Original Article

Serum Selenium Levels: Correlation with Inflammatory Biomarkers and Oxidative Stress in Diabetic Nephropathy

Levels of Selenium in Patient with Diabetic Nephropathy

Hanan M. Al-Nadawi and Waseem Yousif M Al-Dulaimy

ABSTRACT

Objective: To study levels of selenium in patient with diabetic nephropathy.
Study Design: Descriptive cross-sectional study.
Place and Duration of Study: This study was conducted at the Department of Chemistry and Baquba General Hospital's Nephrology and Haemodialysis Unit in Ibn Sina Dialysis Centre from 20th October 2023 to 8th January 2024.
Methods: Eighty adults without a history of hematologic or oncologic disorders, malnutrition, or inflammatory disorders (acute or chronic) were identified in the first screening. We examined the hospital library to get the patients' ages, genders, treatment groups, and long-term conditions, such as cardiovascular disease, hypertension, congestive heart failure, arterial disease, and chronic obstructive pulmonary disease. Forty participants served as the control group for this study. They underwent a number of blood tests, including monitoring and recording of serum glucose, urea, creatinine, C-reactive protein, IL-6, glutathione peroxidase, and superoxide dismutase.
Results: Among people with diabetes, smoking was the leading cause of complications and 48 were heavy smokers. The risk of having renal failure increased with the duration of diabetes. Healthy people's urea and creatinine levels were much lower than those of diabetic patients with diabetic nephropathy.
Conclusion: The clear link between selenium, inflammation, and oxidative stress. Selenium was found to have a high positive link with IL-6 but no significant correlation with C-reactive protein. Selenium and glutathione peroxidase were found to have a weakly negative correlation.
Key Words: Diabetic patient, Diabetic nephropathy, Selenium, C-reactive protein, IL-6, glutathione peroxidase

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INTRODUCTION

The prevalence of non-communicable diabetes mellitus (DM) makes it a serious social issue. Worldwide, 537 million people are living with diabetes, and the number is expected to rise to 784 million by 2045, a 50% increase, according to the International Diabetes Federation (IDF).[1-2] The outlook for diabetes remains bleak, despite advancements in research and new medications to lower blood sugar. The rising incidence of micro- and macrovascular diseases leads to greater societal costs due to disabilities and premature deaths.

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Common complications of diabetes include heart disease, PAD, retinal disease, nerve damage, and nephritis. Diabetic nephropathy (DN) affects 40% of people with diabetes and is the third leading cause of death among those with type 2 diabetes, following cancer and cardiovascular disease[3-6]

Diffuse or nodular glomerulosclerosis and Chronic Renal Failure (CRF) develop in diabetic nephropathy (DN) due to elevated glomerular pressure and changes in the kidney's blood arteries, arterioles, glomeruli, and tubules. Diabetic nephropathy affects several aspects of kidney function and structure. Albuminuria, proteinuria with preserved renal function, and a progressive decrease in renal function leading to the terminal phase are the traditional classifications of the condition. Because it is preventable, diabetic neuropathy is no longer seen as a lethal consequence of diabetes mellitus.[5,6]

Diagnosing preclinical diabetic nephropathy in its early stages has also become easier and faster. While albuminuria was previously thought to have a pivotal role in the development of glomerular damage, new evidence has cast doubt on this long-held belief. Twenty to twenty-five percent of kidney units stiffen

when protein is present in the urine, according to research on cell structure.[7] Changes to renal tissue can occur with normal albumin excretion rates. When sclerosis has spread to 50–70% of the kidney mass, proteinuria or chronic albuminuria.[7] The mesangial, tubular, interstitial, and vascular components of the kidney can be damaged by complex and poorly understood mechanisms brought about by emetic agents. Obesity, smoking, and metabolic syndrome are additional vascular risk factors that worsen these consequences. Both hypertension and early glomerular hyperfiltration are affected by these factors. The disruption of the modulation of arteriole tone in the renal tubules by systemic artery pressure affects intraglomerular pressure, leading to chronic hypertension. It is common for albuminuria to be the outcome of podocyte abnormalities and podocytopathy.[8-10] Some of the theories put out to explain glomerular damage include albuminuria, tubulo-interstitial fibrosis, glomerular hyalinosis, mesangial matrix enlargement, and nodular glomerulosclerosis. Renal function declines and eventually leads to end-stage renal failure; proteinuria and hypertension are common. Damage to kidney structures can occur as a result of hyperglycemia in several ways: increased oxidative stress reactions, activation of the sympathetic nervous system and the RAAS, endothelial dysfunction, insulin resistance, and the accumulation of advanced glycation end products (AGEs).[10] Atherosclerotic plaques and diabetic rat kidneys contain 8-hydroxy-2-deoxyguanosine (8-OHdG), a marker of oxidative stress. DNA oxidation leads to vasculopathy and atherosclerosis by damaging both telomeric and non-telomeric DNA, accelerating cell aging. Increased RNA oxidation produces 8-oxoGuo, impairing ribosomal function, protein synthesis, and protein output. RNA and DNA oxidation is common in early-stage diabetic nephropathy, with elevated oxidized purines and pyrimidines found in eye tissues of individuals with diabetic glaucoma, Selenium is crucial for numerous processes, including infection response, DNA synthesis, antioxidant defense, and thyroid metabolism. Selenoproteins and enzymes like glutathione peroxidase and thioredoxin reductases require selenocysteine, a genetically encoded amino acid. Selenium deficiency can accelerate conditions like heart disease, diabetes, RA, nephritis, and asthma.[11]

Selenium deficiency is increasingly linked to long-term health issues. Selenium supports metabolism, reduces inflammation, and protects against free radicals. Selenoproteins contribute to cellular antioxidant defense, suggesting selenium (Se) may help prevent T2DM. Environmental and genetic factors affect the main symptoms of type 2 diabetes, including hyperglycemia, insulin resistance, and poor insulin production. Persistent high blood glucose can lead to atherosclerosis, hypertension, cardiovascular disease, and stroke. A study in China found that soil selenium levels impact glucose regulation in both hyperglycemia and hypoglycemia. Oxidative stress accelerates diabetes development.[12]

METHODS

This research was conducted at the Baquba General Hospital's Nephrology and Haemodialysis Unit in Ibn Sina Dialysis Centr examined blood selenium levels in patients diagnosed with diabetic nephropathy from 20th October 2023 to 8th January 2024 with ethical standards stipulated in the Declaration of Helsinki. Before taking the sample, the patient's informed written and verbal agreement was obtained, after the review and approval of the study protocol and subject's information by the local ethics committee according to the document number 59148 in 22/10/2023. Eighty adults without a history of hematologic or oncologic disorders, malnutrition, or inflammatory disorders (acute or chronic) were identified in the first screening. We examined the hospital library to get the patients' ages, genders, treatment groups, and long-term conditions, such as cardiovascular disease, hypertension, congestive heart failure, arterial disease, and chronic obstructive pulmonary disease. Forty participants served as the control group for this study. They underwent a number of blood tests, including monitoring and recording of serum glucose, urea, creatinine, C-reactive protein, IL-6, glutathione peroxidase, and superoxide dismutase. The study also involved a cohort with a medical history, encompassing blood pressure, duration of diabetes, and the presence of a genetic predisposition to the condition. In addition to the primary groups, the participants were further separated into secondary groups based on age, specifically those over and <40 years old. The data was entered and analzyed through SPSS-27.0 Chi-square and ‘t’ tests were applied, $P<0.05$ was considered as significant.

RESULTS

In the over-50 group, there were 25 patients (31%) with a mean age of 63.56±7.35 and 55 patients (68.75%) under 50 with a mean age of 44.56±3.98. A significant difference was observed ($p<0.0001$) [Table 1]. Being overweight or obese is a major avoidable cause of diabetic nephropathy. BMI classified individuals as non-obese (BMI <25), overweight (BMI 25-29.9), and obese (BMI ≥30). Nearly half of the patients were overweight, with no significant difference between the patient groups ($p>0.05$), and the control group showed a 32% rate without significance [Table 2].

The duration of diabetes and smoking were significant risk factors for renal failure. The likelihood of kidney failure increased with the duration of diabetes (Tables 3-4). Urea and creatinine levels were significantly higher in diabetic patients. The average urea level in the

patient group was 124.85, compared to the normal 32.74 (P<0.001). The creatinine level was significantly lower in patients at 5.30, compared to the normal 1.14 (P<0.001) [Tables 5-6].

Table No. 1: Comparison of diabetic nephropathy and control groups of age

Group	Mean±SD	P value
Patients	59.3375±10.0	<0.0001
Controls	55.26±4.681	

Inflammatory markers showed significant correlations between diabetic patients with renal failure and the control group (Table 7). Selenium was positively associated with IL-6 (r=0.480, p=0.0015), but no significant link was found with CRP (r=-0.089, p=0.579). No significant correlation was found between GPX and selenium (r=-0.051, p=0.7537), nor between SOD and selenium (r=0.093, p=0.564). However, a strong correlation was observed between GPX and SOD (r=0.872, p<0.0001) [Table 8].

Table No. 2: Comparison of body mass index of control and patient groups

BMI (kg/m^2)	Controls	Patients
≤24.9	22.43±0.28	23.0±0.72
25-29.9	28.63±1.4	29.33±1.7
≥30	33.6 ± 1.77	35.0 ± 2.0
P value	0.439	

Table 3: Comparison of risk factors and case history of patient and control groups

Variable	Patients (n=80)	Controls (n=40)	P value
Risk Factor			
Family history	19 (24 %)	-	>0.003
Duration of DM (>10 years)	33 (41%)	-	<0.003
Smoking	48 (60%)	22 (55%)	<0.05
Case history			
Hypertension	34(42.5%)	-	<0.05
Kidney disease	3 (3.75%)	-	NS

Table No. 4: Result of random blood sugar

Random blood sugar	Patients	Control	T-test	
Sample size	80	40	Difference	-77.1125
Mean	172.4125	95.3000	Pooled Standard Deviation	60.8033
95% CI for the mean	155.9703 to 188.8547	91.6803 to 98.9197	Standard Error	11.7745
Variance	5458.9290	128.1000	95% CI of difference	-100.4292 to -53.7958
SD	73.8846	11.3181	Test statistic t	-6.549
SE	8.2605	1.7896	Degrees of Freedom	118
			Two-tailed probability	P<0.0001
F-test for equal variances			P<0.001	

Table No. 5: Result of blood urea in studied groups

Blood urea	Patients	Control	T-test	
Sample size	80	40	Difference	-92.1138
Mean	124.8513	32.7375	Pooled Standard Deviation	33.5036
95% CI for the mean	115.8161 to 133.8864	30.3178 to 35.1572	Standard Error	6.4880
Variance	1648.3777	57.2434	95% CI of difference	-104.9617 to -79.2658
SD	40.6002	7.5659	Test statistic t	-14.198
SE	4.5392	1.1963	Degrees of Freedom	118
			Two-tailed probability	P<0.0001
F-test for equal variances			P<0.001	

Table No. 6: Result of serum creatinine in studied groups

Serum creatinine	Patients	Control	T-test	
Sample size	80	40	Difference	-4.1567
Mean	5.2957	1.1390	Pooled Standard Deviation	1.5861
95% CI for the mean	4.8649 to 5.7266	1.0948 to 1.1832	Standard Error	0.3071
Variance	3.7480	0.01909	95% CI of difference	-4.7650 to -3.5485
SD	1.9360	0.1382	Test statistic t	-13.534
SE	0.2164	0.02184	Degrees of Freedom	118
			Two-tailed probability	P<0.0001
F-test for equal variances			P<0.001	

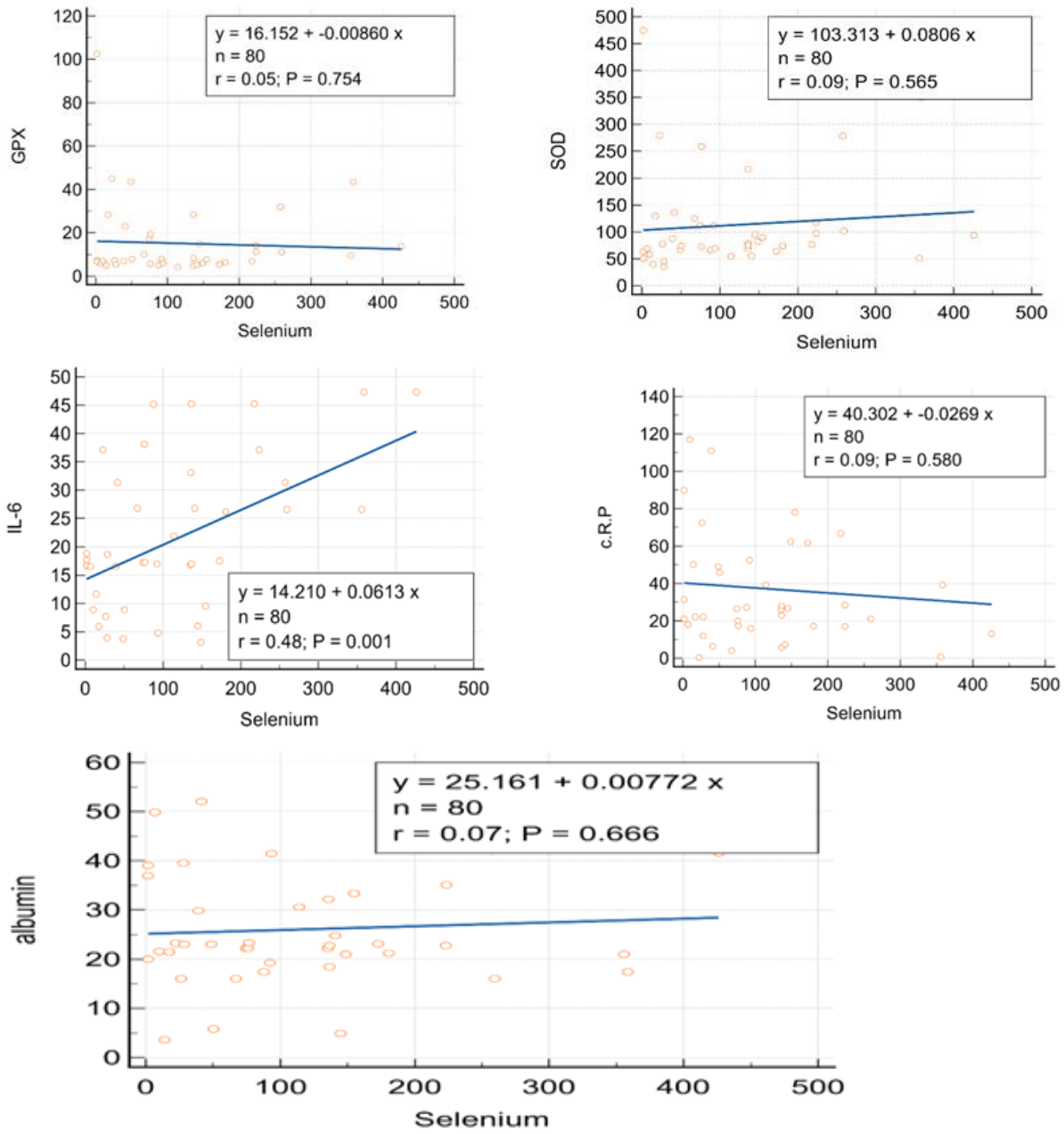

Figure No. 1: Coloration between Selenium and GPX, SOD, IL-6, C.R.P and Albumin

Table No. 7: Result of inflammatory marker in patient and control groups

Inflammatory marker	Patients	Controls	P value	
			T-test (assuming equal variances)	
IL-6	21.3925±13.2493	3.7571±0.8790	Difference	-17.6354
			Pooled Standard Deviation	10.3443
			Standard Error	2.9051
			95% CI of difference	-23.4675 to -11.8032
			Test statistic t	-6.071
			Degrees of Freedom	51
			Two-tailed probability	P<0.0001
CRP	40.3625±3.3700	1.9576±0.9925	Difference	-38.4049
			Pooled Standard Deviation	23.6910
			Standard Error	6.6533
			95% CI of difference	-51.7619 to -

				25.0478
			Test statistic t	-5.772
			Degrees of Freedom	51
			Two-tailed probability	P<0.0001

Table 8: ROC curve for inflammatory and oxidative stress in studied groups

Parameters	Area under the ROC curve (AUC)	Standard Error	95% Confidence interval	Z statistic	Specificity	Sensitivity	Significant value
Selenium	0.55	0.140	0.405 to 0.699	0.395	50	57.1	0.693
GPx	0.774	0.123	0.630 to 0.882	2.229	50	81	0.026
SOD	0.581	0.205	0.408 to 0.741	0.396	60	78	0.692
IL-6	0.938	0.0411	0.806 to 0.991	10.653	40	90.6	P<0.01

DISCUSSION

In living things, selenium primarily plays a role in the production of selenoproteins, which aid in the reduction of oxidative stress.[13-15] The antioxidant properties of selenium led to the belief that it could provide protection against type 2 diabetes (T2DM).[16] Elevated selenium levels may be associated with insulin resistance and type 2 diabetes, according to recent epidemiological research. The selenium exposure increases the risk of developing type 2 diabetes and its function in glucose homeostasis.[17,18]

Damage to the tubules and glomeruli, as well as impaired renal function and decreased filtration, are the main symptoms of diabetic nephropathy, which is mostly caused by hyperglycemia and oxidative stress. The degree of protein oxidation and damage in diabetic nephropathy is correlated with elevated IL-6 levels which may indicate the existence of oxidative stress.[19,20] Chronically elevated blood glucose levels in diabetes may be linked to the increased production and buildup of advanced glycation end products (AGEs). By activating inflammatory pathways and cross-linking proteins, AGEs can worsen kidney damage and functioning. People with diabetic nephropathy are more likely to experience renal sequelae if their PC and AGE levels are high.[21]

With the exception of the heart, no organ contains a greater concentration of mitochondria than the kidneys. The mitochondria set the stage for ATP production, ultra-filtrate absorption, and dissolved chemical absorption. Systems including mitochondrial oxidative phosphorylation and fatty acid β-oxidation generate reactive oxygen species (ROS), which are essential for the proper functioning of the kidneys. When antioxidant defense (AOD) systems are in equilibrium with mitochondrial production of reactive oxygen species (ROS), renal mitochondrial function is optimal. According to research, the progression of diabetic nephropathy is intimately linked to mitochondrial dysfunction and an increase in oxidative stress. Kidney cells, including endothelial and podocyte cells are also exhibit mitochondrial abnormalities. Through a variety of signaling channels, the operating system can halt the cell cycle and cause cell death, which includes podocytes. Endothelial cell death, inflammation, autophagy, and fibrosis are caused by the activation of certain pathways, such as PI3K/Akt, TGF-ſ1/p38-MAPK, and NF-kB. The iron-dependent lipid peroxidation (LPO) mechanism known as ferroptosis has recently attracted a lot of attention because it offers novel ways to study the course of diabetic nephropathy (DN). Cultured human proximal tubule cells exposed to high glucose levels exhibit elevated iron levels, reduced antioxidant ability, and elevated levels of lipopolysaccharides and reactive oxygen species.[22,23] Our findings contrast with other studies on diabetic nephropathy, which link it to oxidative stress, glycation, glycol oxidation, and elevated reactive nitrogen and oxygen species (RNS). DN (stages 3a and 3b) shows a significant decline in antioxidant enzyme function, correlating with glycol oxidation and glycation diseases. Due to low SOD activity, DN may struggle to combat oxidative damage. As SOD and GPx activity decrease in DN stages 3a and 3b, the antioxidant defense weakens, while catalase activity increases due to higher oxidative stress. The absence of this enzyme may accelerate DN development and progression.[24,25]

CONCLUSION

Oxidative stress and inflammation are implicated in the occurrence and progression of diabetic nephropathy. The research demonstrated that healthy people's urea and creatinine levels were much lower than those of diabetic patients. In people with diabetic nephropathy, the study discovered a clear link between selenium, inflammation, and oxidative stress. Selenium was found to have a high positive link with IL-6 but no significant correlation with CRP. Selenium and GPX were found to have a weakly negative correlation..

Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Hanan M. Al-Nadawi
Drafting or Revising Critically:	WaseemYousif M Al-Dulaimy
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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