Research Article ISSN 2693-2458

Journal of Diabetes and Endocrinology Research

ROC Analyses of Plasma Oxidative Stress Markers for Prediction of CKD Complications of Type 2 Diabetes

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Submitted : 15 Jun 2024 ; Published : 10 July 2024

Citation : Derouiche, s. et al. (2024). ROC analyses of Plasma oxidative stress markers for Prediction of CKD complications of type 2 Diabetes. J Diabetes Endocrinol Res; 5(1):1-7.

Abstract

Background and Aims: *Chronic Kidney Disease (CKD) is one of the most important complications of diabetes. Many physiological and biochemical changes may cause these complications to appear. The objective of this study was to evaluate the variation oxidative stress for the diagnosis and prediction of renal complication in type 2 diabetic patients.*

Material & Methods: *Sixty voluntary individuals were divided into two diabetic groups with and without CKD complication on which we assayed some biochemical and oxidative stress parameters. Sensitivity and Specificity of Oxidative stress biomarkers in serum were estimated using receiver operating characteristics (ROC) curve design.*

Findings: *The results obtained in the present study clearly show that diabetes is confirmed by the hyperglycemia observed in all diabetic patients. The results obtained also show a significant increase ($P < 0.05$) in the concentration of urea, creatinine, uric acid, potassium and serum albumin in diabetic patients with nephropathy compared to diabetics. On the other hand, it was shown that a significant increase ($P < 0.05$) in the concentration of MDA, GSH and total thiol in the serum of diabetic patients compared to diabetics with complications of CKD. ROC assay analysis showed that serum GSH and MDA are predictive markers with high specificity (100%) of nephrotic complications of diabetes.*

Conclusion: *The present study reveals that diabetes induces metabolic and physiological alterations and an imbalance of oxidant / antioxidant status, which can cause nephrotic complications suggesting the use of GSH, MDA as predictive markers for this complication of the disease.*

Keywords : Diabetes, CKD, oxidative stress, ROC.

Introduction

Diabetes is a major public health problem, a growing pathology with heavy human as well as socio-economic consequences (Derouiche et al., 2017) a disorder of glucose metabolism characterized by abnormal blood sugar levels resulting from the body's inability to make or use insulin (American Diabetes Association[ADA],2013) . According to estimates, there will be 642 million cases of diabetes worldwide by 2040, up from 415 million cases (8.8%) in 2015, with the greatest changes anticipated in the urban populations of low- and middle-income countries (LMICs). More than 90% of those with diabetes have type 2 diabetes mellitus (T2DM), with 477.9 million impacted persons living in urban areas and 163.9 million in rural regions, the gap is expected to widen globally by 2040 (Jitraknatee et al., 2020). Responsible for nearly 4 million deaths each year, this pathology is considered by WHO as an epidemic whose prevalence has increased dramatically in recent years (Deshpande et al., 2008). This pathology is most often accompanied by complications related to chronic hyperglycemia and associated cardiovascular risk factors (Stratton et al., 2000). They are numerous and affect several organs, following a micro or macroangiopathy (Chawla et al., 2016). Currently, Diabetes poses a real public health problem due to its prevalence and the weight of its chronic complications dominated by cardiovascular complications, diabetic foot, chronic renal failure and retinopathy (Chetehouna et al., 2024). Among the chronic complications of diabetes (microvascular) nephropathy, it is a degenerative disease which by specific glomerular involvement (Collart, 2003).

Nephropathy is arguably the disease with the worst prognosis. Besides the risk of end stage renal disease (Shahbazian & Rezaii, 2013). More than 3.5 Million Algerians with all-stage

CKD were identified. Additionally, there were nearly 25.000 cases of ESKD patients, with an estimated prevalence of 600 pmp (patients per million population) and incidence of 200 pmp (Berkache et al., 2021). According to nephrologists' consultations, 14% of kidney failure is caused by diabetes, and in 2011 over 2,000 diabetics needed dialysis (this number was relatively low because only about 5% of the population is 65 or older). 50 to 100 new instances of renal failure are reported year on average. A little more than one-third of patients had macroproteinuria, while one in five patients had microalbuminuria. In 0.52 percent of people with type 2 diabetes, end-stage renal disease was discovered (Alicic et al., 2017).

In Algeria, it is estimated that 25% of dialysis patients are diabetic. Chronic dialysis patients have a risk of vascular death twice as high as non-diabetic dialysis patients. Mortality is greater than 25% in the two years following dialysis in diabetics (Ramache, 2010). With 40% of the causes of end-stage renal disease, diabetic nephropathy is at the forefront of nephrology concerns. It typically develops in 30% of type 1 diabetic patients after 10 to 25 years of evolution. Its prevalence is higher than that of subjects with T2D; 5-10% but due to the higher prevalence of type 2 diabetes; more patients suffer from CKD (Gheith et al., 2015). The incidence of CKD of diabetic origin is progressing the fastest at around 10 to 15% per year. This increase in incidence is attributed to several factors, including in particular the aging of the population, socio-nutritional factors and a reduction in cardiovascular mortality, in particular linked to myocardial infarction and stroke, thus allowing the expression of diabetic nephropathy (Cabrera et al., 2020).

These complications are strongly linked to the release of free radicals and oxidative stress (Chetehouna et al., 2021). Oxidants or free radicals are atoms or molecules that are capable of having an independent existence that contain one or more unpaired electrons (Derouiche et al., 2022). Free radicals (RL) are responsible for biological alterations, they inhibit, among other things, insulin secretion and interfere with different stages of the stimulus / secretion coupling (Fu et al., 2013). Several studies on in-vitro cell lines have shown that oxidative stress inhibits insulin signal transduction. The deleterious effects of oxidative stress on molecules make it possible to understand its role in a large number of major pathologies (Styskal et al., 2012). It is well established that increased ROS production in the kidneys of diabetic patients can be affected by enzymatic and non-enzymatic pathways (Singh et al., 2022). Evidence suggests that elevated glucose acts through the activation of protein kinase C (PKC) in diabetic glomeruli via de novo synthesis of diacylglycerol (DAG). Then, PKC creates ROS thus causing enhanced mesangial expansion, thickening of GBMs and endothelial cell dysfunction resulting in diabetic kidney disease (Jha et al., 2016). Furthermore, high levels of glucose induce nicotinamide adenine dinucleotide phosphate oxidase (NOX) isoforms, particularly NOX-4 which results in endothelial dysfunction, inflammation and consequently apoptosis (Mahmoodnia et al., 2017). Additionally, the other glucose autooxidation pathways such as increased AGE formation, polyol pathway flux, and protein glycation are implicated in both direct and indirect kidney damage by producing a significant proportion of ROS (Derouiche & Benmoussa, 2022). In light of this information, our goal for this work is to assess some diagnostic and prognostic markers and even the prediction of nephrotic complications of type 2 diabetes.

Material and Methods

Study Population

We randomly enrolled 60 volunteer man patients who visited the Hospital of Touggourt from October 01, 2021 until april 30, 2022, were divided into 2 groups of 30 individuals each: a group of type 2 diabetics with average age (53.75 ± 15.48 years) and a group of type 2 diabetics with nephropathy complication aged (53.46 ± 13.49 years). Our work was approved by the ethics committee and all subjects participated voluntarily. Groupe 1 (n = 30): Patients suffering from diabetes mellitus without "Diabetic" complications. Groupe 2 (n = 30): Patients suffering from diabetes mellitus with nephrotic complication "Diabetic nephropathy".

This work is carried out in the city of Touggourt exists in the region of Rued Righ which is a located in the northeast of the Algerian Sahara. It covers a South North axis whose latitude is 32 °, 54 'to 39 °, 9' North and longitude 05 °, 50 to 05 °, 75 East. This region is naturally divided into bloks called trios: Upper Oued Righ (Touggort), in the center (Djamaa) and at the bottom of this region (M'gheir region). Sampling was carried out during the period from October 2021 until the end of april 2022.

The patients excluded in the present study are elderly diabetics, diabetics suffering from other complications other than nephrosis or diabetics with other acute or chronic diseases. The patients included in the present study are patients who are Confirmed of the diagnosis of diabetics and diabetic nephropathy, diabetics and diabetic nephropathy live in the Touggourt region, Facilitation of contact allowing rigorous monitoring of the experiment and Control persons in good health, showing no pathology.

Laboratory Investigation

All analyses were performed in the biological laboratory of El-Oued University and sliman Amirat Hospital (Touggourt), 5 ml of blood are taken on a zero (dry) tube after almost 12 hours of fasting and under perfectly sterilized conditions. These samples were brought quickly to the laboratory to avoid any deterioration and external contamination, centrifuged, aliquoted and stored at -18◦C until the time of analysis and to make the parameters they need to be done quickly.

Serum urea, uric acid, creatinine, serum protein and serum lipid levels were determined using the commercial kit from Spinreact, Spain (ref: urea-20141, uric acid-20091, creatinine-20151, Albumin-1001291 and iron-20111). The determination of the ionogram parameter (sodium and

potassium) is by automatic electrolyte analyzer (Easylute). The MDA assay is based on the condensation of MDA in an acidic medium and hot with thiobarbituric acid. The reaction results in the formation of a pink complex between two molecules of thiobarbituric acid which can therefore be measured by absorption spectrophotometry at 532 nm according to the method of (Yagi, 1976). Regarding the GSH assay, the complex formed between GSH and 5,5'dithiodis-2-nitrobenzoic acid (DTNB), which releases thionitrobenzoic acid (TNB) which exhibits an absorbance at 412nm according to method (Weckbercker's & Cory, 1988). Serum total thiol was determined according to the method described by Ellman. An aliquot of the supernatant (50 µl) was mixed with 1 ml of Tris (0.25 M) -EDTA (20 mM) buffer and read the absorbance at 412 nm (Elman,1959). The plasma total antioxidant capacity (TAC), i.e. its capacity to absorb free oxygen radicals (ORAC: Oxygen Radical Absorbance Capacity) is estimated by the capacity of red blood cells to resist hemolysis induced by free radicals in vitro in the presence of plasma according to the method of (Oyaizu, 1986). This method is based on the monitoring as a function of time of the hemolysis of red blood cells induced by a free radical generator.

Sample Size

The sample size in the present study was calculated by the following formula equation (Charan & Biswas, 2013), the sample size will be chosen to obtain the estimated prevalence of CKD Diabetes with a 95% confidence interval. The expected prevalence of CKD Diabetes to be used is about 9 %. The calculated the sample size n satisfies the relation given above.

$N = (Z\alpha/2)^2 (P) (1-P)/ e^2$
The reliability coefficient ($Z\alpha/2$) = 1.96
Estimated prevalence of CKD Diabetes (P) = 0.09
Estimated prevalence of non- CKD Diabetes (1-P) = 0.91
The margin of error (e) = 0.05
$n= (1.96)^2 (0.09) (0.91)/ (0.05)^2$=125.85 diabetic patients
After filtration of patients abounded in this study, we estimated that a total of 60 diabetic patients would be needed to detect a difference between groups.

Statistical Analysis Methods

The statistical evaluation is carried out by the student's T test and ROC test by regression analysis. The results are given as the mean ± SD. So we use MINITAB, STATISTICA and EXCEL software which helps us to do the tests. The means are considered to be significantly different when P <0.05.

Results

Total of 60 individuals were included in this study, with a mean age of 53.60 years. The populations studied were identified by measurement of blood pressure, body mass index (BMI) and other biological parameters. the results obtained show a highly significant increase (P <0.01) in the concentration of urea, creatinine and uric acid in the group of diabetic patients with nephropathy compared to the diabetic group without nephropathy. The other criteria for identifying two main groups are summarized in Table 1.

Parametes	Group 1 (n=30)	Group 2 (n=30)	P-value
Age (Years)	53.75±15.48	53.46±13.49	0.362
Weight (kg)	74.61±15.81	70.89±5.09	0.625
Height (m)	1.70±0.06	1.68± 0.07	0.284
BMI (kg/m^2)	25.68±1.04	24.79±1.41	0.185
SBP (mmHg)	13.582±1.84	14.071±0.35	0.963
DBP(mmHg)	7.77±1.32	6.929±0.267	0.092
FBP (g/l)	1.98±0.23	1.69±0.15	0.067
Serum Albumin (g/l)	44.67±0.87	50.23±4.73	0.052
Creatinine (mg/l)	9.22±0.43	93.07±8.65	<0.001
Urea (g/l)	0.36±0.03	1.02±0.06	<0.001
Uric Acid (g/l)	43.21±3.79	58.46±2.89	<0.001
Potassium (meq/l)	4.17±0.09	5.30±0.361	0.042
Sodium (meq/l)	136.77±0.50	134.54±1.52	0.145

FBP= fasting plasma glucose, SBP= systolic blood pressure, DBP= diastolic blood pressure

Table 1: Demographic, clinical and laboratory features between the study groups (n=60).

	Group I (n=30)	Group II (n=30)	*P-value*
MDA (µmol/ mg Hb)	16.10±1.53	23.64±3.39	<0.001
GSH (mmol/ mg Hb)	1.79±0.11	2.59±0.15	<0.001
Vit C (mmol/l)	1.31±0.16	1.86±0.37	0.075
Total thiol (mol/l)	0.26±0.030	0.86±0.061	<0.001
TAC (UI/l)	1.003±0.06	0.99±0.03	0.062

MDA : Malondialdehyde, GSH : reduced glutathion, Vit C : vitamine C, TAC : Total Antioxydant Capacity

Table 2: Concentration of serum oxidative stress markers in study groups

Regarding the ROC test (table 3 and figure 1), our result reveals that MDA and GSH in serum were significant predictors (P <0.05) with percentages of specificity (18.2 and 0.00%), high percentages of Sensitivity (36.4 and 72.2%) and ZSC values (0.092 and 0.104) respectively.

	Sensitivity %	Specificity %	AUC	ES	IC 95%	P-value
MDA	36,4	100	0.814	0.092	0.633-0.993	0.013
GSH	72.7	18.2	0.822	0.104	0.619-1.00	0.010
Vitamine C	45.5	0.00	0.731	0.116	0.505-0.958	0.066

Table 3: AUC, Sensitivity and Specificity values of oxidative stress parameters

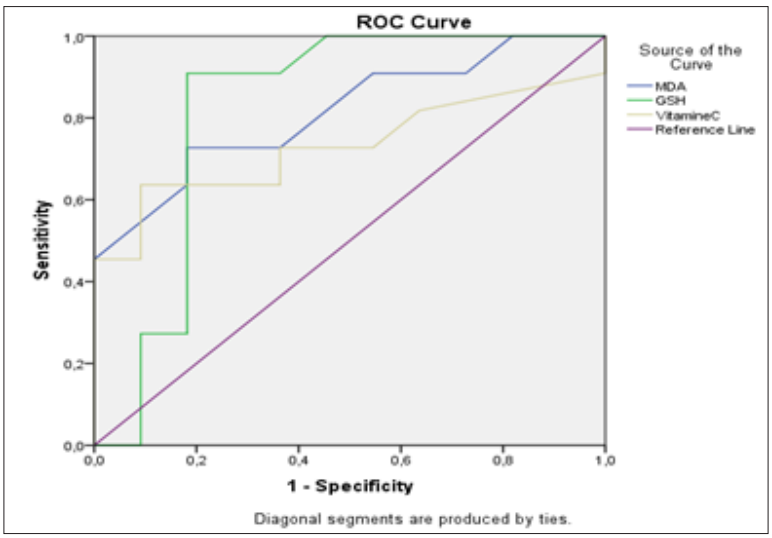

Figure 1: ROC curve analysis to determine the best cut-off value of MDA, GSH et Vit C used to predict CKF in patients with diabetes

The results obtained (table 4) show that there is a significant correlation between the variation of MDA and the variation of urea (P=0.047, R=0.61), between MDA and creatinine (P=0.042, R=0.64), between MDA and uric acid (P=0.046, R=0.7) and between GSH and urea (P=0.046, R=0.65) in diabetes patients with CKD but no significant correlation between GSH with other renal markers in diabetic patients with or without CKD.

	GSH			MDA
Parameters	Group I	Group II	Group I	Group II
Serum Creatinine	P=0.75 R=-0.28	P=0.46 R=-0.26	P=0.042 R=0.64	P=0.99 R=0.07
Serum Urea	P=0.046 R= - 0.65	P=0.86 R=-0.07	P=0.047 R=0.61	P=0.63 R=0.09
Serum uric Acid	P=0.95 R=0.11	P=0.65 R=-0.02	P=0.046 R=0.7	P=0.37 R=0.033

Table 4: Correlation between Serum oxidative stress markers and study parameters in diabetes patients with and without CKF (n=30)

Discussion

Patients are divided according to their degree of kidney damage due to complications from diabetes. The results obtained show that the fasting blood glucose is increased in the diabetic nephropathy compared to the diabetic group, which confirms that the glycemia remains the most important marker for the diagnosis of diabetes or the control and followed the development or the nephrotic complication of the disease. disease. Several studies in patients with type 1 than type 2 diabetes have shown that hyperglycemia plays a causal role in the pathophysiology of the initial stages of diabetic nephropathy (Roussel, 2011). On the other hand, our results show an increase in renal function parameters (urea, creatinine, uric acid and albumin) in the diabetic nephropathy group against the diabetic group. Creatinine is considered among the most important markers of renal dysfunction and glomerular filtration (Tsinalis & Binet, 2006). Several studies clearly show that the level of blood creatinine increases from the early stage of diabetic nephropathy (Bouattar et al., 2009).

Regarding the concentration of urea, it is obvious that an increase in serum urea reflects a deficit in the excretion function of the kidneys (Richet, 2005). Urea accumulates in the blood and becomes a toxic factor which results in an alteration of renal function (Vanholder, 2003) due to the fact that renal failure by metabolic acidosis that it induces is responsible for catabolism exaggerated muscle mass. Serum urea assay is less precise for assessing renal function than creatinine assay and should therefore be discontinued (Gowda et al., 2010). But for the increase in uricemia which is explained by the linear progression of impaired renal function and the inability to eliminate wastes from catabolism. Hyper uricemia is considered to be a marker of renal dysfunction rather than a risk factor for progression of renal disease (Kang et al., 2002). Otherwise, the high level of circulating uric acid can be interpreted during cell damage, a rapid degradation of nucleic acids releasing in large quantities of purines which will subsequently be transformed into uric acid is observed. Uric acid is the end product of purine metabolism in humans, it plays a dual role, both as a pro-oxidant and therapeutic as an antioxidant (Shabana et al., 2012).

The results of our study show a state of oxidative stress associated with diabetes and its nephrotic complication with high specificity for MDA and GSH for predicting diabetes nephropathy. Hyperglycemia associated with diabetes is a limiting factor for oxidative stress (Chetehouna et al., 2024). In diabetes, when the glucose level increases, the hexokinase is then saturated and the excess glucose is partly metabolized via the polyol pathway in the insulin-independent tissues. Aldose

reductase reduces glucose to sorbitol using as a cofactor NADPH, H + coming from the pentose-phosphate pathway and which will be oxidized to NADP +. The expression of this enzyme appears to be increased in diabetes (Yabe, 1998). Then sorbitol dehydrogenase oxidizes part of the sorbitol formed into fructose using NAD + as a cofactor. Activation of the polyol pathway also induces an alteration in the redox potential of cells. The formation of sorbitol is accompanied by a decrease in NADPH resources to the detriment of other reactions which also require this cofactor. Among which glutathione reductase requires high levels of NADPH to reduce oxidized glutathione (GSSG) and thereby restore endogenous reduced glutathione (GSH) levels (Yan, 2018). The decrease in NADPH hinders the redox cycle of GSH regeneration and thus results in the generation of oxidative stress in many tissues and thus contribute to the pathogenesis of diabetic complications (Bravi et al., 1997).

In our result we reported an increase in the activity of GSH in the serum of diabetic patients, we can explain this increase probably by the effect of the latter as a protector of these cells against the oxidative stress that induced by the hyperglycemia (Matough et al., 2012). On the other hand, Malondialdehyde (MDA) is a major player in low density lipoprotein (LDL) (Vidya, et al., 2011). It is a well-known by-product of lipid peroxidation which is formed during the attack of polyunsaturated lipids by reactive oxygen species generated by certain contaminants, they can be used as the most important markers of oxidative stress (Nakhjavani et al., 2010).

Our results show that total thiol is increased in the diabetic nephropathic groups compared to diabetics reflecting the antioxidant activity of thiol. The natural amino acids only cysteines containing thiol in their side chain, which can undergo a variety of different nucleophilic reactions. The sulfhydryl group makes cysteines a popular choice for active sites in enzymes, binding sites for prenylation and palmitoylation markers, as well as high affinity binding sites for metals, such as zinc or iron (Boulaares et al., 2024). However, the most defining characteristic of cysteine thiols is their ability to undergo reversible and irreversible oxidation reactions. Deprotonation of the sulfhydryl group to the corresponding thiolate anion increases its reactivity in nucleophilic reactions (Ulrich & Jakob, 2019).

In our study, there was a statistically significant correlation between MDA and renal parameter in diabetic patients without CKD which reflects on the effect of diabetes in causing oxidative stress and lipid peroxidation which increases the risk of renal complication in diabetics. The oxidative stress to have a central role in the pathophysiological process of uremia and its complications. However, there is little evidence to suggest how early oxidative stress in a starts developing during the progression of CKD (Derouich et al., 2020).

Conclusion

The present study showed that an elevated GSH and MDA were associated with an increased risk of CKD in type 2 diabetic patients. This indicated that an oxidative stress is associated with the type 2 diabetes which contributes to imbalance of antioxidant defense system and overexpression of free radicals and leads to cells membrane alteration and disease complication in to the CKD.

Acknowledgement

The author thanks the staff of laboratory of Faculty of natural and life sciences and staff of laboratory of hospital Sliman Amirat (Touggourt) for providing research facilities to carryout present work.

Conflict of Interest

The authors declare that there is no conflict of interest.

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