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Study of the Correlational Relationship between Endostatin and Kidney Function Indicators and Total Proteins in Iraqi Male Patients with Diabetic Nephropathy

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Abstract: ***The study aimed to assess the relationship between endostatin levels and several kidney function indicators, as well as total proteins, in male patients with diabetic nephropathy in Kirkuk province. The study included 100 samples, 70 of which were from patients with diabetic nephropathy, and 30 samples from healthy individuals as a control group. The hospitals and clinics, both public and private, provided the samples. during the period from January, 2024, to June, 2024.The Pearson correlation coefficient was used in statistical analysis to ascertain the association between endostatin and the following markers. : urea, creatinine, total proteins, and glomerular filtration rate. The results showed a statistically significant positive correlation at a probability level of 0.01 between endostatin levels and each of urea, creatinine, and total proteins. Additionally, a positive correlation was observed at the same significance level between endostatin and glomerular filtration rate, suggesting a potential effect of endostatin on kidney function and the progression of diabetic nephropathy .This study provides a deeper understanding of the role of endostatin as a potential biomarker for evaluating kidney function deterioration in diabetic patients, which could help improve diagnostic and therapeutic monitoring strategies.***

Keywords: Diabetic Nephropathy, Correlation, Endostatin, Kidney Function, Glomerular Filtration Rate, Albumin, Globulin.

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1. INTRODUCTION

Diabetes is a major cause of death and disability worldwide, affecting individuals regardless of country or gender. In 2021, there were 529 million people with diabetes globally, with a standardized global prevalence of 16% (5.8–6.5) (Ong et al., 2023). The number of diabetes cases and its prevalence are rapidly increasing. It is a progressive chronic condition that leads to numerous complications, early mortality, and a financial strain on any healthcare infrastructure (Pinchevsky et al., 2020).

As per the 2019 report of the International Diabetes Federation (IDF), the approximate global population with diabetes was predicted to be 463 million, signifying 9.3% of the total population. By 2030 and 2045, respectively, this number is expected to increase to 578 million (10.2%) and 700 million (10.9%). In 2019, the estimated prevalence of diabetes was 9.0% among women and 9.6% among men. . Aging contributes to a higher prevalence of diabetes, with 19.9% (111.2 million) of individuals aged 65–79 years affected. The prevalence is higher in high-income countries (10.4%) than in low-income countries (4.0%), and in urban regions (10.8%) than in rural areas (7.2%). Of those with diabetes, one in two (50.1%) are not aware that they have the disease. According to estimates, 7.5% (374 million) of people worldwide have impaired glucose tolerance in 2019. By 2030, that number is predicted to rise to 8.0% (454 million), and by 2045, it will reach 8.6% (548 million).(Saeedi et al., 2019). Patients with Type 1 Diabetes Mellitus (T1DM) or Type 2 Diabetes Mellitus (T2DM) may experience diabetic complications that can lead to significant morbidity and mortality. The most common consequences of diabetes are microangiopathy and macroangiopathy, with the former occurring much more frequently than the latter (Wei et al., 2022). Peripheral neuropathy, retinopathy, diabetic nephropathy, heart failure, coronary heart disease, stroke, and peripheral vascular disease are examples of diabetic consequences. (Tomic et al., 2022).

A chronic consequence of diabetes called diabetic nephropathy is marked by a steady decline in kidney function as a result of tiny blood vessel damage brought on by high blood sugar levels (Hamad et al., 2024). It is one of the most frequent side effects of diabetes and a major contributor to end-stage kidney disease (ESKD). It is a very common ailment worldwide. Haemodynamic, metabolic, and inflammatory pathways are the three main variables that contribute to the development of diabetic nephropathy. In a clinical sense, the condition is defined by persistent albuminuria accompanied by a gradual decline in the glomerular filtration rate (GFR) (Rico-Fontalvo et al., 2023).

The aim of the current study is to determine the correlational relationship between endostatin and kidney function indicators, including urea, creatinine, and glomerular filtration rate. Additionally, the study will investigate the correlation between endostatin and total proteins, albumin, and globulin in patients with diabetic nephropathy in Kirkuk City.

2. RELATED WORKS

The study was compatible with the findings of Salem et al (2019), and Lee et al .,(2021), which showed that the height of the endocrines was greatly associated with the risk of DN diabetes in patients with diabetes and had a good prediction effectiveness and also showed

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that the intellectual fibrosis Training of tubes is one of the known risk factors for weak kidney function in patients with DN diabetes. The study also was also compatible with the study of Jia et al (2020), as it showed that the endostecin in patients with diabetes is a promising indication of predicting the development of kidney disease, as well as that the high levels of endostene are a possible diagnostic sign of the occurrence of diabetes and its association with chronic diseases Kidney associated. It was compatible with the study of Babaliche et al (2019), as they indicated the association of a decrease in the rate of Kabbi nomination in people with diabetes with an increase in the level of endostene.

In the study by Carlsson et al. (2016), it was found that patients with type 2 diabetes can have circulating endostatin levels that independently predict the progression of kidney disease and mortality, regardless of known markers of kidney disease. The clinical benefit of endostatin as a risk marker in such patients deserves further studies.

In the study by Chen et al. (2012), these results indicate that elevated plasma endostatin levels are strongly and independently associated with chronic kidney disease. There is a need for future studies and clinical trials to examine the causal relationship between endostatin and the risk of developing chronic kidney disease, as well as to develop new interventions targeting circulating endostatin with the aim of reducing the risk of chronic kidney disease.

In the study by Kanbay et al. (2016), higher levels of endostatin were associated with an increased risk according to traditional risk factors (age, gender, smoking status, diabetes, systolic blood pressure, HDL, and total cholesterol) as well as kidney-specific factors (estimated glomerular filtration rate, proteinuria, and hsCRP).

In the study by Gordin et al. (2019), elevated blood glucose levels in individuals with diabetes were associated with increased synthesis of extracellular matrix (ECM) proteins, enhanced cell proliferation, and dysfunction of endothelial cells, alongside tubular atrophy, interstitial fibrosis, and thickening of the glomerular basement membrane. Endostatin levels rise as a result of inflammation and oxidative stress, as well as the expansion of glomerular mesangial cells and excessive glomerular filtration.

A study by Dunkler et al. (2015) indicated that the glomerular filtration rate and albumin levels are useful in predicting the risk of kidney function deterioration in patients with diabetes who have normal kidney function. However, the glomerular filtration rate only reflects the condition of the renal glomeruli, and there is a lack of markers that assess other aspects of kidney injury. One of the important aspects of kidney injury in diabetes is endothelial and vascular damage, as endothelial dysfunction is an integral part of the development of diabetic nephropathy. Physiological indicators representing this endothelial damage have been identified, including elevated levels of endostatin. An increase in endostatin levels is an indicator of endothelial damage and is significantly associated with the deterioration of kidney function. This damage is prominently expressed in the renal glomeruli and the blood vessels surrounding the renal tubules.

A study by YU et al. (2021) found a correlation between elevated glucose levels and increased activity of the enzyme cathepsin, which plays an important role in the rise of endostatin levels associated with collagen eighteen in the heart muscle of diabetic patients. The cathepsin enzyme is activated by the breakdown of the inactive zymogen in an acidic environment. After this breakdown, cathepsin releases endostatin from collagen eighteen by cleaving the active region at the C-terminal of collagen eighteen.

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3. METHODOLOGY

Study Design:
"This study was conducted from January 2024 to the end of May 2024 at public and private hospitals and specialized medical clinics in Kirkuk City. The study included 70 male patients with diabetes-related complications, aged between 40 and 70 years, after confirming their condition. Additionally, a reference group of 20 healthy individuals from the same age range was included."

Blood Samples:
"Blood samples were collected from patients in a volume of 5 mL from a vein. Four mL of the blood were placed in glass tubes containing a gel and clot activator (Vacuum tube with gel and clot activator). The samples were left at room temperature for 30 minutes to allow blood clotting, and then the tubes were centrifuged for 15 minutes at 3000 RPM to obtain the serum".

Physiological and Biochemical Tests
The concentrations of physiological and biochemical indicators in the studied groups were measured as follows: Endostatin levels were determined using ready-to-use kits from Sunlong (China) with the Sandwich ELISA technique. Concentrations of biochemical indicators, including creatinine and urea, in serum were measured using kits from Biolabo (France) (Hussein et al., 2022).
Using an eGFR calculator, the glomerular filtration rate (GFR) was calculated from the plasma concentrations of endogenous chemicals such creatinine (Levey and Stevens, 2010). Using a kit from Biolabo (France), the total protein content of serum samples was determined using chromatography and optical absorption measurement with a spectrophotometer (Narwal et al., 2018).

Statistical Analysis
The results obtained from the current study were analyzed using the SPSS statistical software. The T-test was employed to compare the mean values between patients and healthy individuals, with statistical significance set at ($P \leq 0.01$). "The values of variables were described as Mean ± Standard Deviation".

4. RESULTS AND DISCUSSION

A. Correlation Between Endostatin and Kidney Function
The study results, as shown in Table (1), indicated a positive correlation ($r = 0.243$) with statistical significance ($p \leq 0.021$) between endostatin and urea. The results in Table (1) also showed a positive correlation ($r = 0.301$) with statistical significance ($p \leq 0.004$) between endostatin and creatinine. These findings are consistent with the study by Chauhan et al. (2019), It discovered that individuals with diabetic problems had higher baseline levels of plasma endostatin and that there was a 2.5-fold increase in risk of kidney illness for every 2-logarithm rise in plasma endostatin..When compared to conventional predictions, plasma

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endostatin showed a good correlation with renal outcomes in individuals with Type 2 Diabetes Mellitus, maintaining an estimated glomerular filtration rate and enhancing risk differentiation. The results of this investigation are consistent with those of Lee et al. (2021), who showed a substantial correlation between high endostatin levels and the risk of diabetic nephropathy (DN) in individuals with diabetes. The research also demonstrated the good predictive efficacy of endostatin and indicated that tubular atrophy and interstitial fibrosis are established risk factors for decreased kidney function in patients with DN.

In the study by Han and Zhou (2019), increased serum endostatin was significantly associated with the likelihood of diabetic nephropathy (DN) in individuals with Type 2 Diabetes Mellitus, and it showed a strong ability to predict outcomes. Likewise, the research conducted by Chu et al. (2020) showed that serum endostatin concentration is a predictive factor for assessing kidney function, indicating higher sensitivity to risk compared to traditional factors, such as glomerular filtration rate (GFR) and proteinuria.Renal tubular cells secrete endostatin in response to inflammatory stimuli, and excessive expression of endostatin leads to tubular fibrosis. Several clinical studies have also shown that serum endostatin levels are elevated and associated with rapid progression of kidney damage in patients with diabetes and other chronic kidney diseases (Kato et al., 2018; Zhai et al., 2021).
Elevated blood sugar levels cause endothelial dysfunction, leading to cellular oxidative stress and increased generation of free radicals (Meza et al., 2019). The increased production of reactive oxygen species (ROS) results in abnormal response to hyperglycemia through the control of many genes, such as adhesion molecules and inflammatory cytokines. Numerous mechanisms that promote inflammation are also involved in oxidative and antioxidant processes. Consequently, the imbalance between enzymatic and non-enzymatic antioxidants and ROS production leads to endothelial dysfunction, elevated endostatin levels, increased endothelial permeability, and both necrosis and programmed cell death in endothelial cells (Safi et al., 2022; Wang et al., 2022).

Compared to variations in blood urea concentrations, changes in serum creatinine levels more accurately reflect variations in the glomerular filtration rate (GFR). The GFR is the main determinant of creatinine's blood levels, which are generated continuously from creatine (Griffin et al., 2008). As a result, assessing blood creatinine levels and estimating GFR are essential for figuring out whether a person has kidney impairment. These examinations offer important information about how Type 2 Diabetes Mellitus develops and the risk of renal failure that goes along with it.(Riyani et al., 2024). The equilibrium between the liver's generation of urea and the kidneys' excretion of it in urine is reflected in the serum urea concentration. Therefore, increased urea production, decreased urea elimination, or a combination of the two can lead to raised plasma urea. The greatest values are usually noted in conjunction with a significant decline in glomerular filtration rate (GFR) and decreased urea excretion in urine as a result of severe renal disease. Since it assesses renal function, GFR is a crucial clinical indication. Reduced GFR is seen in all patients with decreased kidney function, irrespective of the underlying reason, and there is a relationship between GFR and the severity of kidney disease. (Higgins, 2016).

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Patients with diabetes who have diabetic nephropathy (DN) frequently have elevated urea levels, suggesting that urea concentration may be a key indicator of renal failure and glucose intolerance. A common pathophysiological mechanism in diabetic kidney disease (DN) is prolonged hyperglycemia, which causes excessive oxidative stress and consequent inflammation and microvascular endothelium dysfunction. Furthermore, there is a strong correlation between the human body's metabolic activity and elevated urea levels, which could indicate decreased blood flow, hypercoagulability, or oxidative stress. Elevated urea levels in DN patients may be explained by important factors in the disease progression, such as reduced blood flow in the microvascular system and oxidative stress.(Yamanouchi et al., 2019).

B. Correlation between Endostatin and Total Serum Proteins

The study results, as shown in Table (1), indicated a positive correlation ($r = 0.304$) with statistical significance ($p \leq 0.004$) between endostatin and total serum proteins. However, no significant correlation was observed between endostatin and albumin ($r = 0.030$, $p \leq 0.778$). Additionally, there was a positive correlation ($r = 0.268$) with statistical significance ($p \leq 0.011$) between endostatin and globulins. These findings suggest that while endostatin is positively associated with total serum proteins and globulins, its relationship with albumin is not significant**,** The results of this study are consistent with the findings of Nazki et al. (2017), which reported a correlation between endostatin and total serum protein levels in patients with diabetic nephropathy. A persistently elevated blood sugar level and decreased synthesis of total serum proteins result from cells responding poorly to insulin effects when insulin levels are inadequate. In diabetes, elevated blood sugar contributes to the production of free radicals, which induce oxidative stress and impair the body's own antioxidant defence system.(Nazki et al., 2017).

Serum albumin has been shown to have clear protective effects in a number of diseases, including cardiovascular disease and myocardial infarction (Yoshioka et al., 2020). Other reports have also suggested that patients who have had an acute ischaemic stroke and have relatively low serum albumin levels are at a higher risk of dying. Additionally, elevated albumin levels are protective against the progression of chronic kidney disease (Arques, 2018). GLB levels in urine rise significantly in cases of damage to the glomerular filtration membrane, and GLB can be a sensitive indicator for early kidney damage in diabetic patients (Liu et al., 2023).The accumulation of toxic wastes due to normal renal filtration and excessive sugar consumption could be the cause of the decline in total protein and globulin concentrations. Decreased albumin levels can also be brought on by notable losses of globulins, albumin, and total protein in the urine. When diabetic problems arise, albumin and globulins serve as biomarkers and transport proteins (Santos et al., 2012). Increased lipolysis and proteolysis in the liver, along with the conversion of glucogenic amino acids into glucose and thus raised glucose levels, are the reasons for the decrease in total protein levels. This drop might also be caused by blood dilution. Due to higher blood glucose levels, diabetic patients urinate more frequently, which prompts the cells to hydrate the blood and dilute urine more effectively, hence increasing the excretion of glucose (Hasan and Abdulsattar, 2015).

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C. Correlation Between Endostatin and Glomerular Filtration Rate (GFR)

The study results, as shown in Table (1), indicate a positive correlation ($r = 0.346$) with statistical significance ($p \leq 0.01$) between endostatin levels and the estimated glomerular filtration rate (eGFR). These findings are consistent with the study by Quiroga and Diez (2023), which demonstrated that a gradual decline in eGFR, leading to chronic kidney disease (CKD), is associated with an increased risk of cardiovascular diseases. This correlation is attributed primarily to the elevated endostatin levels, which are linked to worsened cardiovascular outcomes and increased cardiovascular complications.The findings of this study are also in line with those of studies by Xu et al. (2023) and Ramezankhani et al. (2023), which also reported a decreased glomerular filtration rate (GFR) in patients with diabetes. These earlier studies all showed that a lower estimated GFR (eGFR) is a marker for impaired kidney function in patients with diabetes retinopathy, diabetic neuropathy, and other complications related to diabetes, in addition to diabetic nephropathy. As such, eGFR evaluation is critical in One important element in the development of diabetic nephropathy is the length of diabetes. Several research investigations have demonstrated a correlation between the length of diabetes and the degree of nephropathy , with a 40% correlation between diabetes duration and reduced glomerular filtration rate (Nata et al., 2020). Additionally, diabetic nephropathy often remains asymptomatic until very advanced stages. Chronic kidney disease (CKD) stages are typically assessed using the estimated glomerular filtration rate (eGFR). Studies have shown that by stage 3 of CKD, corresponding to an eGFR of less than 60 mL/min/1.73 m^2, the risk of cardiovascular diseases and mortality increases significantly (Sharma et al., 2010). The risk increases, and cardiovascular diseases and mortality rise (Sharma et al., 2010). Glomerular filtration rate (GFR) and albumin levels are valuable in predicting the risk of renal function deterioration in diabetic patients with initially normal kidney function. However, GFR only reflects the condition of the glomeruli and there is a lack of markers that assess other aspects of kidney damage. An important aspect of kidney injury in diabetes is endothelial and vascular damage. Endothelial dysfunction is an integral part of the development of diabetic nephropathy. Physiological markers that represent this endothelial damage include elevated levels of endostatin. High endostatin levels are indicative of endothelial damage and are significantly associated with renal function deterioration. This damage is notably expressed in the glomeruli and the surrounding peritubular capillaries (Hamad and Abdulrahman, 2024).

5. CONCLUSIONS

Based on the study's findings, it can be concluded that there is a statistically significant positive correlation between endostatin levels and kidney function indicators, including urea, creatinine, total proteins, and glomerular filtration rate in patients with diabetic nephropathy. This suggests that endostatin may play an important role in assessing the progression of nephropathy in diabetic patients, making it a potential biomarker for determining the extent of kidney function deterioration. These results pave the way for future studies on the role of endostatin in the development of kidney diseases. They may also contribute to the development of new therapeutic strategies aimed at mitigating kidney function decline in patients with diabetic nephropathy.

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Table 1. The correlation between endostatin levels and several kidney function indicators and total proteins, in male patients with diabetic nephropathy

Correlations

		creatinine	Urea	Total_protien	Albumin	eGFR
Indostatin	Pearson Correlation	.301**	.243*	-.304**	.030	-.346**
	Sig. (2-tailed)	.004	.021	.004	.778	.001
	N	90	90	90	90	90

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).

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