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A case control study to determine N-terminal pro-B-type natriuretic peptide levels in patients of heart failure combined with diabetes

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Heart failure (HF) is a disorder in which the heart muscle becomes weaker than normal. This condition occurrence increases when patient has previous diagnosis of diabetes mellitus (DM). This study focused on determination of NT-proBNP biomarker and many routine parameters in HF patients that already have DM. 120 blood samples from males and females (80 patients and 40 controls) were collected. The patients and controls were all between the ages of 40 and 70. Patients' samples were taken from Ibn Al-Bitar Diagnostic Center for Heart Surgery in Baghdad/ Iraq. Serum levels of sugar, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were calculated spectrophotometrically. Glycated hemoglobin (HbA1C) level was determined using biochemical kit. Finally, NT-proBNP and insulin levels were measured using ELISA kits. Serum levels of glucose, HbA1C, insulin, and NT-proBNP were significantly higher (p=0.000) and there are significant differences between patients and control groups. Lipid profile parameters except cholesterol and SLDL have a significant difference. NT-proBNP was negatively correlated to glucose concentration, whereas it was positively correlated to heart failure and insulin concentration. In Cluster analysis, NT-proBNP was organized in one cluster with SLDL. The best cutoff value for NT-proBNP protein was (54.1) ng/mL according to ROC analysis.

KEYWORDS

Heart failure; diabetes mellitus; NT-proBNP; lipid profile; insulin.

Introduction

HF is a condition that causes the heart to become unable to pump enough blood and oxygen to meet the body needs. It can be caused by any structural or functional cardiac disorder which impairs the ability of the ventricle to fill with or eject blood. Because the tissues are receiving less blood and oxygen, they are unable to perform their functions properly. This usually occurs gradually over a period of time. Many types of heart diseases are provoked by diabetes mellitus. Myocardial defects and diabetes have a well-established causal association. For a substantial proportion of diabetic patients, coronary artery disease, hypertension, and dilated cardiomyopathy are all causes of heart failure. [1]. Cholesterol, triglycerides, and low density lipoproteins levels are examined to see whether there is a risk for heart disease, or not [2]. LDL-C levels which are too high are responsible for about half of the risk of myocardial infarction and heart failure [3].

Diabetes mellitus is a collection of metabolic illnesses marked by elevated blood sugar (glucose) levels caused by insulin secretion, action, or both [4]. Patients with diabetes mellitus have significantly weaker clinical outcomes than those without diabetes mellitus when it comes to heart failure [5]. Individuals with diabetes are at a significantly greater risk of developing cardiomyopathy and heart failure [6]. Individuals with cardiovascular disease, who are also diagnosed with type 2 diabetes, have a worse prognosis. The presence of these two illnesses raises the risk of large- and small-vessel disease morbidity and death [7]. There are several heart failure diabetic related parameters of which N-terminal pro B-type natriuretic peptide (NTproBNP) is mentioned. B-type natriuretic peptide (BNP) is a hormone generated by the heart. BNP and NT-proBNP are generated from the same BNP gene. After being transcribed and translated from the BNP gene, a BNP precursor (proBNP (1–108)) is generated, and is then cut into the physiologically inactive NT-proBNP (76 amino acids from the N-terminal (1–76)) and the physiologically active mature BNP (the remaining 32 amino acids (77–108)). BNP and NT-proBNP are both released in response to variations in heart pressure. These variations can be related to heart failure and other cardiac problems. The levels goes up when heart failure develops, or gets worse, and levels goes down when heart failure is stable. In most cases, BNP and NT-proBNP levels are higher in patients with heart failure than people who have normal heart function [8,9]. In addition, lipid profile, glucose, Insulin, and HbA1C are a set of tests that are frequently used in conjunction to determine the risk of heart disease. These tests can aid to determine whether a person is at risk for a heart attack or stroke caused by blood vessel blockage or artery hardening [10, 11]. Lipid profiling included Total Cholesterol (TC), Low Density Lipoprotein-Cholesterol (LDLC), High Density Lipoprotein-Cholesterol (HDLC), Triacylglycerol (TAG), and calculating Very Low Density Lipoprotein-Cholesterol (VLDLC) [12]. The current study focused on the role of NT-proBNP in cases with heart failure disease which already have diabetes mellitus.

Materials and methods

Patients

The present study has been done on 120 samples from males and females (80 patients with heart failure disease which already have diabetes mellitus and 40 samples without any disease). The patients and controls were all between the ages of 40 and 70. Blood samples were taken from the patients who attended in Ibn Al-Bitar Diagnostic Center for Heart Surgery in Baghdad/ Iraq.

Samples collection

Fasting samples of blood were collected from cubital veins of the arm from both patients and healthy controls by ten milliliters disposable syringe. In tubes containing (1.5 mg/mL) ethylene diamine tetracetic acid (EDTA), two milliliters were delivered for HbA1C estimation, while the other part transferred to serum separating tube, and then submitted to the lab for the reason of performing and processing of glucose, lipid profile, insulin, and NT-proBNP. The processing of blood samples includes two steps procedure: 1- centrifugation of blood samples at 3000xg for 5 min and 2- determination of the level by specific chemical kits.

Selectivity of blood samples

Many criteria have been excluded through blood samples collecting like patients who have para-thyroid disease, liver disease, kidney disease, cigarette smoking, alcohol intake, or they who have any overlapping doses.

Procedures

Serum glucose and lipid profile (Total cholesterol (TC), serum triglycerides (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), and very low density lipoprotein (VLDL)) determination occurs by standard assays that were used in hospitals. The glucose and lipid profile assays were performed using a multi-channel Abbott Spectrum auto-analyzer (Abbott Laboratories, C4000, USA) according to the manufacturer instructions, except for LDL was calculated using the Friedewald equation (15): LDL = (TC-HDL-[TG/5]), and VLDL was calculated by dividing total serum TG by 5 [13]. Estimation of HbA1C levels occurred directly after sample collecting by the kit supplied by Alere Technologies / Osio, Norway and using Afinion™ 2 Analyzer/ Abbott Laboratories/ Sweden. Enzyme Linked Immune Sorbent Assay (ELISA) / sandwich technique was used for quantitative determination of insulin and NT-proBNP. ELISA kits were supplied by Solarbio Life Science/ Beijing, China [14].

Statistical analysis

The findings were analyzed using a statistical analysis program (SPSS 25). The major findings were described using a general descriptive statistic, and the groups were compared using an independent T-test. The correlation was done by using Pearson correlation, cluster analysis of multivariate has been used, as well. The receiver operating characteristic curve (ROC) analysis was further used to determine the parameters cutoff value.

Results and discussion

It was a case control study to determine NT-proBNP levels in patients who have heart failure with diabetes in Iraq as they were 120 people. The participants in this research were in the age range of 40 to 70 years old. Probability sampling is a method for determining sample size (random selection). They were grouped into 2 categories of patients and controls. As a patients group, 80 Iraqi samples of heart failure with T2DM were selected from (Ibn Al-Bitar Diagnostic Center for Heart Surgery in Baghdad/ Iraq) during December 2020-April 2021. These patients were without liver disease, kidney disease, and hypertension. Likewise, smoker and alcoholism patients were excluded. In addition, control group composed of 40 samples were collected from individuals who were healthy in term of non-diabetic, non-heart disease, non- hypertensive and they were free from acute illness. Furthermore, they had no history of alcohol drinking or smoking.

The following table indicates baseline features related to the etiologies of heart failure. Age, sex, body mass index, diabetes, and heart failure duration showed statistical significant variations.

TABLE 1 Etiologies data in patients group which have heart failure with diabetes mellitus and control group

Parameters	Group	Mean ± SE	P-value
Age	Patient	57.3509 ±1.120	0.000
	Control	43.8108 ± 0.690	
BMI	Patient	28.6007 ±0.635	0.31
	Control	26.6065 ± 0.560	
Diabetes duration	Patient	10.7719 ±1.058	
	Control	-	
Heart failure duration	Patient	5.2982 ±0.707	
	Control	-	

The biochemical features of the study population are depicted in the table below (Table 2) reporting statistical significant variations in glucose, HbA1C, triglycerides, HDL, LDL, VLDL, insulin, and NT-proBNP. Except for cholesterol, which was non-significant, all of these biochemicals exhibited a substantial rise in the patient group as compared with the control group.

TABLE 2 Clinical data of people with diabetes mellitus who have heart failure and control group

Parameters	Group	Mean ± SE	P-value
Glucose	Patient	238.0175 ± 9.92347	0.000
	Control	94.7297 ± 2.64281	
HbA1C	Patient	9.6763 ± 0.25315	0.000
	Control	5.5649 ± 0.04621	
Cholesterol	Patient	179.2105 ± 8.08057	0.340
	Control	168.9730 ± 4.52064	
Triglyceride	Patient	161.2281 ± 11.10781	0.001
	Control	109.7838 ± 5.50527	
HDL	Patient	33.0877 ± 1.26607	0.000
	Control	46.0270 ± 1.76532	
LDL	Patient	109.0702 ± 4.94410	0.057
	Control	95.7838 ± 3.89793	
VLDL	Patient	33.3860 ± 1.96520	0.000
	Control	23.4054 ± 1.49245	
Insulin	Patient	2.1136 ± 0.14494	0.000
	Control	4.4238 ± 0.29380	
NT pro BNP	Patient	112.6031 ± 8.15531	0.001
	Control	57.3754 ± 3.01108	

The mean value of glucose and HbA1C levels for patients indicate high increase up to the range value. Glucose and HbA1C increasing emphasizes diabetes mellitus occurrence and is considered as highly predictive factor for detecting diabetes on the contrary, means of these parameters falls in normal range (65-110) for glucose and (4.5%-6.3%) for HbA1C for controls. P-value of glucose and HbA1C indicate that there is a significant difference between patients and controls.

All lipid profile parameters except HDL (total serum cholesterol, triglycerides, LDL, and VLDL) level have been increasing in heart disease patients than controls. P-values of cholesterol and LDL demonstrate that there is no significant difference on the contrary of TG, HDL, and VLDL which have been significantly different between the groups [15].

Although there is a slight increase in cholesterol means levels for patients than controls, this has not been considering as a good indicator for the diagnosis of heart disease, but it is still as a risk factor [16]. Taking caution from cholesterol and LDL bound cholesterol increase is good for reducing the probability of heart disease.

P-value of insulin demonstrates that there is a significant difference between individuals which have DM than for those without it [17].

The elevation of mean ± SE for NT-proBNP in patients over control species conflict the diagnosis role of this biomarker on heart disease even with DM presence. In addition, the significance of P-value (0.001) of this marker indicates that the difference is significant between patients and control samples [18].

Pearson correlation analysis of chosen variables in the population under study:

The authors studied the link among various variables in patients group. Serum NT-proBNP has a positive correlation with the duration of heart failure and insulin concentration. However, it was negatively correlated with

glucose (Table 3). In selected circumstances, NT-proBNP is linked to insulin resistance. Whenever insulin level increased in the serum, NT-proBNP is increased, too. Moreover, the correlation results showed a significant correlation between lipid profile items (TG, HDL, and VLDL), while in the control group, only serum insulin was significantly positive correlated with NT-proBNP only (Table 4).

TABLE 3 Correlation analysis of variables related with patient subjects (heart failure and diabetes mellitus)

		SEX	AGE	BMI	DIABETES date	HEARTFAILURE date	Glu	HbA1C	Cholesterol	TG	HDL	LDL	VLDL	Insulin	NTproBNP
SEX	P	1	0.26*	0.177	0.040	-0.12	-.01	0.231	0.300*	0.067	0.110	0.256	-0.03	-0.10	-0.01
	R		0.04	0.18	0.76	0.35	0.90	0.08	0.02	0.62	0.41	0.05	0.77	0.44	0.94
AGE	P		1	-0.07	0.28*	0.24	-0.18	-0.12	0.10	-0.05	0.031	-0.06	-0.11	-0.11	-0.13
	R			0.579	0.031	0.070	0.176	0.375	0.460	0.695	0.817	0.656	0.389	0.402	0.307
BMI	P			1	-0.272*	-0.157	0.139	0.071	-0.105	0.162	-0.16	-0.00	0.026	-0.08	-0.164
	R				0.041	0.243	0.303	0.599	0.438	0.228	0.220	0.967	0.846	0.546	0.224
Diabetes period	P				1	0.598**	-0.01	-0.16	0.131	0.051	-0.06	0.021	0.071	-0.07	0.106
	R					.000	0.925	0.218	0.333	0.709	0.626	0.878	0.602	0.561	0.432
Heart failure period	P					1	-0.21	-0.19	0.113	-0.03	-0.22	0.099	-0.04	0.070	0.324*
	R						0.107	0.140	0.403	0.788	0.094	0.464	0.716	0.607	0.014
Glu	P						1	0.31*	0.06	0.09	0.04	0.06	-0.01	-0.13	-0.35**
	R							0.01	0.60	0.47	0.75	0.63	0.90	.030	0.00
HbA1C	P							1	0.13	-0.06	0.05	0.24	-0.13	-0.15	-0.22
	R								0.336	0.64	0.68	0.06	0.30	0.24	0.087
Cholesterol	P								1	0.44**	0.142	0.58**	0.34**	0.01	0.00
	R									.001	0.29	0.00	0.01	0.89	0.95
TG	P									1	-0.13	0.12	0.76**	0.07	-0.02
	R										0.32	0.36	0.00	0.58	0.84
HDL	P										1	-0.07	-0.12	-0.01	-0.10
	R											0.55	0.35	0.93	0.43
LDL	P											1	0.19	-0.07	-0.05
	R												0.13	0.58	0.68
VLDL	P												1	.053	0.13
	R													0.69	0.30
Insulin	P													1	0.60**
	R														0.00
NTproBNP	P														1
	R														

TABLE 4 Correlation analysis of variables related with control subjects

		SEX	AGE	BMI	Glu	HbA1C	Cholesterol	TG	HDL	LDL	VLDL	Insuline	NTproBNP
	SEX	P	0.32	-0.63**	0.04	-0.07	-0.40*	-0.47**	0.28	-0.42**	-0.46**	-0.04	0.18
		R	1	0.00	0.78	0.64	0.01	0.00	0.08	0.00	0.00	0.80	0.26
AGE		P		-0.02	0.31	0.26	0.01	0.34*	-0.21	0.06	0.11	-0.02	0.08
		R		0.99	0.06	0.11	0.95	0.03	0.21	0.72	0.51	0.90	0.60
BMI		P		1	-0.13	-0.06	0.35*	0.30	-0.16	0.24	0.43**	0.07	-0.22
		R			0.43	0.72	0.03	0.06	0.32	0.14	0.00	0.66	0.17
Glu		P			1	0.52**	-0.20	0.22	-0.23	-0.22	0.13	-0.03	0.26
		R				0.00	0.22	0.18	0.15	0.17	0.43	0.85	0.12
HbA1C		P				1	-0.11	0.13	-0.24	-.020	.038	-.005	.128
		R					0.49	0.41	0.14	0.90	0.82	0.97	0.44
Cholesterol		P					1	0.01	0.11	0.46**	0.06	0.26	-0.11
		R						0.93	0.48	0.00	0.68	0.11	0.49
TG		P						1	-0.51**	-0.16	0.89**	-0.17	0.03
		R							0.00	0.34	0.00	0.30	0.85
HDL		P							1	0.17	-0.46**	0.39*	-0.03
		R								0.30	0.00	0.01	0.83
LDL		P								1	-0.11	0.07	-0.29

VLDL	R	0.50	0.66	0.07
	P	1	-0.15	0.02
Insulin	R		0.36	0.87
	P		1	0.43**
NTproBNP	R			0.00
	P			1

* At the 0.05 level, the correlation is significant (2-tailed).
** At the 0.01 level, the correlation is significant (2-tailed).
Sig. (2-tailed) = R
Pearson Correlation = P

Cluster analysis of multivariate

The wards technique is one of the most common cluster analysis methods. A dendrogram is commonly used to illustrate this strategy. There is no previous assumption of clustering made in this test. The cluster analysis was performed to find commonalities between the variables analyzed. The variables in all examined groups were sorted into seven clusters based on coefficients, with minor shifting in certain groups.

Chart 1 regarding the patients data showed that (heart failure date, insulin, HbA1C, diabetes date, HDL, and VLDL) were distributed in one group, the second group was (LDL and NT-proBNP), the third group was (LDL, cholesterol, and NT-proBNP), the fourth group was (TG and cholesterol), and the last group included the combination of glucose with lipid profile and NT-proBNP (Glu). The results indicated the similarity between lipid profile and NT-proBNP in diagnosis of heart failure cases.

Whereas in control data, the data were organized into several clusters depends on open their similarity Chart 2. HbA1C, insulin, and LDL were organized in the first cluster group, insulin VLDL and HDL were organized in the second cluster group, whereas NTproBNP and HDL were organized in the third cluster, Glucose and LDL were distributed in the fourth group, glucose, LDL, and TG were distributed in the fifth group, cholesterol, glucose, LDL, and TG were distributed in the sixth group.

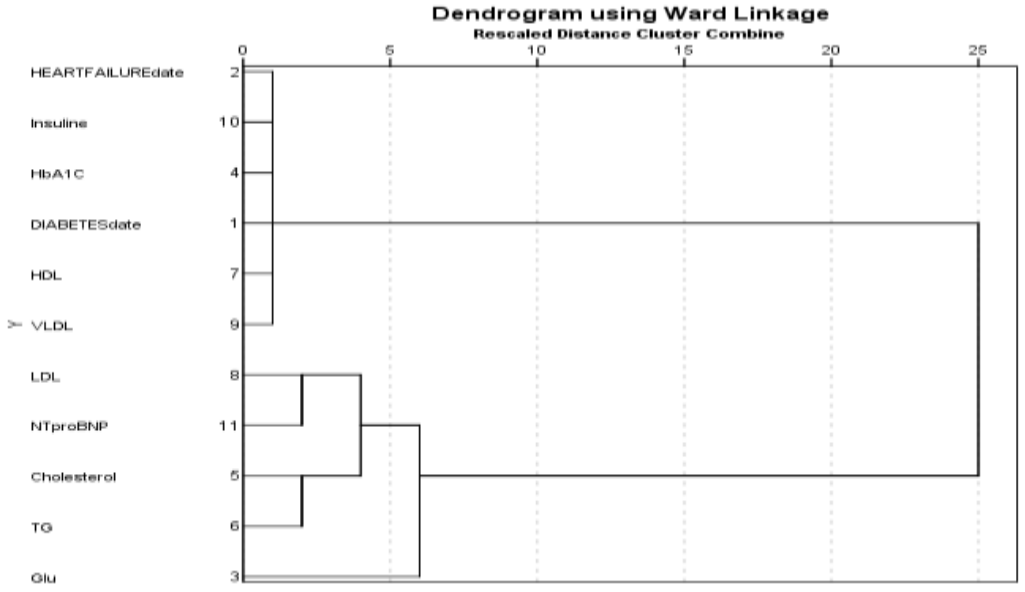

CHART 1 Cluster diagram of studied variables in the serum of heart failure with diabetes mellitus patients

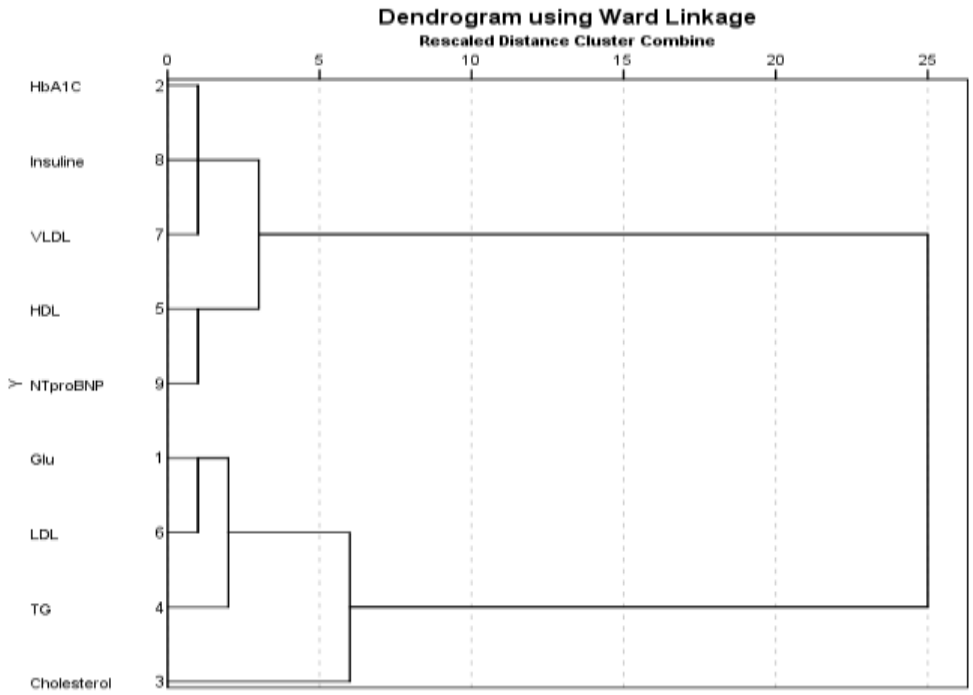

CHART 2 Cluster diagram of studied variables in the serum of control subjects ROC curve and cute-off analysis

The optimal cutoff value for NT-proBNP, according to the Receiver Operating Characteristic (ROC) curve, is (77.5) ng/mL, with a sensitivity of (59.6) and a 1-specificity of (0.027). As demonstrated, a test value more than (77.5) ng/mL indicates an atypical case, whereas a number less than (77.5) ng/mL reveals healthy circumstances, as depicted in Chart 3.

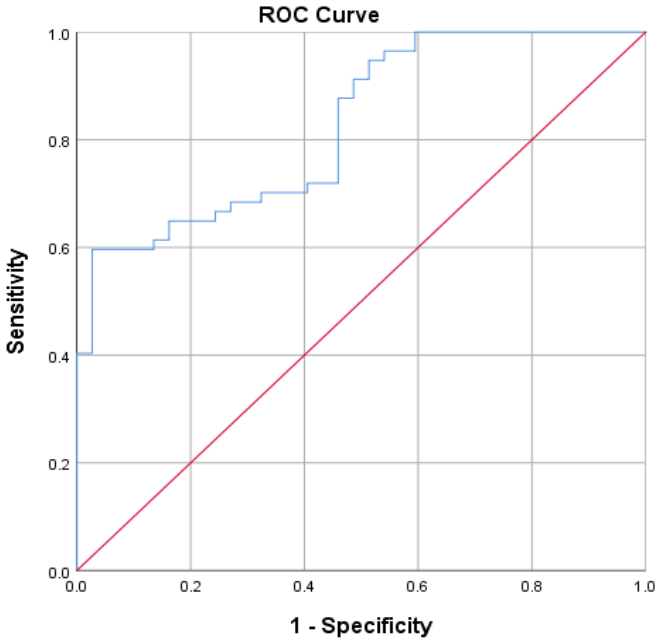

CHART 3 The analysis of predictive value of NT-proBNP serum concentration in the examined population by ROC curve (AUC is 0.829; $p < 0.05$)

Conclusion

NT-proBNP was found to be strongly linked to heart failure patients with diabetes. Likewise, it was correlated with duration of heart failure, insulin concentration, and it was correlated inversely with glucose. As a result, we proposed that serum NT-proBNP can be utilized as a diagnostic test in individuals with DM who had heart failure, and considered the optimum cutoff value to distinguish between patients and controls was 77.5 ng/mL.

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Abbreviations

HF, Heart Failure; DM, Diabetes Mellitus; T2DM, Type Two Diabetes Mellitus; HbA1C, Glycated Hemoglobin; HDLC, High Density Lipoprotein-Cholesterol; LDLC, Low Density Lipoprotein-Cholesterol; VLDLC, Very Low Density Lipoprotein-Cholesterol; TC, Total Cholesterol; TAG, Triacylglycerol; NT-proBNP, N-terminal pro-B type natriuretic peptide; BNP, B-type natriuretic peptide; EDTA, Ethylene Diamine Tetracetic Acid; ROC, Receiver Operating Characteristic curve; BMI, Body Mass Index; Glu, Glucose; ELISA, Enzyme Linked Immuno Sorbent Assay.

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