene resides on chromosome 3q27, which has been mapped as Met. S quantitative trait locus. 2) fetuin-A interference with insulin effect at peripheral tissues through interaction with the insulin effect at peripheral tissues leading to the Met. S phenotype.[9]

A positive correlation between fetuin-A and T2D has been observed among participants with elevated plasma glucose fetuin-A levels in comparison to the non-diabetic patient. The close relationship between fetuin-A and IHD have been reported in many studies. In a case-Cohort study, Weikert *et al*. study a 4-fold rise in the risk of development of myocardial infarction and ischemic stroke with higher fetuin-A concentrations in a patient if compared to the person with low fetuin-A levels. Many authors found that high serum fetuin-A level may be a sensitive marker of macrovascular complications in diabetics.[10,11]

The study aims to evaluate serum fetuin-A concentrations in type 2 diabetic patients with and without IHD and compare them with healthy individuals. Assessment of serum glucose, insulin levels, and HOMA-IR in T2D patients and IHD and comparing them with healthy individuals.

SUBJECTS, MATERIAL, AND METHOD

The current study is a case-control study that incorporated 120 patients with end-stage MI (60 of them have DM with IHD and 60 having DM without IHD, group 2 and group 3, respectively) Iraqi patients who attended AL-Yarmouk Teaching Hospital and Iraqi Center for myocardial infarction, Medical City Hospital, Baghdad during the period from November 2020 until February 2021. Their ages ranged from 30 to 70 years. The diagnosis of MI is based on medical reports, laboratory, and clinical tests for heart disease. The results were compared with 60 healthy individuals' age range 30 to 65 years as a control group (group 1). Venous blood samples were taken to estimate serum blood sugar, HbA1c, serum insulin, homeostasis model assessment-estimated insulin resistance (HOMA-IR), and fetuin-A. Patients with neuropathy, retinopathy, thyroid dysfunction, and liver diseases were excluded from the study.

Body mass index is calculated by dividing the weight in kilograms by the height square in meters (kg/m2), presenting to the following equation:-

$$BMI = Weight\ (Kg)/(Height)^2\ (m^2)$$

Normal range 18-24.9 kg/m, a BMI lower than 18.5 kg/m^2 is underweight, 25-29.9 kg/m as overweight and ≥30 kg/m obesity.[12]

The determination of serum insulin using DRG® Insulin ELISA Kit, Normal Values: 2 to 25 μIU/mL.

Determination of serum fetuin-A using a kit based on sandwich enzyme-linked immunoassay (ELISA) technology.

The following formula calculated the HOMA-IR: [fasting insulin (uIU/mL) × fasting blood glucose (mmol/L)]/22.5

RESULT

In Table 1, the age, sex, and BMI of the participant are shown. The age is divided into four categories, in which the age group of most of the participants in group 2 were 41 to 50 and 51 to 60 with 48.30 and 41.7% respectively. The age group distribution in group 3 showed that 28.30% of patients are 30 to 40 years, but 50% of them have age fall in the age group 41 to 50. A statistically significant difference in age between the three studied groups, p-value ≤ 0.05. Female: male ratio is almost 1:1 in the three studied groups.

Most patients in group 2 had a BMI fall in the 25.0 to 29.9 category (53.3%), while 46.7% had BMI > 30. The BMI of the majority of the participant in groups 3 and 1 fell in 19-24.9 category (Table 2). All three groups showed a statistically significant difference in BMI.

The association between the diseased groups and disease duration was statistically insignificant in the current study as p was >0.05, despite that 68.3% with T2DM for 1 to 10 years. Develop IHD, and 13.3% of the T2DM who have had the disease for 11-15 years develop IHD (Table 2).

The measured parameters are shown in Table 3. The result indicates significant differences in FBS and HBA1c between

the groups, p-value <0.05. The mean of FBS and HBA1c in both diabetic groups 2 and 3 were higher than in control. Insulin levels were also significantly higher in both groups 2 and 3 than in the controlled group, epically in group 3. The mean was 17.37 ± 26.28.

HOMA-IR level was significantly higher in diabetic groups compared to the control and higher in DM patients with IHD than in the DM patient without IHD. The result of fetuin-A measured mean level was also significantly different between the three groups, with the lowest mean level in the control group, which get higher and higher levels in both diabetic groups (highest mean level in group 2, 27.63 ± 13.31).

The correlation between the fetuin-A and the studied parameter in both diabetic groups is presented in Table 4. The result states that there is only a significant moderate positive correlation between the level of insulin in DM patients with

Table 1: Age, sex, and BMI of the participant.

			T2DM with IHDM (N = 60)	T2DM without IHDM (N = 60)	Controls (N = 60)	Total	p-value
Age groups	30–40	N, (%)	5 (8.30%)	17 (28.30%)	42(70.00%)	64(35.60%)	0.000*
	41–50	N (%)	29 (48.30%)	30 (50.00%)	18(30.00%)	77(42.80%)	
	51–60	N (%)	25 (41.70%)	13 (21.70%)	0 (0.00%)	38(21.10%)	
	61–70	N (%)	1 (1.70%)	0 (0.00%)	0 (0.00%)	1 (0.60%)	
Sex	Male	N (%)	32 (53.30%)	30 (50.00%)	28(46.70%)	90 (50.0%)	0.76
	Female	N (%)	28 (46.70%)	30 (50.00%)	32(53.3%)	90 (50.0%)	
Categorical BMI	19–24.9	N (%)	0 (0.00%)	59 (98.30%)	29(48.30%)	88(48.90%)	0.000*
	25–29.9	N (%)	32 (53.30%)	1 (1.70%)	17(28.3%)	50(27.80%)	
	>30	N (%)	28 (46.70%)	0 (0.00%)	14(23.30%)	42(23.30%)	

*p-value is significant if ≤ 0.05.

Table 2: The association of disease duration and development of IHD.

			Diabetic groups			
			T2 DM with IHD	T2 DM without IHD	Total	p-value
Duration	<1 year	N. (%)	11 (18.3%)	8 (13.3%)	19 (15.8%)	0.308
	1–10 yrs.	N. (%)	41 (68.3%)	48 (80.0%)	89 (74.2%0	
	11–15 yrs.	N. (%)	8 (13.3%)	4 (6.7%)	12 (10.0%)	
Total		N. (%)	60 (100.0%)	60 (100.0%)	120(100.0%)	

*p-value is significant if ≤ 0.05.

Table 3: Clinical parameters between T2DM with IHD, T2DM without IHD, and control groups.

Clinical Parameters	T2DM with IHD (N = 60)G3	T2DM without IHD(N = 60)G2	Control (N = 60)G1	p-value
	Mean ± SD	Mean ± SD	Mean ± SD	
FBS (mg/dL)	197.52 ± 53.18	171.95 ± 55.37	88.55 ± 7.11	0.000*
HbA1c %	8.51 ± 1.37	7.89 ± 1.62	4.79 ± 0.315	0.000*
Insulin level (μU/ml)	17.37 ± 26.28	10.19 ± 6.43	9.71 ± 2.28	0.000*
HOMA-IR	8.83 ± 16.38	4.32 ± 2.61	2.12 ± 0.51	0.000*
Fetuin-A(ng/dL)	27.63 ± 13.31	12.39 ± 5.61	9.93 ± 5.1	0.000*

*p-value is significant if ≤ 0.05.

Table 4: Correlations between Fetuin A level and diabetic parameter among patients with IHD and without IHD.

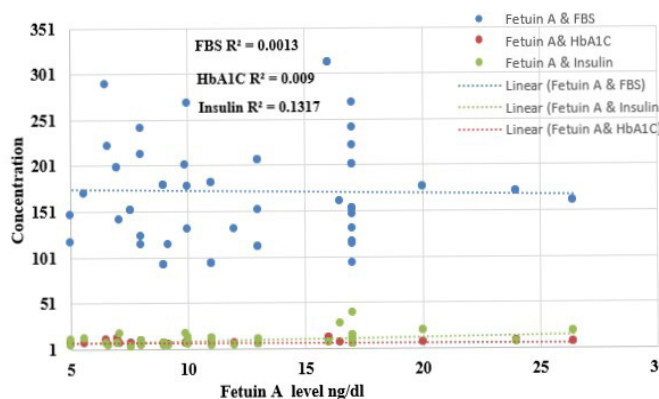| No	Factors	T2DM with IHD		T2DM without IHD	
		r	(p-value)	r	p-value
1	Ag (Years)	0.43	(0.0)	0.29	(0.01)
2	BMI(Kg/m2)	0.41	(0.0)	-0.19	(0.23)
3	W/ H ratio	0.43	(0.0)	0.2	(0.2)
4	Duration	0.16	(0.2)	-0.26	(0.4)
5	FBS (mg/dL)	0.15	(0.9)	0.152	(0.97)
6	HbA1C %	0.16	(0.8)	0.16	(0.8)
7	Insulin	0.69	(0.04)	0.69	(0.45)

Figure 1: Scatter diagram represented the correlation between Fetuin-A levels with diabetic parameters among patients without IHD.
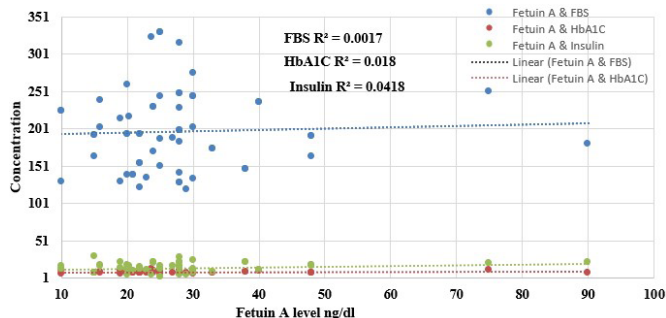

Figure 2: Scatter diagram represented the correlation between Fetuin-A Levels with diabetic parameters among patients IHD.

IHD and fetuin-A. Figures 1 and 2, show the correlation between fetuin-A and the studied parameter in T2DM with IHD and T2DM without IHD, respectively.

DISCUSSION

The current study's data revealed that most patients with DM who have IHD fall in older age group, which is consistent with the nature of the disease formal, because T2DM was frequently well-defined as late-onset diabetes,[11] and the disease is developed over a long time.

Almost all the studies that deal with DM found a very strong association between DM and obesity, which is supported by the increasing global incidence of T2DM, which is tied to growing rates of obesity,[12] 46.7% of the participant in group 2 in the current study have BMI > 30, which support the foundation of other studies.

According to Nordström, 2016,[12] study prevalence of diabetic patients is different on the sexual bases, with a higher prevalence among males (14.6%) than females (9.1%), which is inconstant with the current study result. That may be related to the difference in sample size.

The FBS, HbA1c, and insulin levels were significantly higher in diabetic patients who develop IHD. The result agreed with Kaur 2019,[13] study that investigated FBS in a diabetic patient with and without IHD as a predictor of the development of IHD, in which FBS was also high in a diabetic patient with IHD in compare to those without IHD.

Zhao's 2014 study,[14] indicates that HbA1c has a positive association in risk to develop IHD among both African American and white diabetic patients with low socioeconomic status.

The level of HOMA-IR was increased in the diabetic patient with and without IHD, which support the association between metabolic syndrome and IR to develop IHD. In Bonora 2002,[15] study HOMA-IR was an independent factor in predicting IHD in DM patients.

In Keskin 2017[16] study, the level of fetuin-A was significantly lower in the control group compared to diabetic groups, considering fetuin-A as a marker of IHD. The results correlate with the current study, which also shows lower fetuin-A in the control group compared to diabetic groups. But many studies disagreed, which found a low fetuin-A is associated with the development of cardiac disease, Chen, 2017 study,[17] Saad, 2019 study,[18] and other studies.

No statistically significant association is found between fetuin-A and other studies biomarkers in both diabetic groups except for the positive association between insulin level and fetuin-A, which can be explained by the relation of both of them to metabolic syndrome and DM development.

The current results are consistent with Yin 2014 study,[19] that found a negative correlation between fetuin-A and fasting serum insulin and a positive correlation with HOMA-IR. Fetuin-A could be considered a marker for the development of macro-angiopathy in a diabetic patient.

While in Song 2011 study,[20] the results agreed with the current study, in which fetuin-A were associated with elevated HOMA-IR and insulin in studied groups with or without T2D.

CONCLUSION

Fetuin-A level is higher in diabetic groups in compare to non-diabetic. The level gets higher in a diabetic group with IHD, which supports the association of fetuin-A with DM and IHD. Fetuin-A can be used as a predictor of IHD.

ETHICAL CLEARANCE

The Research Ethical Committee at scientific research by ethical approval of both MOH and MOHSER in Iraq

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