

Estimation of Macrophage Inhibitory Cytokine (MIC-1) and Phosphorylated Protein in Chronic Kidney Disease Among Type 2 Diabetic Patients

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ABSTRACT

Background: Diabetic kidney disease (DKD) is recognised as one of the most frequent and severe complications of diabetes mellitus, contributing significantly to morbidity and mortality worldwide. Identifying reliable biomarkers that can reflect disease progression remains a critical challenge. **Objective:** This study aimed to evaluate the diagnostic potential of Macrophage Inhibitory Cytokine-1 (MIC-1) and Protein Phosphatase 2A (PP2A), alongside oxidative stress markers and biochemical variables, in patients with chronic kidney disease (CKD) with and without diabetes. **Materials and Methods:** A total of 150 participants were enrolled: 50 with CKD and type 2 diabetes mellitus (G1), 50 with CKD without diabetes (G2), and 50 healthy controls (G3). Biochemical parameters, including cholesterol, triglycerides, HDL, LDL, and fasting blood sugar (FBS), were measured using a CS-T180 automated biochemical analyser. HbA1c was assessed using an icroma instrument. Serum MIC-1, insulin, PP2A, SOD, GSH-Px, and LPO levels were quantified by ELISA. HOMA-IR and estimated glomerular filtration rate (eGFR) were calculated. **Results:** Age and sex distribution did not differ significantly between groups. Patients in both CKD groups demonstrated significantly higher FBS, urea, creatinine, lipids, and HbA1c compared to controls ($P < 0.01$), with eGFR markedly reduced. Haemoglobin, iron, and ferritin levels were significantly lower in diabetic CKD patients. MIC-1 and PP2A levels varied strongly across groups ($P < 0.0001$), with diabetic CKD patients showing the highest elevations. Insulin and HOMA-IR levels were also significantly increased in diabetic patients. Receiver operating characteristic (ROC) analysis revealed that MIC-1 and PP2A had strong diagnostic accuracy, with AUC values ranging from 0.96 to 0.98. **Conclusion:** The study demonstrates that MIC-1 and PP2A are significantly elevated in diabetic CKD patients and correlate with disease severity, highlighting their potential as valuable biomarkers for the early detection and monitoring of diabetic kidney disease. Incorporating these markers alongside traditional biochemical parameters may enhance diagnostic precision and improve disease management.

Keywords: DKD, MIC-1, PP2A SOD, GSH-Px, and LPO

INTRODUCTION

Diabetes mellitus (DM) is one of the most serious and widespread metabolic disorders, defined by persistently elevated blood glucose levels that arise either from a defect in the pancreatic β -cells leading to inadequate insulin secretion, or from a reduced ability of the body's tissues to effectively utilize the insulin that is produced[1]. In many cases, the disease may develop as a consequence of hereditary genetic factors, while in others it appears secondary to a range of metabolic dysfunctions. Type 2 diabetes mellitus (T2DM) is particularly important because it has become one of the foremost underlying conditions responsible for the development of chronic kidney disease (CKD) across the globe [2]. Prolonged hyperglycemia, when left uncontrolled, damages the delicate network of blood vessels within the kidneys, compromising their ability to filter waste products efficiently. Over time, this culminates in progressive renal impairment and eventual kidney failure. Therefore, continuous monitoring and strict control of blood sugar levels remain central strategies for diabetic patients in order to slow or prevent the progression of CKD[3]. A number of metabolic markers are routinely assessed to predict complications of diabetes. Among them, glycated hemoglobin (HbA1c), fasting blood glucose concentration, and indices of insulin resistance (IR) are widely acknowledged as strong predictors of both microvascular and macrovascular complications of T2DM [4]. As the disease advances, patients frequently develop diabetic kidney disease (DKD), which represents one of the most severe complications[5]. Dyslipidemia—manifesting as elevated triglycerides (TG), increased low-density lipoprotein (LDL), and high levels of total cholesterol

(CH)—has been consistently shown to have an independent and strong association with DKD. CKD itself is formally characterized as a persistent abnormality in the structure or function of the kidneys lasting longer than three months, most often identified by an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m². When diabetes is the primary cause of renal impairment, CKD takes on an even more aggressive and progressive course [6]. Widely used biochemical indicators for evaluating kidney function include measurements of serum creatinine and blood urea levels, both of which are reliable markers of renal impairment in diabetic patients[7]. Beyond purely metabolic disturbances, DM and CKD are now recognized as conditions that involve significant inflammatory processes. Inflammation not only plays a central role in the initiation but also in the progression of these disorders and their complications [8]. Patients suffering from CKD frequently exhibit a phenomenon known as protein-energy wasting, which is strongly associated with chronic systemic inflammation. This inflammatory state is reflected in elevated levels of circulating inflammatory cytokines and oxidative stress biomarkers[9]. CKD is marked by enhanced production of reactive oxygen species (ROS), which arise from the upregulation of numerous enzymatic systems, including nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, xanthine oxidase, the mitochondrial respiratory chain, lipoxygenase, and uncoupled nitric oxide synthase (NOS)[10]. The harmful effects of oxidative stress are further aggravated by reduced activity of endogenous antioxidant defense mechanisms. Enzymatic antioxidants such as selenium-

dependent glutathione peroxidase, catalase, and superoxide dismutase (SOD) are normally vital in maintaining cellular redox balance, but in CKD their levels and activity are markedly compromised, amplifying tissue damage[11]. Another element increasingly studied in relation to metabolic and renal disorders is the macrophage-derived apoptosis inhibitor of macrophage (AIM) protein. This protein plays an important role in promoting lipolysis within adipose tissue and in facilitating the recruitment of macrophages into adipose depots. Elevated levels of AIM are frequently observed in individuals with obesity, further linking it to metabolic and inflammatory dysregulation. Closely related in significance is macrophage inhibitory cytokine-1 (MIC-1), a member of the transforming growth factor-beta (TGF- β) superfamily. MIC-1 is secreted in response to macrophage activation, and elevated serum levels of this cytokine have been associated with a range of chronic inflammatory conditions, including cardiovascular and kidney diseases. Because MIC-1 serves both as an indicator of macrophage activity and as a mediator of inflammation, it is gaining attention as a biomarker with potential diagnostic and prognostic value in DKD[12, 13]. Another crucial molecular player is protein phosphatase 2A (PP2A), a serine/threonine phosphatase composed of structural, regulatory, and catalytic subunits.

PP2A is central to numerous cellular processes, functioning by dephosphorylating target proteins involved in signaling pathways. [14]. Within the kidney, PP2A contributes to development, growth regulation, and the control of ion-transport proteins, thereby playing a crucial role in maintaining normal renal physiology. Dysregulation of PP2A activity, however, has been implicated in pathological conditions affecting the kidneys. For example, TGF- β -induced nitration enhances the activity of the PP2A catalytic subunit (PP2Ac), which has been shown to increase PP2A activity in endothelial cells. This dysregulated PP2A activity disrupts cytoskeletal organization and facilitates endothelial-to-mesenchymal transition (EndMT), a process known to generate myofibroblasts that contribute directly to renal fibrosis. Thus, PP2A not only plays a physiological role but also contributes to the pathogenesis of CKD when abnormally regulated [15, 16]. Considering the above, the combined study of MIC-1 and

PP2A in the context of diabetes-associated CKD is of substantial importance. Both biomarkers are linked to inflammation, oxidative stress, and cellular dysfunction—key mechanisms in DKD progression. Exploring their diagnostic and prognostic significance may therefore yield valuable insights into disease mechanisms and highlight potential therapeutic targets for intervention [17].

MATERIAL AND METHODS

The study included 150 volunteers from July 1, 2024, to September 30, 2024, each group comprising 50 patients with (CKD) (G1) diabetes, 50 without CKD (G2), and 50 healthy controls (G3). The volunteer patients were recruited from Al-Yarmouk Teaching Hospital and Baghdad Teaching Hospital, and included 71 males and 79 females. Participants' ages ranged from 30 to 70 years. Quantitative analysis of CH, TG, HDL, LDL, FBS levels was performed using an automated biochemical analyzer CS-T180, and HbA1c% estimated by icroma instrument. ELISA was used to measure MIC-1, insulin, Pp2a, glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), and lipid peroxidase (LPO). The formula [fasting insulin (μ U/mL) $\times$ fasting glucose (mmol/L)]/22.5 was used to calculate the HOMA-IR [18], The GFR was estimated using the Modification of Diet in Renal Disease equation [19].

Statistical Analysis

The expression of data was done throught percentages, mean, and standard deviation. In our study, the independent t-test, one-way ANOVA test, LSD test, and receiver operating characteristic (ROC) were used too. The significance threshold of < 0.05 was considered as significant. The SPSS 24 program was used to examine current data.

RESULTS AND DISCUSSIONS

In the current study, 150 participants were enrolled. The age was non-significant difference between CKD patients with and without T2DM compared to the patients in the control group as displayed in table (1) and figure (1).

Table 1: Age of the Patients in Study Groups

Age (Year)	Control No. (%)	CKD Patients		P-Value	Sig.
		DM No. (%)	Non-DM No. (%)		
30-40 yr.	10 (18.4%)	10 (20.00%)	11 (22.00%)	0.56	NS >0.005
41-50 yr.	13 (26.5%)	2 (4.00%)	12 (24.00%)	0.743	
51-60 yr.	13 (26.5%)	18 (36.00%)	16 (32.00%)	0.452	
61-70 yr	14 (28.6%)	20 (40.00%)	11 (22.00%)	0.721	

Chi-square test, No: Number, NS: No Significant

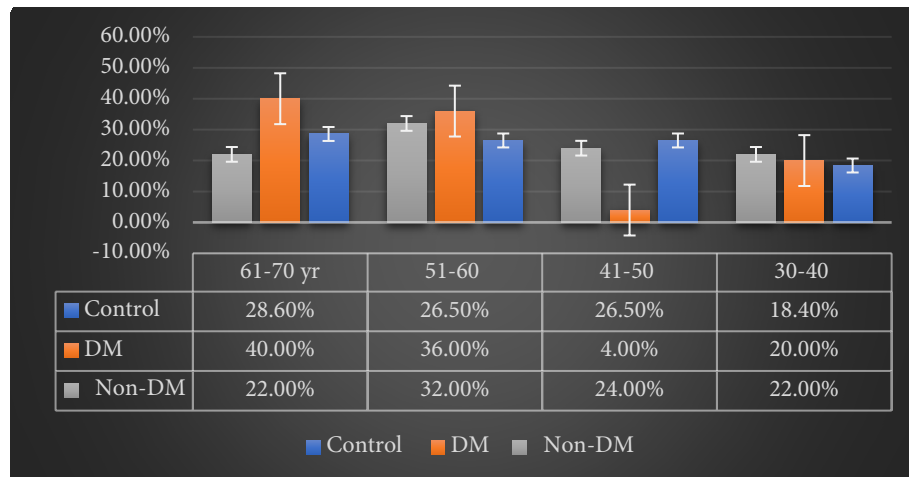


Figure 1: Distribution of the Study Groups by Age (Year)

In table (2) and figure (2) show there is no statistically significant was observed in gender distribution ($p>0.005$) between CKD compared to control groups. As shown in table (3), the (mean $\pm$ SD) of serum FBS, HbA1c%, eGFR, urea, creatinine ferritin, CH, TG, and LDL were all greater in the two CKD groups relative to controls, with the diabetic

group CKD showing the most severe alterations. These differences were statistically highly significant ($P<0.01$). Patients (diabetic and non-diabetic patients) showed significantly lower (0.0082) hemoglobin and serum iron levels describing as anemia along with suggesting iron derangement in diabetes.

Table 2: Demographic Characteristics of the Studied Group According to Gender

Gender	Control No. (%)	CKD Patients		P-Value	Sig.
		DM No. (%)	Non-DM No. (%)		
Female	21(40.8%)	25(50%)	25(50%)	>0.005	NS
Male	29(59.2%)	25(50%)	25(50%)		

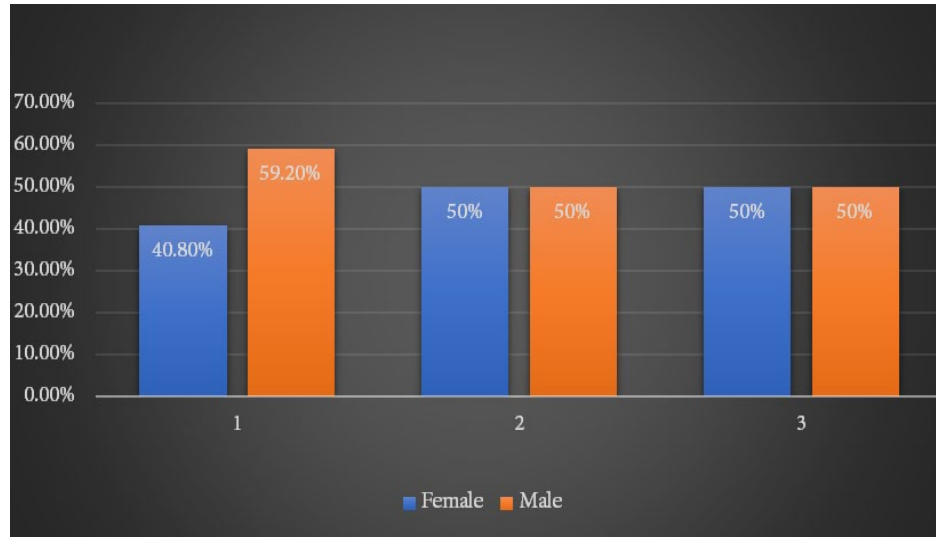


Figure 2: Distribution of the Study Groups by Gender

Table 3: Serum Level of BIOMARKER in the Studied Group

Parameters	Control Mean $\pm$ SD	CKD Groups		P –Value	Sig
		DM Mean $\pm$ SD	Non-DM Mean $\pm$ SD		
HbA1C%	5.21 $\pm$ 0.2	11.06 $\pm$ 7.1	6.13 $\pm$ 0.2	0.01	H.S
Fasting blood sugar (mg/dl)	85.72 $\pm$ 9.16	211.8 $\pm$ 54.3	86.72 $\pm$ 9.16	0.01	
eGFR (ml/min)	110.70 $\pm$ 1.66	5.09 $\pm$ 0.31	7.17 $\pm$ 0.46	0.01	
Urea (mg/dl)	36.40 $\pm$ 5.33	148.04 $\pm$ 38.56	151 $\pm$ 50.3	0.01	
Creatinine (mg/dl)	2.25 $\pm$ 0.17	8.84 $\pm$ 1.18	7.8 $\pm$ 2.17	0.01	
Ferritin (ng/dl)	166.7 $\pm$ 24.69	755.36 $\pm$ 243.4	763.46 $\pm$ 244.69	0.01	
Hb (g/dl)	12.6 $\pm$ 1.12	9.37 $\pm$ 1.23	8.62 $\pm$ 1.62	0.01	
Iron (μ mol/l)	19.16 $\pm$ 4.42	14.63 $\pm$ 4.37	11.2 $\pm$ 3.92	0.01	
CH (mg/dl)	160.2 $\pm$ 12.4	222.0 $\pm$ 64.43	214.9 $\pm$ 41.2	0.01	
TG (mg/dl)	117.93 $\pm$ 20.8	216.4 $\pm$ 89.9	179.7 $\pm$ 30.	0.01	
HDL (mg/dl)	78.75 $\pm$ 16	44.78 $\pm$ 12.0	55.6 $\pm$ 13.3	0.01	
LDL (mg/dl)	86.63 $\pm$ 10.9	118.0 $\pm$ 34.6	92.74 $\pm$ 24.9	0.01	

Table (4) showed that biomarkers MIC-1, Pp2A was highly significant differences ($P \leq 0.0001$) among the studied groups in CKD (DM and NDM) groups relative to controls, especially in the diabetic group that association as diabetes- kidney injury. Antioxidant markers GSH and SOD were significantly lower in CKD groups, especially in diabetic's patients.

LPO, a marker of oxidative stress, was elevated, especially in diabetic CKD patients. As well as, a significantly higher insulin and HOMA-IR were gotten in the diabetic group, indicating the presence of insulin resistance. Increased oxidative stress, reduced antioxidant capacity, and disrupted metabolic regulation suggest that CKD is linked to diabetes

Table 4: Serum Level of BIOMARKER in the Studied Group

Parameters	Control Mean $\pm$ SD	CKD Groups		P –Value	Sig.
		DM Mean $\pm$ SD	Non-DM Mean $\pm$ SD		
MIC-1	561.55 $\pm$ 47.16	1860.48 $\pm$ 479.9	1195.24 $\pm$ 240.85	≤ 0.0001	H.S
Pp2A	44.40 $\pm$ 17.90	142.81 $\pm$ 22.16	122.96 $\pm$ 51.20	≤ 0.0001	H.S
GSH	19.33 $\pm$ 5.39	5.82 $\pm$ 1.39	11.29 $\pm$ 5.30	≤ 0.0001	H.S
LPO	1.53 $\pm$ 0.56	6.09 $\pm$ 1.53	3.03 $\pm$ 1.27	≤ 0.0001	H.S
SOD	5.34 $\pm$ 1.08	1.25 $\pm$ 0.54	2.88 $\pm$ 0.84	≤ 0.0001	H.S
Insulin	1.83 $\pm$ 0.3	9.61 $\pm$ 4.6	5.08 $\pm$ 2.76	≤ 0.0001	H.S
HOMA-IR	0.46 $\pm$ 0.09	4.40 $\pm$ 2.42	1.49120 $\pm$ 0.81	≤ 0.0001	H.S

In table 5 and based on LSD multiple comparison analysis are extremely significant ($P \leq 0.0001$) among parameters for diabetic CKD patients (G1), non-diabetic CKD patients (G2), and the control group (G3). HbA_{1c} did not showed significant difference in its level between

G2 and G3 ($P=0.5$). Furthermore, there was no significant difference in TC levels between G1 and G2 ($P = 0.43$). LDL, also no significant differences were noted between G2 and G3, as well as between G1 and G3 ($P < 0.0001$).

Table 5: Multiple Comparisons of Biochemical Parameters

Parameters	G1&G3		G2&G3		G1&G2	
	P-Value	Sig.	P-Value	Sig.	P-Value	Sig.
HbA _{1c} %	≤ 0.0001	H.S	0.5	NS	≤ 0.0001	H.S
Fasting blood sugar (mg/dl)	≤ 0.0001	H.S	≤ 0.0001	H.S	≤ 0.0001	H.S
eGFR (ml/min)	≤ 0.0001	H.S	≤ 0.0001	H.S	≤ 0.0001	H.S
Urea (mg/dl)	≤ 0.0001	H.S	≤ 0.0001	H.S	≤ 0.0001	H.S
Creatinine (mg/dl)	≤ 0.0001	H.S	≤ 0.0001	H.S	≤ 0.0001	H.S
Ferritin (ng/dl)	≤ 0.0001	H.S	≤ 0.0001	H.S	≤ 0.0001	H.S
Hb (g/dl)	≤ 0.0001	H.S	≤ 0.0001	H.S	≤ 0.0001	H.S
Iron (μ mol/l)	≤ 0.0001	H.S	≤ 0.0001	H.S	≤ 0.0001	H.S
Cholesterol (mg/dl)	≤ 0.0001	H.S	≤ 0.0001	H.S	0.43	NS
Triglyceride (mg/dl)	≤ 0.0001	H.S	≤ 0.0001	H.S	≤ 0.0001	H.S
HDL (mg/dl)	≤ 0.0001	H.S	≤ 0.0001	H.S	≤ 0.0001	H.S
LDL (mg/dl)	≤ 0.0001	H.S	0.23	NS	≤ 0.0001	H.S

In based on LSD test the results presented in table (6) show that MIC-1, Pp2A, GSH, LPO, SOD, insulin, and HOMA-IR, highly significant differences ($P \leq 0.0001$) in the two CKD groups relative to controls (G1 vs G3, G2 vs G3, and G1 vs G2).

This shows that the both of the diabetic and non-diabetic CKD patients are significantly different from the healthy control patients in their oxidative stress and insulin resistance along with another biomarker.

Table 6: Multiple Comparisons of Biochemical Parameters

Parameters	G1&G3		G2&G3		G1&G2	
	P-Value	Sig.	P-Value	Sig.	P-Value	Sig.
MIC-1	≤ 0.0001	H.S	≤ 0.0001	H.S	≤ 0.0001	H.S
Pp2A	≤ 0.0001	H.S	≤ 0.0001	H.S	≤ 0.0001	H.S
GSH	≤ 0.0001	H.S	≤ 0.0001	H.S	≤ 0.0001	H.S
LPO	≤ 0.0001	H.S	≤ 0.0001	H.S	≤ 0.0001	H.S
SOD	≤ 0.0001	H.S	≤ 0.0001	H.S	≤ 0.0001	H.S
Insulin	≤ 0.0001	H.S	≤ 0.0001	H.S	≤ 0.0001	H.S
HOMA-IR	≤ 0.0001	H.S	≤ 0.0001	H.S	≤ 0.0001	H.S

Based on LSD TEST (G1- DM G2- non-DM and G3-Contol

The cutoff value for MIC-1, Pp2A, Insulin and HOMA-IR was 674,76,2.20,0.68 with 97%, 96%, 95%, 98% sensitivity and 100%, 98% specificity [according to ROC curve of the level between the patient

groups and the control group]. Moreover, area under the curve (AUC) of 0.98, 0.96, 0.98, 0.96 with highly significant ($P < 0.0001$), as shown in table (7) and figure (3).

Table 7: ROC Curve for MIC-1 and Pp2A (Receiver Operating Characteristic Curve Test)

Mic-1	Auc	P-Value	Cut-Off Point	Sensitivity	Specificity
Pp2A	0.98	0.000*	684	97%	100%
GSH	0.96	0.000*	76	96%	100%
LPO	0.98	0.000*	2.20	95%	100%
SOD	0.96	0.000*	0.68	98%	98%

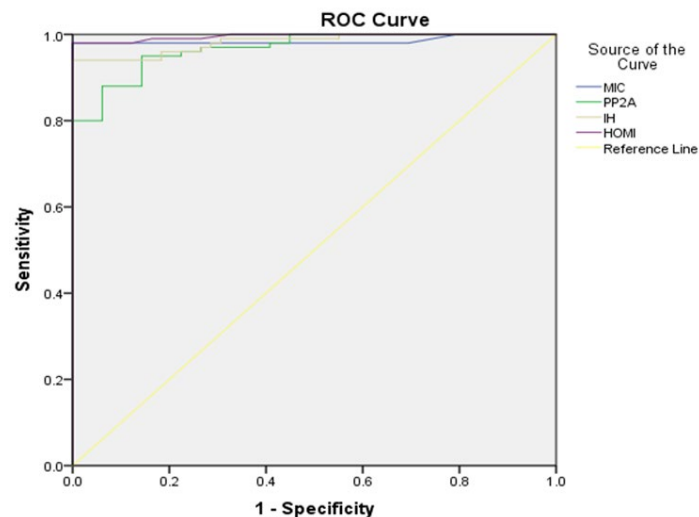


Figure 3: ROC Curve for MIC-1 and Pp2A

Discussion

The kidneys' ability to filter waste products from the blood becomes impaired. As kidney function declines over time, these waste products continue to accumulate in the body, leading to elevated levels in the blood. The chronic hyperglycemia phases of diabetes cause damage to the blood vessels within the kidneys through a method called glycation, where sugar molecules attach to proteins and other molecules, resulting in dysfunction of systems and features. This glycation damages glomeruli, the small filtration units within the kidneys, impairing their ability to filter blood efficiently [20]. Fatty acids can exist in the body either as free fatty acids or in combination with cholesterol esters, TGs, LDL, VLDL and HDL to form complex lipids, these modifications cause lead to several effects in the pathogenesis of T2DM [21]. The activation of inflammatory pathways is a normal physiological response. Following acute aerobic exercise, both healthy individuals and obese nondiabetic subjects exhibit high expression of cytokines such as MCP-1 in skeletal muscle, along with activation of the NF- κ B signaling pathway [22]. Increased incidence of chronic kidney disease was attributed to decline in glomerular filtration associated with aging. Thus, a crucial strategy for improving results was to conduct screenings for chronic kidney disease in older adults [23]. As people age, their total fat mass reorganizes, increasing the deposition of ectopic fat in the abdomen, skeletal muscle, liver, and skeletal muscle. Numerous studies have shown evidence that a reduction in energy expenditure is a significant factor in the fat buildup that occurs as people age [24]. Ferritin levels can rise above normal in patients with CKD who also have diabetes. Chronic kidney disease and diabetes are associated with chronic inflammation. Ferritin is an acute phase reactant, meaning that its levels increase in response to inflammation. Inflammation stimulates the liver to produce more ferritin, leading to higher blood ferritin levels [25]. CKD often leads to disturbances in iron metabolism.

The kidneys are responsible for producing erythropoietin, a hormone essential for stimulating the production of red blood cells. Low erythropoietin levels in CKD can lead to anemia, prompting the body to increase iron storage as ferritin [26]. The kidneys are responsible for filtering and removing various substances from the blood. In CKD, decreased kidney function leads to decreased ferritin clearance, which contributes to its accumulation in the blood [27]. The lipid peroxidation is contributes to the pathogenesis of

complications associated with diabetes mellitus [28], in this environment, the activities of LPO, SOD, and GSH-Px were either increased or decreased [29]. Oxidative stress has a pronounced impact on pancreatic beta cells. This is due to two main factors: elevated endogenous ROS, which beta cells produce in large amounts during insulin secretion; and low antioxidant capacity resulting from the relatively low antioxidant capacity of beta cells. This means that they are not very good at scavenging ROS and protecting themselves from oxidative damage [30, 31]. The findings of this study indicate a reduction in the activity levels of glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) among individuals diagnosed with (T2DM) and those classified as pre-diabetic, comparing to the patients in the control group [1]. The reduced activity of these enzyme may be caused by the depletion of the antioxidant defence system as a result of the excessive formation of free radicals [32]. PP2A is a major serine/threonine phosphatase involved in the insulin signaling pathway and supposed to be one of the causes of insulin resistance leading to T2DM [33]. physiological stress conditions like glucotoxicity and lipotoxicity, can cause hyperactivated PP2Ac protein in various organs, leading to insulin resistance with subsequent dysfunction of the pancreatic β -cell. However, PP2A activity can be regained by affecting gene transcription or protein expression [34]. MIC-1 is regarded as a long-term regulator of metabolism, functioning as an adipokine that promotes lipolysis through paracrine signaling mechanisms [35, 36]. The MIC-1 protein contains PEST sequences, which are rich in serine, proline, threonine, and glutamic acid, and making it prone to rapid degradation through various cellular pathways. Studies have shown that MIC-1 co-immunoprecipitates with PP2A when transfected into CHO cells. Moreover, knockdown of the PP2A/A subunit leads to increased MIC-1 phosphorylation and reduced protein expression. Overall, inhibition of PP2A impairs MIC-1 dephosphorylation, resulting in the rapid degradation of this pro-survival protein, which plays a role in chemoresistance [37].

Conclusion

Increased lipid peroxidation and PP2A may represent an additive effect to the metabolic imbalance associated with T2DM and the development of diabetes-associated complications. Additionally, elevated Pp2a levels in the DM group and may be indicators of the pathophysiology of T2DM complications. Thus, elevated Pp2a may be due to increased oxidative stress in T2DM.

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