Determination of Some Biomarkers as Pathological Etiology and Risk Factors in Patients with Type Two Diabetes Mellites

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Abstract
Background: Type 2 diabetes mellitus (T2DM) is the most severe form of diabetes, accounting for 90-95 percent of cases. It is characterized by a combination of insulin resistance and insulin cell secretion pancreatic dysfunction, resulting in a metabolic abnormality. Aims: assess the diagnostic value of FBS, Hba1c, Lipid profile, insulin, Homo insulin resistance, Leptin, Plasminogen activator inhibitors 1, TNF alpha, lipase lipoprotein, Apo B and Apo A1 biomarkers in patients with type two diabetes Mellitus. Materials and methods: A case control study a total of 80 patient and 50 control groups, used Cobas E311 device for measure glucose and lipid profile, HbA1c used D-10 hemoglobin Hba1c device whereas other parameters used ELISA methods were used to analyses 130 samples Results: increased level of Insulin, Tg, HOMA IR, Leptin Apo A1 I and Apo B lipoprotein, whereas decrease level of PAI-1, HDL, TNF and Lipoprotein lipase. Conclusion: FBG, HbA1c, Insulin and HOMA-IR were Highly sensitivity and specificity in the diagnosis accuracy of type 2 diabetes.
Keywords: Insulin, TNF-α, Plasminogen activator inhibitors, Diabetes mellitus

1. Introduction

Diabetes mellitus1 (DM) is a chronic1 metabolic1 disorder characterized1 by 1hyperglycemia caused1 by insulin insufficiency, decreased1 insulin action, or 1both. Hyperglycemia in chronic diabetes has long-term complications for the kidneys, skin, and nerves, as well as an increased risk of cardiovascular disease (CVDs) [1, 2]. DM has become a serious clinical metabolic illness that develops from a complex combination of hereditary and environmental variables, chiefly defined by hyperglycemia, polyphagia and polyuria. Prolonged and uncontrolled diabetes leads to serious complications, some of which may be lead to life-threatening [3].

Type 12 diabetes1 mellitus (T2DM) is the 1most severe form of 1diabetes, accounting1 for 90-95 percent of 1cases. It is characterized1 by a combination1 of insulin 1resistance and insulin cell secretional pancreatic dysfunction, resulting in a metabolic abnormality [2]. T2DM is also 1known as adult 1diabetes mellitus or diabetes 1mellitus non-insulin-dependent (NIDDM) [4], T2DM is defined by a gradual chronic, low-level inflammatory syndrome that follows the complete pathway from its origins to its development into complication. A growing body of research points to a vast variety of potential "causes" of inflammatory 1responses, 1many of which 1are aided by 1poor lifestyle choices and old age. In diabetic1 patients, the quantity and function of both endogenous and acquired immune cells have been changed. Reactive autoantigens may be seen in a subset of patients, and new research suggests that distinct populations of T-lymphocytes, including T-regulating mechanism (Treg) cells, play diverse roles. As a result of these observations, it was hypothesized that part 1of the growing 1inflammatory response1 in T2D is due to an1 autoimmune response [5]. Signs of autoimmune disorders such as TNF-a and cytokine-related proteins (leptin) predicted rapid insulin-requiring diabetes progression [6].

T2D is linked to aging and obesity, both of which are thought to enhance tissue1 and systemic1 chronic inflammation, also known as inflammation and meta inflammation, particularly [7, 8]. Inflammation is not only natural, but also plays a 1key role 1in the progression1 of all major features 1of T2D disease, including insulin resistance, cell 1failure or inability 1to cope with1 increased 1insulin demand, and atherosclerotic plaque formation, the lipid profile and plasminogen activator inhibitor-1play important role in the formation1 of atherosclerotic1 plaque, and fasting blood glucose (FBG) levels. Adequate hemoglobin A1c (HbA1c) control is necessary to prevent long-term micro and macrovascular problems [7, 9, 10].

Aims of this study Measuring the concentration of serum level of (FBS, Hba1c, Lipid profile, insulin, Homo insulin resistance, Leptin, Plasminogen activator inhibitors 1, TNF alpha, lipase lipoprotein, Apo B and Apo A1) biomarkers in patients with diabetes Mellitus compared to the control group, then link the finding with appropriate statistical relationships.

2. Materials and Methods

2.1 Study population and sample collection

A case control study a total of 130 patient and

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control groups [patient type 2 diabetes mellitus group as a total N= 80 (male=38 , female =42), and control group as a total N=50 (male=28, female=22)], with an age range from (33 to 73) years, who attended Al-Shafaa teaching hospital in Basra. All patients in this study were diagnosed by specialist physicians in Al-Shafaa teaching hospital in Basrah throughout the period from November 2021 to February 2022.

2.2 Blood Samples collection and processing

From each participant, five milliliters of blood was drawn, three milliliters were transferred to sterilized test tubes, the sample was coagulated at room temperature for 30 minutes, the sample was separated by centrifugation at 3000 rpm for 15 minutes, the serum was isolated and stored (minus twenty 0C) until analyzed, and 1.8 milliliters of blood were put in an EDTA tube, used Cobas E311 device for measure glucose and lipid profile(Roche / Germany), HbA1c used D-10 hemoglobin Hba1c(D-10 /USA) device whereas other parameters used a ELISA methods(Sun long / Korea) were used to analyses 130 samples.

3. Statistical Analysis

The data is expressed as means ± standard deviations (SD). The t-test and the chi-square test were used to see whether there were any differences in the means of the groups. Variable correlations were also investigated. SPSS for Windows was used to conduct all statistical analyses (version 26, USA). The Mann Whitney test was used in addition to the non-parametric and T-test used for the normal distribution. $P < 0.05$ was regarded statistically significant.

4. Results and Discussion

Table (3-1): Differences of the age, BMI, FBS, Hb A1c and lipid profile indicators between the study groups

Variables	Control (N=50)				Patients (N=80)				P. Value
	Mean±SD	Median	Min	max	Mean±SD	Median	Min	Max	
Age (years)	56.1±8.75	57.0	33.0	72.0	53.1±9.61	53.0	40.0	73.0	0.079
BMI (Kg/m^2)	26.080±7.964	24.710	19.63	78.30	30.160±5.053	29.605	20.06	47.03	0.001
FBS(mg/dl)	89.36 ±8.861	88.00	73	104	189.74±94.623	143.50	110	463	0.001
HbA1C (%)	5.580 ±1.004	5.600	4.10	8.70	8.9275 ±2.335	8.2500	6.10	15.50	0.001
TC (mg/dl)	181.22±33.426	180.00	133	280	177.58±42.916	180.00	100	324	0.530
TG (mg/dl)	142.6±90.072	122.00	59	660	211.88±119.91	186.00	50	650	0.001
HDL (mg/dl)	50.96±15.159	48.00	25	102	42.71 ±8.859	43.00	20	83	0.002
LDL (mg/dl)	102.32±31.442	101.50	36	187	91.29 ±40.097	91.00	5	212	0.066
VLDL(mg/dl)	28.36 ±18.004	24.00	12	132	42.75 ±24.148	37.00	10	130	0.001

This table show statistically significant difference p-value <0.05 for each FBS, BMI, HbA1C, TG, HDL&VLDL whereas TC& LDL were non-significant difference p- value > 0.05, consistent with previos studies [11-13]. Glycated1 hemoglobin1 (HbA1c) levels1 are routinely1 measured1 in diabetics1 to monitor1 their glycemic 1control. The level 1of circulating1 HbA1c is taken as a 1gold standard1 for monitoring glycemic1 control with a goal to achieve a level below 7 in diabetics with treatment. Thus, the level of HbA1c 1could potentially be 1utilized as a possible1 biomarker1 for predicting1 the risk1 of dyslipidemia1 and therefore developing CVD in these patients [14]. Some of the previous studies showed improved glycemic control as indicated by lower HbA1c level has a beneficial effect on the lipid profile of the patients whereas the other studies showed either no considerable relationship or a negative relationship among the above parameters [15-17]. Increased serum TG is associated with atherosclerosis. The mechanism, however, is unclear. High TG levels are often accompanied by low high-density lipoprotein (HDL) cholesterol level and increased small dense LDL (sdLDL) particles that are more easily oxidized and are more atherogenic [12]. Diabetes patients with high TG but normal or low LDL-C may have higher sd-LDL. It was hypothesized that the TG/LDL-C ratio would be useful for predicting higher sd-LDL or apolipoprotein-B (apoB)-containing lipoproteins as an alternative to non– HDL-C. The present study clarified whether the TG/ LDL-C ratio is more valuable than non–HDL-C or other lipid markers in predicting SD-LDL level in type 2 diabetes patients treated with or without statins [13].Patients1 with Type-II 1DM who also had 1additional signs of 1insulin resistance, 1such as 1hyperinsulinemia, 1hypertension, and central 1obesity, were more likely1 to have 1dyslipidemia (increased1 triglycerides, high 1cholesterol, and reduced1 HDL), which is closely linked to 1atherosclerosis. A 1significant risk factor for heart1 disease emerged1 from the Framingham 1Heart Study: low HDL-C [11]. A triglyceride1 level >130 mg/dl 1and/or a 1triglycerides-to-HDL-C1 ratio above1 three is highly1 predictive of tiny, 1dense LDL 1particles, and 1these characteristics1 are present in 1obese Type-II 1DM 1participants. The 1most significant 1proatherogenic 1lipoprotein is LDL. The 1genetic form of LDL-C known as Lp(a) has an 1aberrant protein 1called apo(a) connected 1to it and is the most harmful1 lipoprotein; 1smaller, denser LDLs were 1more atherogenic1 than bigger, 1buoyant LDLs [18, 19]. The course1 of coronary1 heart disease is 1impacted by 1hyperglycemia 1and dyslipidemia, and the death 1rate in diabetic 1individuals rises. LDL-C levels are elevated1 and HDL-C levels are low, which1 causes endothelial1 dysfunction. Therefore, intensive1 cholesterol

control in 1conjunction with 1anti-diabetic therapy decreases1 both mortality and the 1consequences of Type-II 1diabetes mellitus [4, 20, 21].

Table (3-2): Differences of the biomarker levels indicators between the study groups

Variables	Control (N=50)				Patients (N=80)				P. Value
	Mean±SD	Median	Min	Max	Mean±SD	Median	Min	Max	
Insulin mlu/L	13.0480 ±9.247	10.1500	1.90	38.90	67.2513±30.08803	68.4000	5.30	150.50	0.001
HOMA IR	2.8596±2.045	2.2500	.37	8.40	34.0201±29.95485	24.6500	1.50	157.10	0.001
TNF ng/L	68.3566±59.717	52.6000	5.90	325.30	54.8964±67.36606	39.3500	.10	422.20	0.049
Leptin ng/ml	30.5484±30.811	19.7000	2.60	166.00	76.4338±35.24778	77.0500	2.60	189.70	0.001
PAI-1 Au/ml	18.5468±17.364	12.8500	1.40	77.80	5.6123±7.58196	3.8500	.10	43.00	0.001
Lipoprotein lipase pg/ml	1579.69±1670.381	818.740	54.9	5612.0	1362.92±1658.788	454.700	202.6	5766.0	0.277
Apo A1 lipoprotein ng/ml	19.8404±19.582	12.5000	2.40	89.40	79.1875±48.60912	81.5000	4.50	220.30	0.001
Apo B lipoprotein ng/ml	196.6926±145.642	182.200	11.8	589.80	387.9290±316.796	226.115	77.21	990.30	0.003
* Mann Whitney-U Test									

In this table (3-2) shown increase significant level P value 0.001 for insulin and HOMA IR, this study match with previous studies [21, 22]. In 1general 1population, insulin 1resistance precede1 in many years 1before onset of 1T2DM and 1it is also multi-factorial such as genetic component [23, 24]. Insulin1 resistance 1and reduction1 in insulin1 production1 are the 1major characteristics1 of the T2DM pathogenesis [25, 26].

Insulin 1resistance can be1 brought1 on by modern1 lifestyle 1factors such as physical1 inactivity, 1abdominal obesity, 1and an excess of 1adipokines. 1Normal glucose1 tolerance is first 1maintained by 1compensatory hyperinsulinemia. 1Insulin 1resistance is 1caused by 1about 25% of 1non-diabetic subjects1 in the same 1individuals. 1Impairment in 1glucose 1tolerance 1developed as a result1 of the 1ongoing 1increases and/or 1declines in 1insulin secretory compensatory1 responses1 reported in T2DM 1patients. Increased1 levels of glucose, 1 FFA, and1 insulin cause1 an increase in oxidative1 stress and ROS generation1 as well as the activation1 of stress transduction1 factor pathways. This may1 speed up the onset1 of T2DM by 1inhibiting insulin 1action and 1secretion [23, 26].

In this table (3-2) shown significant decrease level P value= 0.049 in patient diabetes mellitus compared to control groups, our study match with [27, 28], an adipocytokine1 that has a 1role in systemic inflammation1 and activates1 the acute phase1 reaction is tumour1 necrosis 1factor alpha 1 (TNF-α). The 1majority of cells1 that release1 TNF- α are1 macrophages, but there are 1many other 1types of cells including1 adipocytes1 that do as1 well. TNF- α affects1 the metabolism1 of glucose1 and inhibits the 1transduction of insulin. TNF- α 1metabolism 1disturbances have 1been linked to 1metabolic diseases1 such 1obesity and insulin1 resistance, 1suggesting that1 they may have an impact1 on the 1development of type 2 1diabetes mellitus1 and its 1course. But it's unclear1 how TNF- α 1affects the 1severity and 1spread of the1 illness [27, 29].

In our 1study shown plasma 1leptin 1levels in T2DM1 patients were significantly increase P value = 0.001 compared to control group, this study agree with previous study [30, 31], Elevated1 leptin levels1 are associated1 with insulin resistance1 and T2DM1 development [30, 31], It has1 been 1reported that CHD 1patients have 1higher 1leptin levels compared1 with 1controls, as also 1supported by a 1metaanalysis. Serum1 leptin concentrations1 are increased1 after 1myocardial 1infarction (MI) [31] also the 1leptin level1 in T2DM 1patients were 1significantly 1associated with the presence 1of smoking, obesity, 1 hypertension, 1dyslipidemia, 1and metabolic 1syndrome [32]. The serine 1protease1 inhibitor (serpins) family1 of proteins 1includes the 50-kDa 1glycoprotein 1known as 1plasminogen activator 1inhibitor-1 (PAI-1). The primary 1controller of the 1endogenous fibrinolytic1 system is PAI-1. Three beta 1sheets and nine1 alpha 1helices 1make up PAI-1. In 1addition to 1interfering with1 proteasome 1activity and 1cell adherence1 to the extracellular1 1matrix, PAI-1 can bind1 to the 1somatomedin B domain. 1The liver1 and spleen are 1only two tissues1 that express1 and produce PAI-1. Insulin, very-1low-1density 1lipoprotein (VLDL), low-density 1lipoprotein (LDL), and 1glucose all 1control the1 production1 of Rabieian et al. [33]. Apo B and Apo A1 increase level in patient compared to control group, this study was agree with previous studies [34, 35], the decrease level of lipoprotein lipase duo to Insulin-induced upregulation of lipoprotein [34], Children1 and adolescents1 with type 2 diabetes1 mellitus1 frequently1 have 1dyslipidemia (T2D). 1Obesity, insulin 1resistance (IR), 1hypertension, 1and a sedentary 1lifestyle are 1common risk 1factors in 1children who 1are at risk. To avoid the 1projected CV 1morbidity, it is 1crucial to 1detect and 1treat dyslipidemia1 since T2D is a 1significant 1independent 1cardiovascular1 (CV) risk factor [36]. Abnormalities1 of lipoprotein 1metabolism 1are one of the major1 factors 1contributing to

1cardiovascular risk1 in patients1 with type1 2 diabetes, and 1diabetic 1dyslipidaemia1 includes1 not only 1quantitative1 but also qualitative1 and kinetic1 lipoprotein1 abnormalities1 that are 1inherently atherogenic [37].

In our1 study, it has1 been found1 that the 1mean of 1Apo B and1 Apo A1 concentrations 1were 1significantly1 higher in patient 1diabetic compared to control1 group, this study agree wih previous1 studies [38-40], Apolipoprotein1 B (Apo B) is 1the protein part of 1Low Density1 Lipoprotein1 (LDL), Very 1Low 1Density Lipoprotein (VLDL) and 1Intermediate 1Density Lipoprotein1 (IDL), 1:1 relationship1 between apoB and 1LDL particles, so if LDL 1increased the Apo B increased1 [39, 40] Apolipoproteins1 B (apoB) and AI (apoAI) are strong 1predictors 1of cardiovascular1 disease1 (CVD), [39] mention1 that 1patients with 1type 2 diabetes1 had elevated1 apoB, 1LDLC, 1apoAI, 1HDLC and 1apoB:apoAI, 1and/or high TG. 1By contrast, patients1 with type 2 1diabetes had1 elevated 1apoB, LDLC, 1apoAI, HDLC and1 apoB:apoAI, and 1low LDLC:apoB. 1In addition, 33% 1had 1high apoB, TG, and 121% high 1apoB alone, 1compared 1with 11% 1and 7% in 1the reference1 1population.

Table (3-3): Receiver-operating characteristic (ROC) curve analysis for the values of serum biomarkers for the diagnosis of Diabetes Mellitus type two.

Variables	Area under the ROC curve (AUC)	p-value (AUC0=0.5)	Best cut-Off criterion	Sensitivity (%)	Specificity (%)	Total Agreement	Positive predictive value	Negative predictive value
BMI (kg/m^2)	81%	.000	28.7100	0.625	0.920	26.1%	39.5%	7.4%
FBG (mg/dl)	100%	.000	104.00	1.000	1.000	0%	0.0%	0.0%
HbA1c (%)	92.5%	.000	6.0000	1.000	0.840	6.15%	0.0%	9.1%
Insulin (uU/mL)	95%	.000	39.4000	0.825	1.000	10.8%	21.9%	0.0%
HOMA- IR	97.1%	.000	7.3500	0.913	0.980	6.15%	12.5%	1.4%
Cholesterol (mg/dl)	39.7%	.049	203.00	0.263	0.860	50.8%	57.8%	25.0%
Triglycerides (mg/dl)	71.2%	.000	156.50	0.675	0.680	32.31%	43.3%	22.9%
LDL (mg/dl)	40.4%	.066	189.50	0.038	1.000	39.23	60.6%	0.0%
HDL (mg/dl)	33.5%	.002	19.00	1.000	0.000	100%	61.5%	38.5%
VLDL (mg/dl)	71.7%	.000	28.50	0.725	0.640	30.8%	40.7%	23.7%
TNF	39.7 %	.049	89.4000	0.238	0.860	52.23%	58.7%	26.9%
Leptin	87.3 %	.000	55.3000	0.788	0.900	16.92%	27.4%	7.4%
PAI	18.2%	.000	-0.9000	1.000	1.000	100%	61.5%	38.5%
Lipoprotein lipase	44.3%	.277	175.1500	1.000	0.120	33.84%	0.0%	35.5%
Apo A1 Lipoprotein	88%	.000	61.8500	0.650	0.980	22.30%	36.4%	1.9%
Apo B Lipoprotein	65.8%	.003	204.4000	0.600	0.700	36.20%	40.7%	23.7%

In the table (3-3) shown in patients Diabetes Mellitus type two the Area under the ROC curve (AUC) FBS(AUC=100%) excellent diagnosis for Diabetes Mellitus type two was more than HbA1c (AUC=92.5%), Insulin (AUC=95%), HOMA- IR (AUC=97.1%) and another parameter. In this study BMI the AUC was 81% , Sensitivity (0.625), Specificity (0.920) and the Best cut-off criterion (28.71 kg/m2) as show in figure (3-1), FBG the AUC was 100% , Sensitivity (1.00), Specificity (1.00) and the Best cut-off criterion (104 mg/dl), HbA1c the AUC was 92.5% , Sensitivity (1.00), Specificity (0.84) and the Best cut-off criterion (6.0 %), Insulin the AUC was 95% , Sensitivity (0.825), Specificity (1.00) and the Best cut-off criterion (39.40 uU/mL), HOMA- IR the AUC was 97.1% , Sensitivity (0.913), Specificity (0.980) and the Best cut-off criterion (7.3500), this study agree with previous study [41].

Also in the table (3-3) shown in patients Diabetes Mellitus type two the Area under the ROC curve (AUC) for Triglycerides (AUC=71.2%) fair diagnosis for Diabetes Mellitus type two but it was more than Cholesterol (AUC=39.7%), , LDL (AUC=40.4%) and HDL (AUC=33.5%), Triglycerides the AUC was 71.2% , Sensitivity (0.675), Specificity (0.680) and the Best cut-off criterion (156.50 mg/dl), Cholesterol the AUC was 39.7% , Sensitivity (0.263), Specificity (0.860) and the Best cut-off criterion (203.00 mg/dl), LDL the AUC was 40.4% , Sensitivity (0.038), Specificity (1.00) and the Best cut-off criterion (189.50 mg/dl), HDL the AUC was 33.5% , Sensitivity (1.00), Specificity (0.00) and the Best cut-off criterion (19 mg/dl), this study was agree with previous study [42].

Also in the table (3-10) shown the marker TNF, PAI and Lipoprotein lipase failed diagnosis for Diabetes Mellitus type two because the AUC below 50% ,

whereas Leptin (AUC=87.3 %) and Apo A1 Lipoprotein (AUC=88%) were considered a good marker for diagnosis for Diabetes Mellitus type match previous study [43], however the Apo B Lipoprotein (AUC=65.8%) was poor diagnosis for Diabetes Mellitus type two, [43].

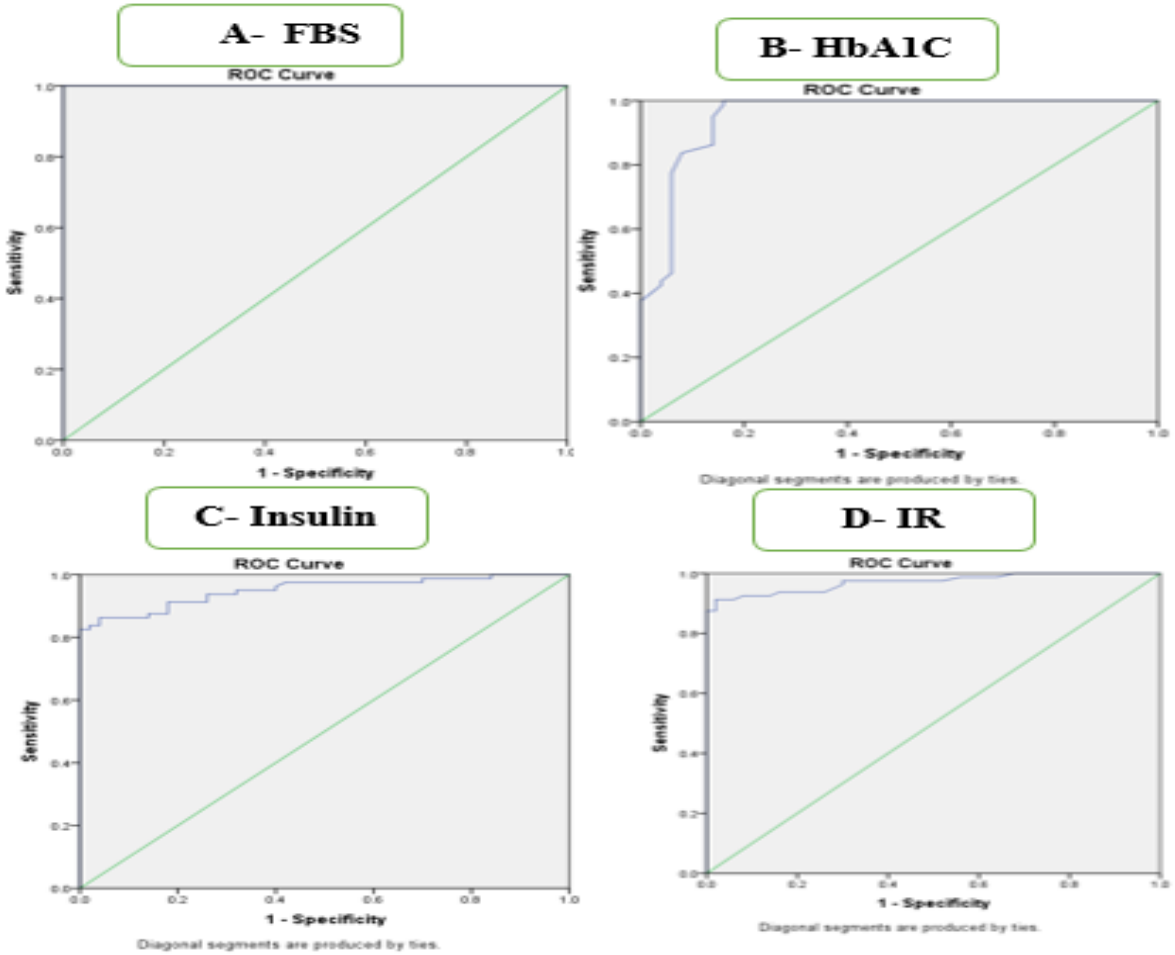

Figure (3.1): Show the ROC curve demonstrates parameters sensitivity and specificity in predicting diagnosis of diagnosis Diabetes Mellitus type two: A- FBA, B- HbA1c C- Insulin D- IR

5. Conclusions

we conclude that FBG, HbA1c, Insulin and HOMA-IR were Highly sensitivity and specificity in the diagnosis accuracy of type 2 diabetes.

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