Association of Protein Z with Diabetes Type 2 in Iraqi Patients that Previously Attacked with Covid 19.

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Abstract

Diabetes mellitus comes in a variety of forms, insulin resistance and absolute or relative insulin insufficiency (T2DM). The ongoing pandemic of COVID-19 has significantly affected blood glucose level in patients with diabetes mellitus. PROZ, a member of the coagulation class, inhibits activated factor X directly at the phospholipid surface, to reduce blood coagulation. PROZ suggested that alterations in their levels may be associated to vascular problems. The study included subjects T2DM with COVID 19, T2DM without COVID 19, Control with COVID 19, and control without COVID 19, for cytokine analysis. Blood samples of the subjects were assessed for PROZ and other parameters. Authors were identified PROTZ that differed by 1-fold or more in at least one out of the three comparisons T2DM with COVID 19 VS. Control with COVID 19, and T2DM without COVID 19 VS. control without COVID 19. Serum PROZ levels were found to be increased in T2DM with COVID 19 and T2DM without COVID 19 compared to those in control ($P<0.005$). There were association between PROZ and hemoglobin HbA1c. PROZ might be an effective biomarker for spotting diabetes.

Keywords: T2DM without COVID19, T2DM with COVID 19, PROZ

Introduction:

Diabetes mellitus comes in a variety of forms, Insulin resistance and absolute or relative insulin deficiency are the main causes of Type2 diabetes mellitus (T2DM), whereas insufficient insulin production is the characteristic of Type1 diabetes mellitus (T1DM). Additionally, people with impaired glucose tolerance or impaired fasting glycaemia have an increased chance of developing T2DM [1,2].The term "insulin resistance" refers to the decreased sensitivity of bodily tissue to insulin, which results in the dysfunction of the insulin receptors and the decline in glucose uptake mediated by insulin. . Insulin resistance is the term used to describe the reduced sensitivity of body tissue to insulin, which causes the insulin receptors to become dysfunctional and the decline in glucose uptake mediated by insulin [3,4,5,53]. With an overall prevalence of 9.3 percent and 463 million individuals globally, diabetes carries significant global impact [6].

Numerous comorbidities and long-term complications are frequently present, include cardiovascular disease, vasculopathy, obesity, hypertension, and a pro-inflammatory and hypercoagulable condition [7,9]. Also, other pandemic disease like COVID -19 contributed with DM [10,11]. Considering COVID-19's rapid spread and high mortality rate, it's critical to evaluate the

risk variables that could affect how the disease develops in COVID-19 patients. [12,55]. Depending on factors such as median age, illness severity, and lifestyle, type 2 diabetes rates in SARS-CoV-2 patients vary [13]. The relationship between DM and COVID 19 seems to be bidirectional. The COVID-19 infection directly impacts the patient's metabolism, leading to noticeable blood glucose increases. It is blamed on the uptick in cytokine and inflammatory mediator release, exacerbating insulin resistance. The goal of this study was to find cytokines that might be used as glucose dysmetabolism indicators. We investigated cytokines linked to glycemic state and examined cytokine profiles in diabetes type2 that previous attracted by covid19. Eventually, we chose and confirmed protein Z as a cytokine (PROZ) [14,15,16].

Material and Methods

Studied groups.

The present research included (60) DM type2 patients, divided into two groups (30) DM patients attracted by COVID 19, and (30) DM patients without COVID 19. A 40 healthy volunteers where divided into (20 with COVID 19, and 20 without covid19) ranging in age from (30 -65) years old. The investigation was conducted from January to March 2022 were recruited from the National Diabetes Center/Al Mustansiriya University/Iraq

Exclusion Criteria

These diabetic patients had no heart disease, liver disease, kidney disease, or hypertension. Patients who smoked were not accepted, with other diabetic complications. Individuals who were healthy in terms of not having diabetes, hypertension, or any other acute illnesses were chosen as the control. Additionally, they had no previous history of smoking or drinking.

Blood Sample

After a 10- to 12-hour overnight fast, each patient and control had their blood drawn. The blood sample was separated into two portions, the first of which (1mL) was transferred to an EDTA-containing tube to determine the amount of glycated hemoglobin(HbA1C). While the second was transferred to a gel tube to separate the serum, then used to measure the levels of glucose, LDH, lipids, and PROZ.

Experimental

Tosoh's automated glycohemoglobin analyzer HLC-723GX was used to measure glycated hemoglobin (HbA1C). The kits that provided by Bio System Spain were used to measure serum fasting blood glucose (FBG), total cholesterol (TC), total triglycerides(TG), and high-density lipoprotein(HDL) using an enzymatic colorimetric technique. An ELISA kit was used to assess the quantities of (LDH, and PROZ) LDH kit was supplied by MyBiosource, Southern California, San Diego (USA). Whereas, PROZ was supplied by abbexa , UK, Houston, TX USA, NO.: abx250269.

Statistical analysis

The outcomes were examined using a statistical analysis program (SPSS 25). The major findings were described using a general descriptive statistic, and group

comparisons were made using one-way and two-way Analysis of Variance tests. Besides employing cluster analysis to determine the groups of variables. The cutoff value for the investigated parameters was determined using the receiver operating characteristic curve (ROC) analysis.

Results

Some Biochemical characteristics were measured in the study population the results were illustrated in (Table 1). Statistically, significant differences appeared between studying groups for FSG, HbA1c, TC, TG, LDL, VLDL, LDH, AIP, and PROZ.

HbA1C, FBG, Cholesterol, TG, LDL, VLDL, LDL, PROS, and AIP, were significantly elevated in DM patients without COVID-19 as compared to the two types of control. Also, all the parameters showed significantly increment in group of DM with COVID-19 as compared to control except HDL.

Table1: Clinical data factor distribution in studied groups in patients having diabetes with/without covid19), (G1 DM without covid19, G2 DM with covid19, G3 control without covid19, G4 control with covid19.

Parameter	**G:I**	**G:II**	**G:III**	**GIV**
HbA1C%	9.45±0.46a,b	8.63±0.28c,d	5.13±0.05	5.33±0.068
FBG(mg/dl)	206.36±16.32a,b	196.42±11.14c,d	87.3478±1.11	87.6± 1.6
Cholesterol(mg/dl)	211.64±12.04a,b	196.57±7.57c,d	126.29±5.11	117.5±3.2
TG(mg/dl)	160.92±12.065a,b	170.06±11.44c,d	92.03±3.27	95.5±3.05
LDL(mg/dl)	134.88±11.003a,b	117.69±7.75c,d	52.54±4.61	47.36±3.098
HDL(mg/dl)	47.18±5.149	43.41±3.68	50.86±1.28	50.6±1.1
VLDL(mg/dl)	31.97±2.39a,b	34.39±2.31c,d	19.62±0.77	19.4 ±0.6
LDH(ng/ml)	2.61±0.14a,b	2.77±0.098c,d	1.57±0.028	1.56±0.09
PROZ(ng/ml)	21.96±1.022a,b	22.83±0.86c,d	9.83± 0.812	10.7±1.1
AIP	0.54±0.048a,b	0.57±0.036c,d	0.25±0.016	0.29±0.009

The data were presented as Mean ± Std. Error
The mean difference is significant at the 0.05 level
ONEWAY /POSTHOC=LSD alpha (0.05).
a: significant difference between control without COVID19 and DM without COVID19
b: significant difference between control With COVID19 and DM without COVID19
c: significant difference between control without COVID19 and DM with COVID19
d: significant difference between control With COVID19 and DM with COVID19
e: significant difference between DM without COVID19 and DM with COVID19
f: significant difference between control without COVID19 and control with COVID1

PROZ showed highly association to DM patient's as shown in figure (2) .

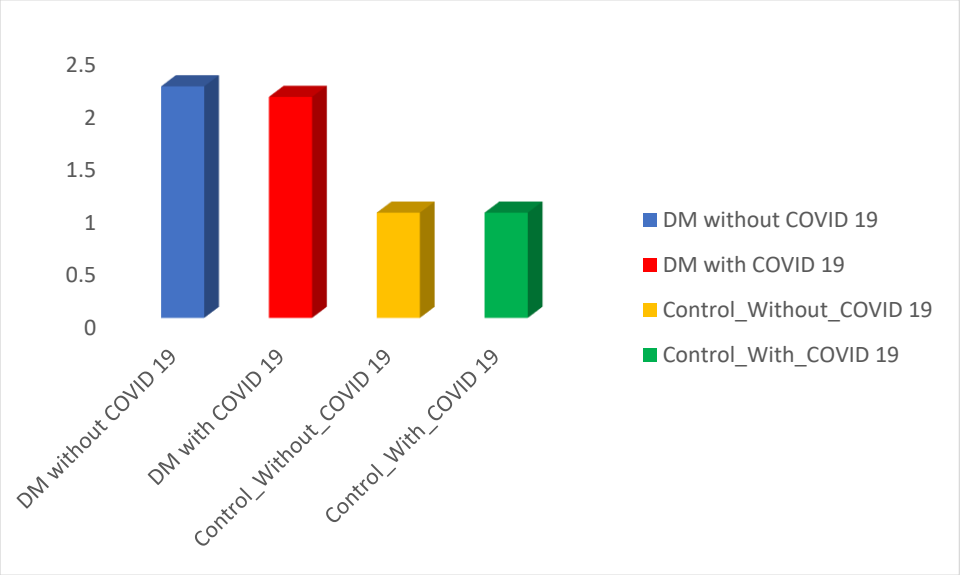

Fig (2): The association of PROZ with type 2 diabetes mellitus (T2DM). Fold changes of PROZ levels in subjects with T2DM with COVID 19, p T2DM without COVID 19, control with COVID 19, and Cntrol without COVID-19

The cluster analysis of Multivariate

cluster analysis of variables Using DM patients without covid19.

The cluster analysis was used to discover the similarities via studied variables. According to coefficients, the variables in all studied groups were distributed into 5 clusters, with mild shifting in some groups.

Figure (3) for DM patients without covid19 showed that (PROZ, LDH,AIP,VLDL, HDL , HbA1c) were distributed in one group, the second group was (TG,LDL), the third group was (TG, FBG) , the group was (FBG , Cholesterol) the fifth group was (PROZ , FBG, TG). The first two groups were similar in the characteristic than groups 4,5 if rescaled distance combine were organized. PROZ was combined to HbA1c in the same distance, so it represents the study similarity to these two variables.

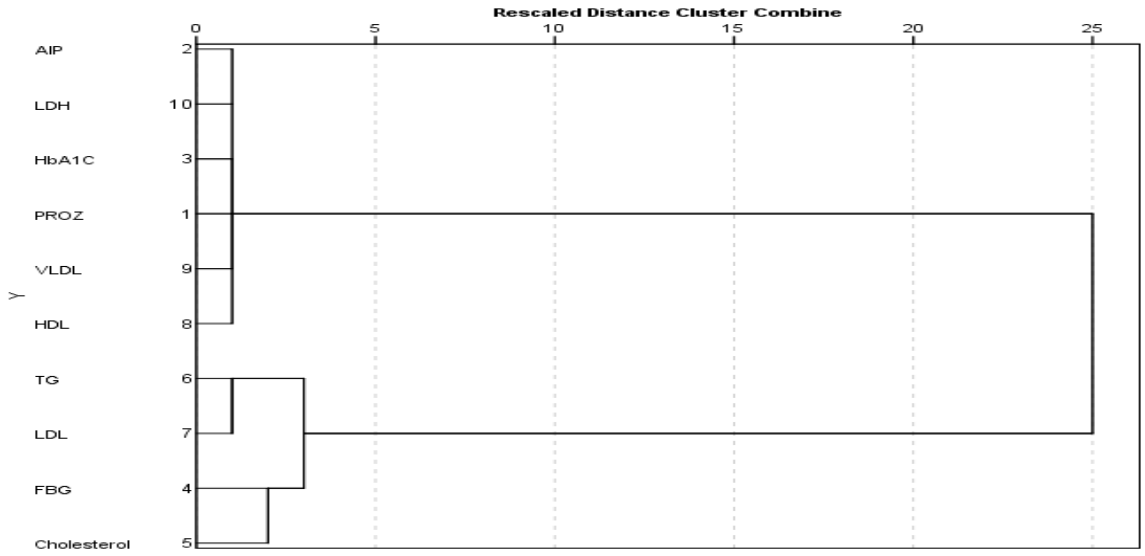

Figure (3): Cluster diagram of studied variables using DM patients without covid19.

cluster analysis of variables Using DM patients with covid19

The cluster analysis was used to discover the similarities via studied variables. According to coefficients, the variables in all studied groups were distributed into 5 clusters, with mild shifting in some groups. Figure (4) for DM patients with covid19 showed that (PROZ, LDH,AIP,VLDL, HDL , HbA1c) were distributed in one group, the second group was (TG, Cholesterol), the third group was (Cholesterol, FBG) , the forth group was (FBG , Cholesterol, LDL) the fifth group was (HbA1c , FBG, Cholesterol, LDL). PROZ was combined to HbA1c in the same distance, so it represents the study similarity to these two variables.

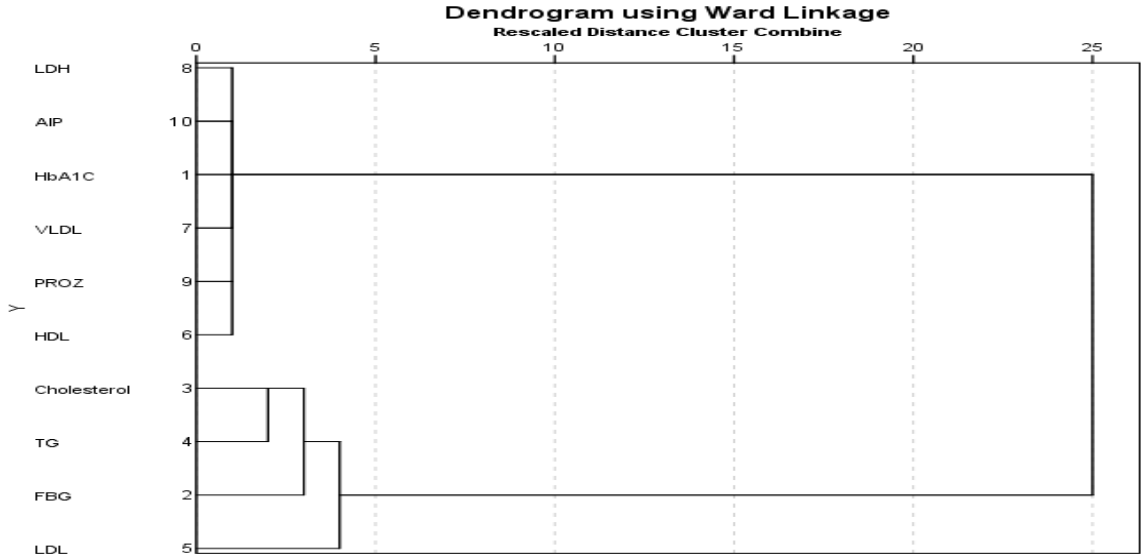

Figure (4): Cluster diagram of studied variables using DM patients with covid 19

Receiver Operating Characteristic (ROC) analysis

Receiver Operating Characteristic (ROC) analysis using patients of DM without COVID 19.

According to the Receiver Operating Characteristic (ROC) curve, the best cut-off point for patients of DM without COVID 19 shows sensitivity for PROZ Protein of (100%) and a specificity of (98%). It is found to be (12.1). In comparism FBG shows a sensitivity of (100%) and a specificity of (100%). Whereas, HbA1c shows a sensitivity of (99%) and specificity of (95%) as shown in Table (2) and Figure (5).

Table (2): ROC test for PROZ in **patients of DM without COVID 19**.

Parameters	Area	Sensitivity	Specificity	Cutoff	Asymptotic 95% Confidence Interval	
					Lower Bound	Upper Bound
PROZ	0.98	100%	98%	12.1	0.95	1
FBG	1	100%	100%	99	1	1
HbA1C	0.99	95%	100%	9.5	0.96	1

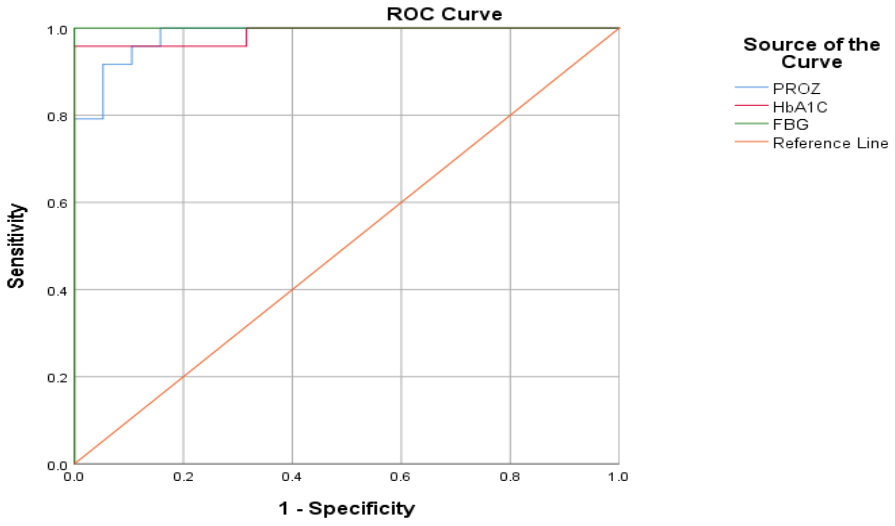

Figure (5): ROC carve for PROZ in patients of DM without COVID 19.

The result showed good sensitivity and specificity for PORZ when compared to the sensitivity and specificity for FBS and HbA1c that indicates the new marker is a good indicator for type II DM.

Receiver Operating Characteristic (ROC) analysis using patients of DM with COVID 19.

According to the Receiver Operating Characteristic (ROC) curve, the best cut-off point for patients of DM without COVID 19 shows sensitivity for PROZ Protein of (100%) and a specificity of (98%). It is found to be (12.1). Compares to FBG the result shows a sensitivity of (94%) and a specificity of (100%). Whereas, HbA1c shows a sensitivity of (100%) and specificity of (100%) as shown in Table () and Figure ().

Table (3): ROC test for PROZ in **patients of DM with COVID 19**.

Parameters	Area	Sensitivity	Specificity	Cutoff	Asymptotic 95% Confidence Interval	
					Lower Bound	Upper Bound
PROZ	0.96	100%	98%	13.6	0.91	1
FBG	0.98	94%	100%	96	0.96	1
HbA1C	1	100%	100%	5.8	1	1

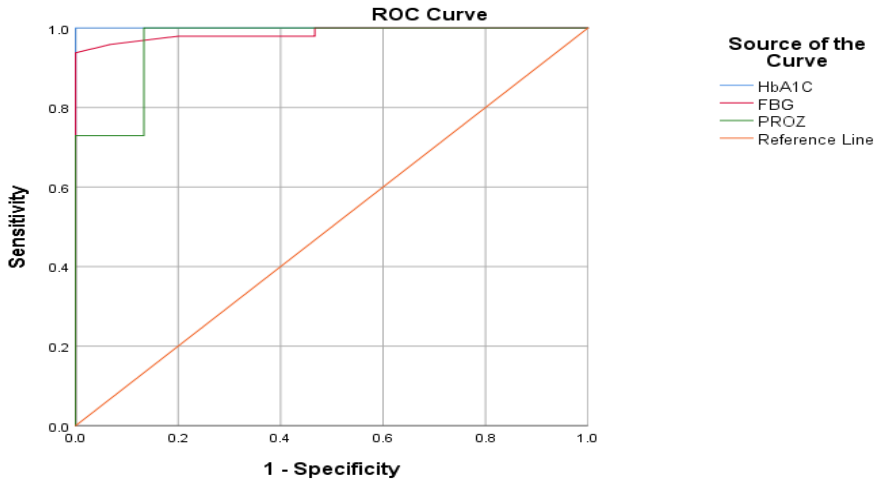

Figure (6): ROC carve for PROZ in patients of DM with COVID 19.

The result showed good sensitivity and specificity for PORZ when compared to the sensitivity and specificity for FBS and HbA1c that indicates the new marker is a good indicator for type II DM even though the patient's attacked with COVID 19.

Discussion

This study investigated how COVID-19 affected type 2 diabetes and compare them with patients that never attacked with COVID-19.

The relationship between diabetes mellitus and COVID-19 is intricate and bidirectional.

Additionally, one of the primary risk factors for a serious COVID-19 course is diabetes mellitus. There are a variety of factors that are likely to be at risk of diabetes mellitus, for instance advanced age, a pro-inflammatory and hypercoagulable condition, and hyperglycemia [17,18,19].

Moreover, the probability of a much more severe COVID-19 outcome and increased mortality is enhanced by diabetes and its associated conditions [20,21,22,54].

It is well known that individuals with diabetes are more susceptible to infections, which is partially attributed to the effects of hyperglycemia, which include immunological dysfunction [23,24,25,26,57].

A cytokine storm, an uncontrolled state of hyperinflammation that results in significant tissue damage, multiple organ failure, and death, is one situation in which COVID-19 is detected in some people. According to a study by Ragab D et al, a cytokine storm, an uncontrolled state of hyperinflammation that results in significant tissue damage, multiple organ failure, and death, is one situation in which COVID-19 is detected in some people [27]. This was also confirmed by Coperchini F et al, COVID-19's development is accelerated by inflammation [28].

Our studies have exhibited statically significant vibration between research groups DM2 with/without covid19 in FBS, and HbA1C when compare with healthy groups (Table1). As a result, COVID-19 causes hyperglycemia indiscriminately, and hyperglycemia enhances COVID-19's effects according to Cyril P. Landstra et al. Diabetes itself, as well as the comorbidities frequently linked to it, all increase the chance of a severe COVID-19 outcome by Cyril P. Landstra et al, [29].

In our study, PROZ level in diabetic type2 with covid-19 patients was higher than healthy controls with/without covid-19 as well, diabetic type 2 patients without covid-19 had higher levels of proteins markers when comparing to healthy control (Table1). PROZ is a member of the coagulation cascade structurally related to several serine proteases , it's a glycoprotein, the residues carboxyglutamate that require Vitamin K to bind Protein Z to phospholipid surfaces by [36,56].

PROZ inhibits activated factor X directly at the phospholipid surface by building complexes with the PROZ-dependent protease inhibitor, to inhibit blood coagulation by *Stegenga ME & Han X et al*,[30,31]. The role of PROZ in patients with cardiovascular disease has been reported in previous clinical research [32,51], Deep vein thrombosis [34,35], ischemic stroke [33], Additionally, other research have suggested that variations in PROZ levels may be connected to vascular problems in prediabetes and T2DM. consistent with Yun-Ui Bae et al,[36].

Tables (2) and (3) illustrated the correlations between PROZ and the other clinical parameters, respectively. In patients without COVID19, PROZ and FPG had statistically significant negative correlations. (Pearson R=-.136, Pearson P=0.517) as well as between PROZ and HbA1c (Pearson R=-.274 Pearson P=0.175). Moreover, in patients with covid19 there was significant negative

correlations between PROZ and FBG (Person R=-.153 Pearson P=.379) whereas it had a positive correlation with HbA1C (Person R=.273 Pearson P=0.124).

In the current study TG, TC, LDL and VLDL comparison to non-diabetics, level was higher in diabetic individuals in (Table 1) the results have showed significant increase in cholesterol, TG, LDL, and VLDL in diabetes type2 patients with/without covid19 as compare as to healthy controls with/without covid19.

Additionally, PROZ and all lipid profile parameters, excluding HDL, had significant negative correlations. We supposed that changes in PROZ levels could be related to vascular complications in diabetes type2 with/without covid 19. In (Table 2&3 respectively). The cytokine storm and significant inflammatory response seen in some patients with COVID-19 are thought to be the cause of hypercoagulation. In the case of COVID-19, patients with diabetes may be more vulnerable to thromboembolic events because they have a more pronounced inflammatory response, both hyperinsulinemia and hyperglycemia, both of which have been shown to accelerate coagulation, which blocks fibrinolytic activity and reduces the propensity for hypercoagulable blood states that cause coronary artery disease, may both have important effects on how diabetic patients develop coronary artery disease. Thromboembolic conditions [30,3] Lactate dehydrogenase (LDH), an enzyme involved in metabolism, is found in most body cells. [38, 39]. LDH primarily works by oxidizing pyruvate to produce lactate. LDH is mostly present in the cytoplasm of cells, becoming extracellular after cell death. Consequently, their leaking from injured tissues is what is responsible for the higher serum activity level. By reducing glycogen synthesis, altering glucose oxidative metabolism, and increasing the whole-body rate of non-oxidative glycolysis, these pathways result in higher lactate in people with insulin resistance compared to those without [40, 41, 43]. In our study we were finding the higher level of LDH enzyme in diabetic patients that previous attacked with covid19 when compared with the healthy non-diabetic patients (Table1). This is in agreement with other studies Malicka B and Hussein H. Dmour et al, that reported higher levels of LDH in diabetic patients compared with control group by Malicka B& Hussein H. Dmour et al, [42,44]. Moreover, we were finding in (Table2&3) there were positive correlation between PROZ and LDH. LDH increase in COVID-19 patients implies lung and tissue damage by Li X et al, [47]. Due to different reasons, such as thrombosis, which causes LDH increase, COVID-19 may result in insufficient tissue perfusion and multiple organ failure [45,46]. Thus, high LDH is indeed a biomarker of the severity of the disease. Age is a feature that could potentially indicate the progression of diabetes. The age ranges of the DM type 2 group in the current investigation were identical. While higher level of DM type 2 when compared with healthy group, but this result give us promising that covid-19 effect on DM with age difference. These findings most likely resulted from significant lifestyle and dietary variations. When treating and managing type 2 diabetes, it is important to

take into account the different negative symptoms that diabetic patients may experience. [57,58] Therefore, it is widely known that weight gain worsens glucose metabolism in T2DM and increases insulin resistance by Emilia Biamonte et al, [28]. Unsurprisingly, we discovered a direct relationship between increased glycated hemoglobin and all anthropometric measurements, including body weight, BMI, AIP and waist circumference [49,50,52].

Conclusion

Current research discovered PROZ, a possible cytokine linked to diabetes and a prospective biomarker of glucose dysmetabolism. The association between PROZ and T2DM with COVID-19 and T2DM without COVID-19 may possibly point to additional processes behind glucose dysmetabolism.

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