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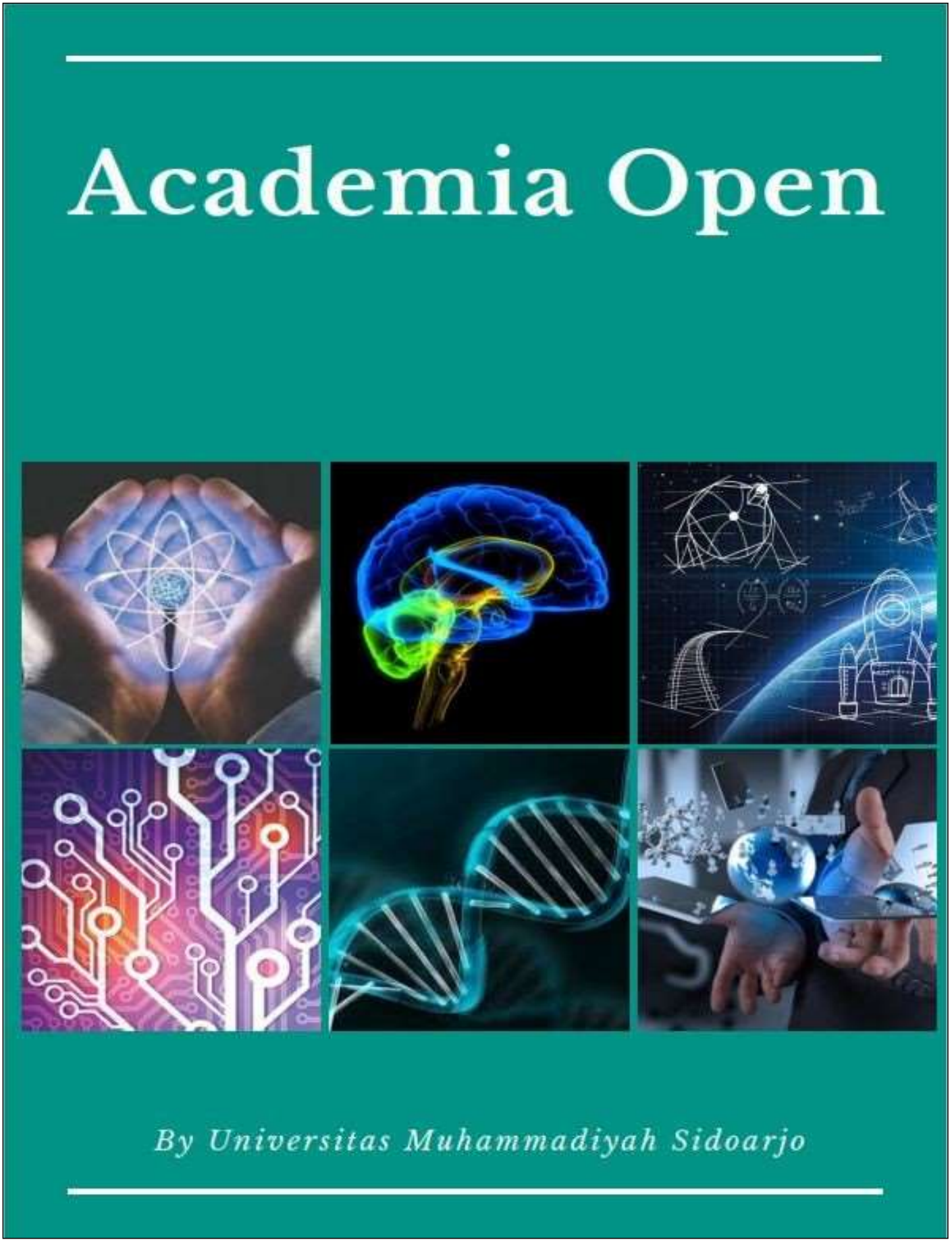

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Serum Pentraxin-3 as a Potential Biomarker for Early Detection of Diabetic Nephropathy in Type 2 Diabetes Mellitus: A Cross-Sectional Study

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Abstract

This cross-sectional study aimed to assess the utility of serum Pentraxin-3 (PTX-3) as a biomarker for the early identification of diabetic nephropathy (DN) in patients with Type 2 Diabetes Mellitus (T2DM). A total of 90 participants, including 30 with T2DM and nephropathy, 30 with T2DM but without nephropathy, and 30 controls, were enrolled. Serum PTX-3 levels were measured, and correlations with clinical parameters were analyzed. The results revealed a significant elevation in serum PTX-3 levels in DN patients with T2DM. PTX-3 exhibited positive correlations with age, disease duration, blood urea, and serum creatinine, indicating its potential relevance to DN development and renal function. Conversely, non-significant negative correlations were observed with BMI and estimated glomerular filtration rate (eGFR). These findings suggest that serum PTX-3 could serve as a valuable biomarker for the early detection of diabetic nephropathy in Type 2 Diabetes Mellitus, potentially aiding in timely intervention and improved patient care.

Highlights:

- Serum PTX-3 levels significantly elevated in Type 2 Diabetes patients with nephropathy, highlighting its potential as an early diagnostic biomarker.
- Positive correlations observed between PTX-3, age, disease duration, blood urea, and serum creatinine, suggesting its relevance to DN development and renal function.
- Serum PTX-3 holds promise for timely identification of diabetic nephropathy, facilitating improved patient care.

Keywords: Diabetic Nephropathy, Pentraxin-3, Type 2 Diabetes, Biomarker, Early Detection

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Introduction

In contemporary times, healthcare has a grave concern that it must address: diabetes mellitus (DM). DM is a dreadful metabolic ailment that poses a severe threat to millions of people. The number of individuals affected by DM has surged from 108 million in 1980 to 451 million in 2017, and the trend continues to rise(1). T2DM is a metabolic disorder arising from a deficit of insulin and characterized by elevated blood sugar levels. T2DM accounts for up to 90% of cases, as opposed to the less frequent T1DM, and is connected to reduced insulin activity. Interestingly, the growing global obesity epidemic has resulted in a significant increase in the incidence of T2DM compared to T1DM. Moreover, T1DM is now being detected more frequently in younger and heavier patients[1]. Elevated blood glucose levels in diabetes have serious long-term consequences on both micro and macrovascular health, as noted in[2][3]. Although commonly associated with retinopathy, neuropathy, and nephropathy, this disease can influence other bodily tissues such as the brain, myocardium, and skin, as specified in[4]. In addition to these microvascular complications, macrovascular issues such as stroke, peripheral artery disease (PAD), and cardiovascular disease (CVD) are also frequent occurrences, as stated in[5]. Diabetic nephropathy (DN) is a common microvascular effect of diabetes that is a significant contributor to end-stage renal disease (ESRD), as reported in[6]. Those with T2DM may experience DN in various forms, with additional glomerular/tubular pathologies and severe peripheral vascular disease potentially playing a role. Typically, early hyperfiltration and albuminuria are followed by a gradual decline in renal function in DN cases[1]. Renal impairment is typically screened for by detecting albuminuria in a random urine sample, according to clinical practice recommendations. However, new research shows that kidney damage may precede an increase in albuminuria, in what is called the normoalbuminuric stage. Furthermore, non-albuminuric renal impairment is seen as a stand-alone condition, independent of albuminuria[7]. Merely identifying proteinuria is insufficient for tracking DN occurrence and progression as one-third of individuals experience renal decline before proteinuria is evident. Research has shown that PTX-3 plays a critical role in detecting early inflammation and the presence of MA(8). This protective indicator appears prior to or concurrently with MA(8) and has been found to be particularly helpful in detecting nephropathy[9]. Pentraxin-3 (PTX-3) plays an important role in angiogenesis, atherosclerotic lesions, and extracellular matrix production, and has been identified as a modulator of the inflammatory process[10]. Researchers have discovered a specific biomarker for localized inflammatory responses and innate immunity in cardiovascular and renal disorders, which is PTX-3[11]. Studies have shown that PTX-3 has a positive effect on the prevention of nephropathy[9]. Various studies have linked classic inflammation indicators such as fibrinogen and High-sensitivity C-reactive Protein (hs-CRP) to DN and DM[11]. For T2DM patients, the progression of kidney disease is mainly attributed to prolonged diabetes and angiopathy in the glomerular capillaries. These factors are responsible for the increased risk of death and illness[12] . Diabetic nephropathy (DN) is understood to be caused by various factors such as abnormalities in glucose and lipid metabolism, hemodynamics, heredity, cytokines, among others, although the specific pathophysiology remains unknown to this day[12]. In renal and cardiovascular conditions, Pentraxin-3 is identified as an acute-phase inflammatory and innate immune response biomarker that signals localized inflammation[11]. As the only long pentraxin protein in renal tissue, pentraxin-3 is associated with kidney damage in DN[13]. Numerous studies have established PTX-3 as a dependable biomarker for inflammation in a variety of clinical situations, including septic shock, rheumatoid arthritis, acute myocardial infarction, and atherosclerotic lesions[14].

Method

Over a period of five months, starting from October 1, 2020, and ending on February 1, 2021, a private clinic in Tikrit City, Salah al-Din Governorate, conducted a case-control study, involving 90 individuals. Of the 90 participants, 60 were suffering from Type 2 diabetes, which was further categorized into three groups. The first group comprised of 30 individuals with diabetic kidney disease and albuminuria, the second group had 30 diabetic individuals with normal urine albumin, and the third group of 30 acted as controls. Patient-reported data was used to collect information during the study. Patients who met any of the following criteria were prohibited from participating in the trial: T1DM, renal disease other than DN, prior use of renin-angiotensin system inhibitors, nonsteroidal anti-inflammatory drugs (NSAID), nephrotoxic medications, immunosuppressants, or pregnancy. The participants had a mean BMI of (25.83+0.38) and their ages ranged from (mean+SE) (51.07+1.35) years. To diagnose diabetic patients with and without nephropathy, the study used random blood glucose, HbA1c, and the presence or absence of albuminurea. Patients and controls were required to provide five milliliters of blood drawn from their antecubital veins, which were allowed to clot for 10 to 15 minutes at room temperature in plain tubes without any anticoagulant. For 15 minutes at a rate of 3000 rpm, the tube was spun in a centrifuge. The serum that was left behind was pipetted into Eppendorf tubes that were empty and fresh. The samples included PTX-3, RBS, Creatinine, Blood urea, and HbA1c%. The samples were placed in a (-20oC) storage until they were required..
"A program called SPSS was utilized to analyze all of the data collected from the assessment of PTX-3 concentrations, which was accomplished through the employment of an enzyme-linked immunosorbent assay (ELISA). Discovering albuminuria using the dipstick methodology and just about 10 milliliters of urine was also conducted. Additionally, both the electronic glomerular filtration rate (eGFR) and BMI were calculated.

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Result and Discussion

In the study, it was revealed that DN patients had a notable difference in their PTX-3 level in comparison to those with diabetes but no nephropathy and the control group. Table 1 displays that the mean+SE of PTX-3 was at its peak (5.39+0.65 ngml) in DN patients.

	Ptx-3(ng\ml)		
	Diabetic Nephropathy	Diabetic	Control
No.	30	30	30
Mean +Se	5.39+0.02	2.71+0.16	1.67+0.10
P .value	<0.01		
	<0.01		

Table 1. *Level of Pentraxin 3 in Patients with Diabetic Nephropathy, Patients without Diabetic Nephropathy, and the Control Group*

According to the Pearson correlation test, Pentraxin 3 levels exhibit various correlations. Its connection with age and blood urea is positive but non-significant (r = 0.1 and r = 0.22, respectively). On the other hand, it has a strong and significant correlation with disease duration and serum creatinine (r = 0.58 and r = 0.56, respectively). The correlation with BMI is negative but not significant (r = -0.14). Meanwhile, the correlation with eGFR is considerably negative and significant (r = -0.5). Meanwhile, Figures 1, 2, 3, 4, 5, and 6 illustrate these correlations.

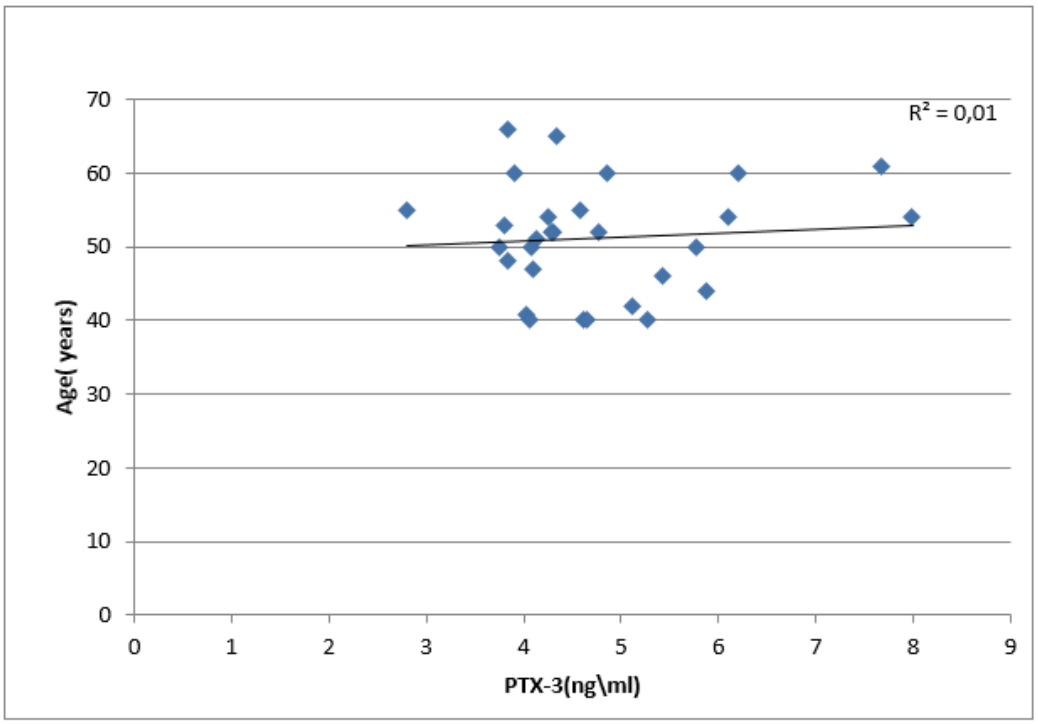

Figure 1. *The association between PTX-3 and age in patients with DN*

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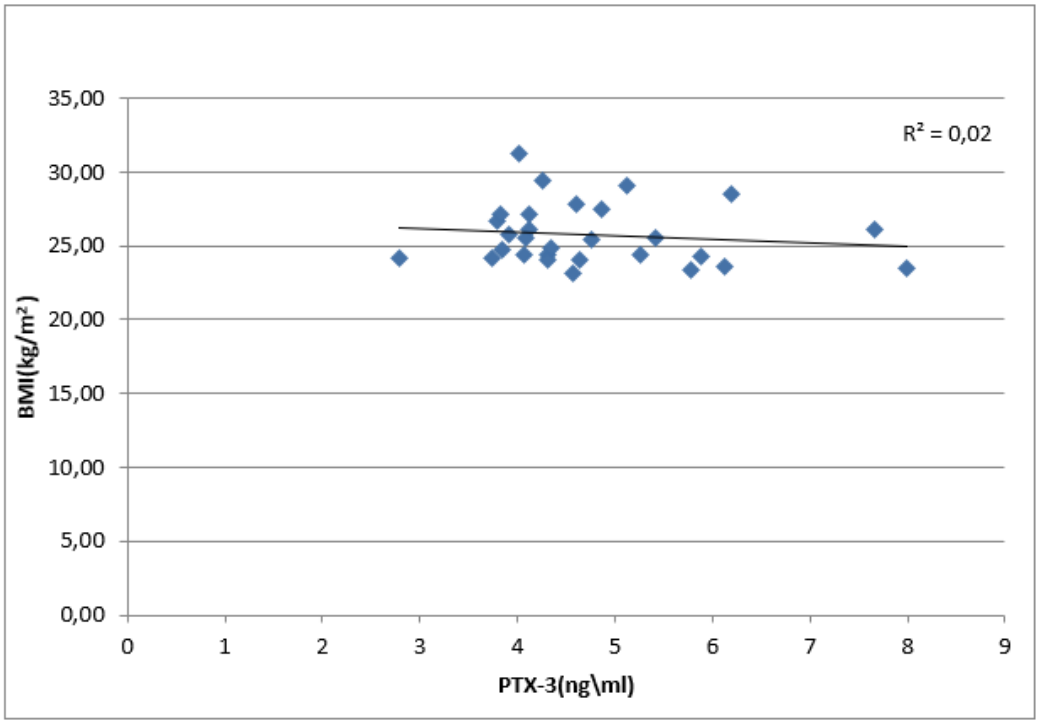

Figure 2. *The association between PTX-3 and body mass index in patients with DN*

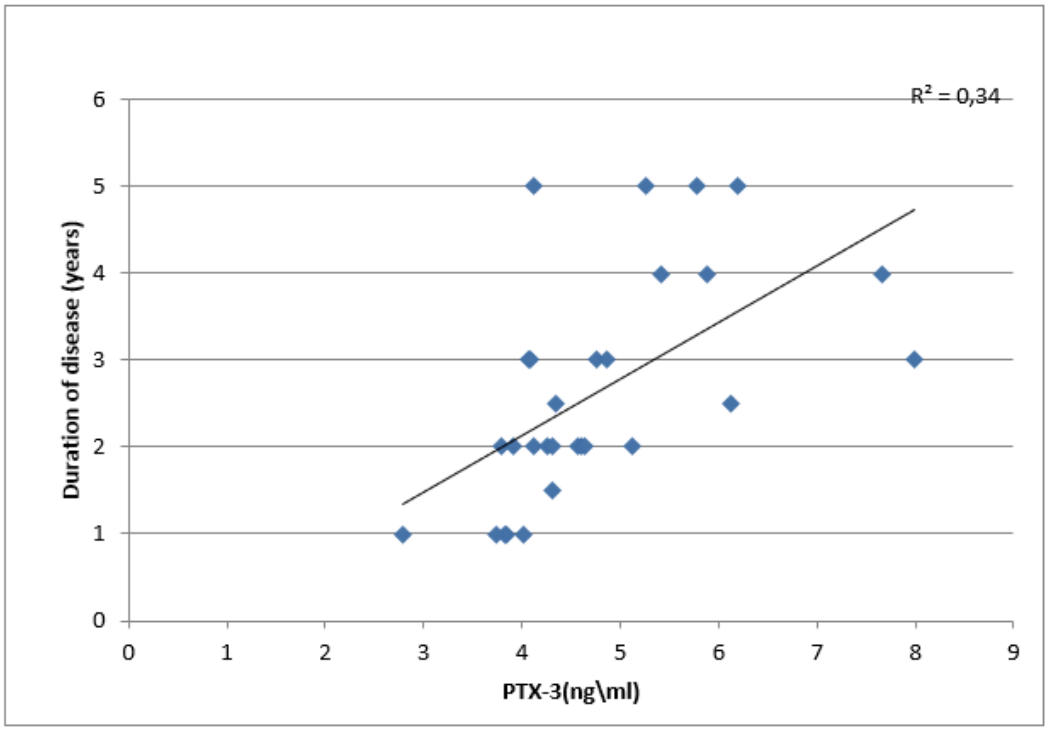

Figure 3. *Correlation between PTX-3 and disease course in patients with DN*

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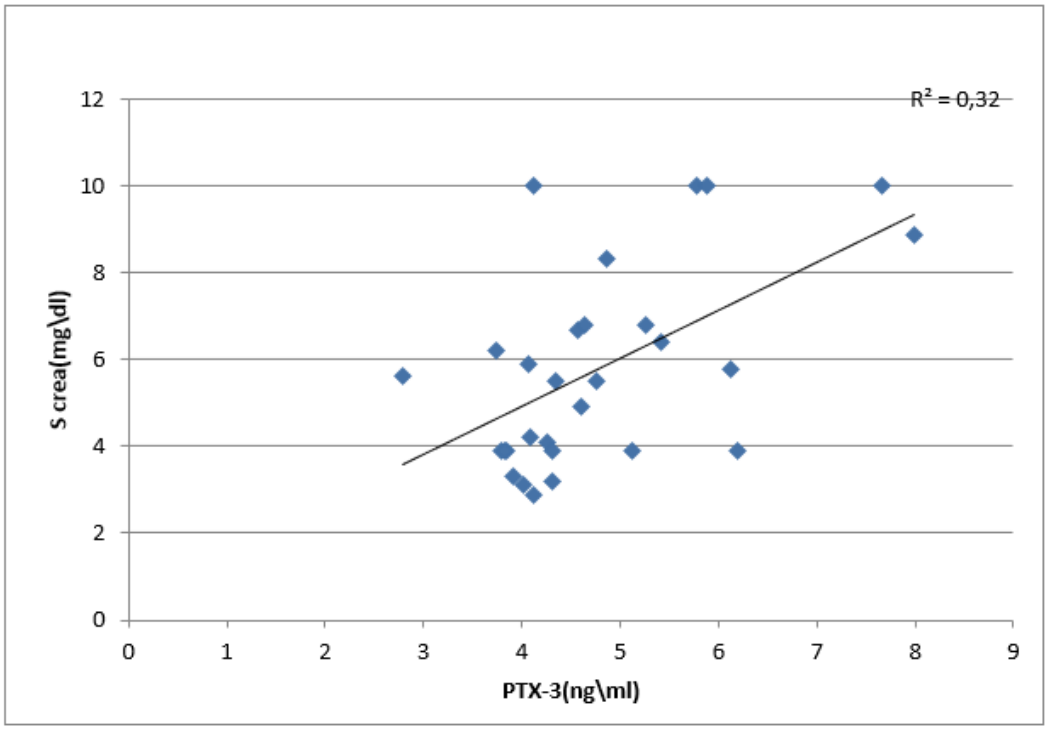

Figure 4. *The association between PTX-3 and serum creatinine in patients with DN*

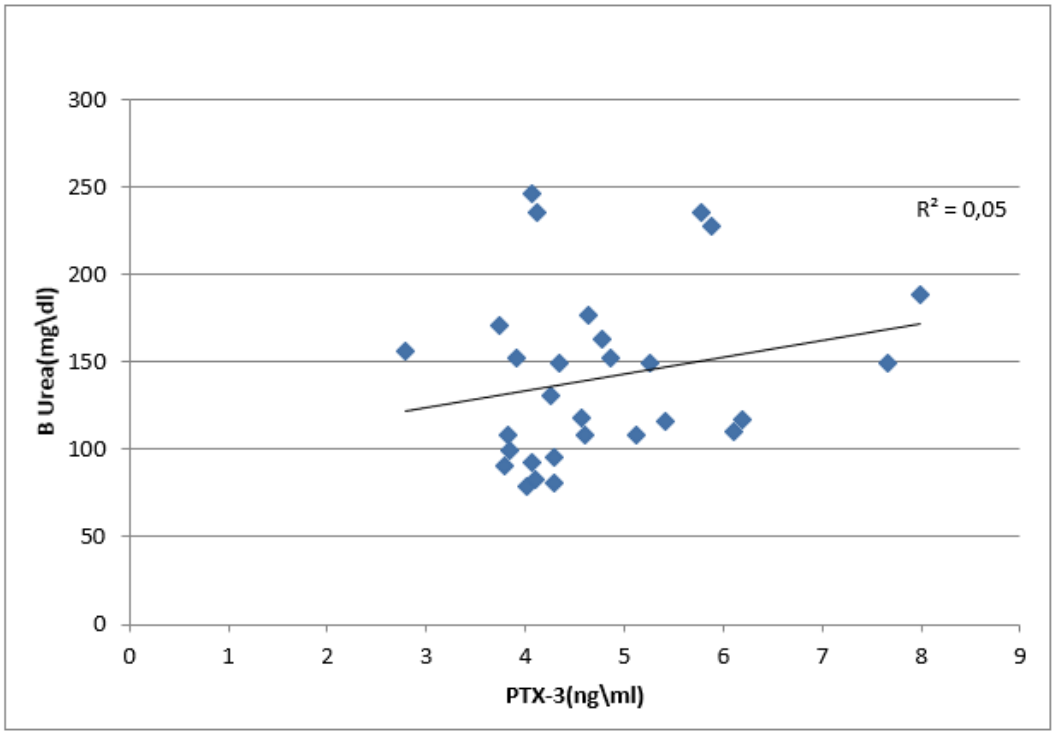

Figure 5. *Correlation between PTX-3 and Blood Urea in patients with DN*

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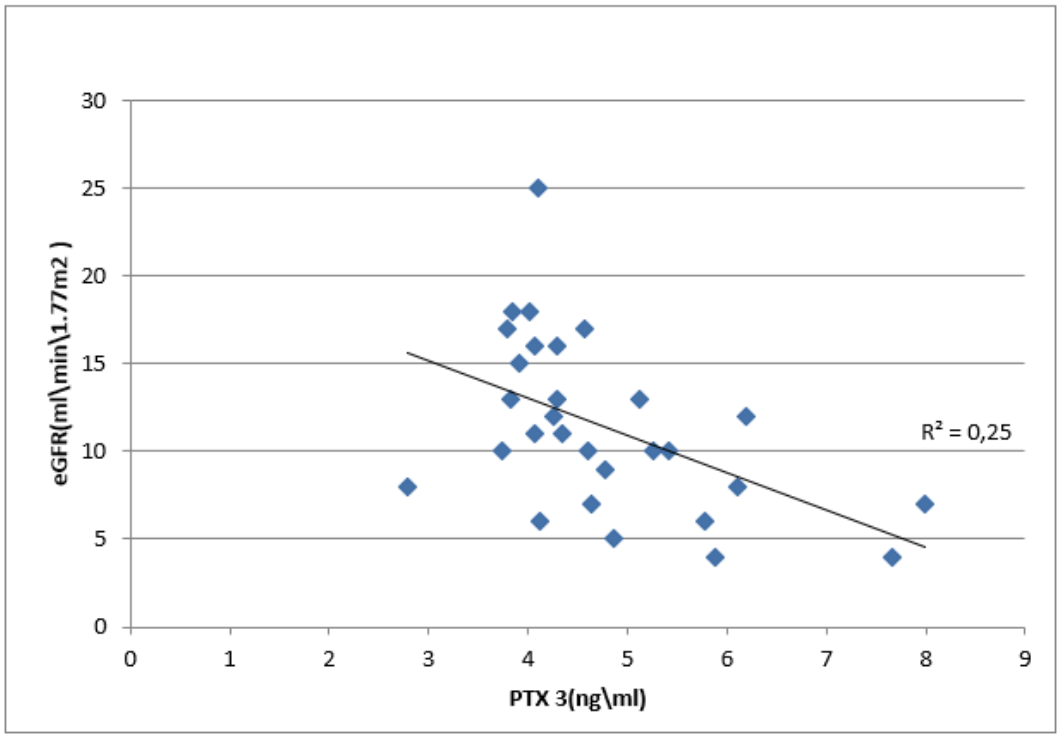

Figure 6. *Correlation between PTX-3 and GFR in patients with DN*

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Discussion

An early hint of the final stage of renal disease in those with T2DM is diabetes-related renal failure, which is a frequently occurring symptom[15]. Standard markers, such as albuminuria and serum creatinine, are not very specific and are not sensitive enough to denote small alterations in renal function or to accurately reflect the destruction of renal tissue. Therefore, there is a need for fresh biomarkers that can detect the presence of DN, which are fast and accurate[16] [17]. Detecting DN in its early stages presents a challenge as a significant portion of kidney function must deteriorate before creatinine levels rise. Our study delves into the correlation between patients' PTX3 levels and other factors to aid in early DN detection. By analyzing Table 1, our findings indicated that the concentration of PTX-3 (measured in ng/ml) was notably higher in DN patients compared to those without kidney disease, healthy individuals, and even patients with diabetes. The average PTX-3 serum level of DN patients was considerably distinct from that of non-DN patients with diabetes or control groups. The role of Ptx3 in DN is significant in alleviating damage to the kidneys. When it comes to the progression and development of DN, Pentraxin-3 may play a part[9]. The study conducted by Mezil et al. confirmed our findings as they discovered that the serum level of PTX-3 was notably higher in people with DN[12]. Between the ages of 40 and 60, 90 T2DM patients (split equally by gender) were examined in a research study. The results showed that the control group had a higher serum PTX3 level compared to the DN group. Another study also confirmed the lower PTX3 levels, which increased to the same extent as those without DN. Al-Barshomy et al. [17] showed that there was a noticeable variance in PTX3 serum levels between those diagnosed with renal disease and those who were not. Meligi et al. discovered that among T2DM patients with no proteinuria and unimpaired renal function, PTX3 concentration in the plasma was significantly higher than in healthy controls. The result aligns with the findings of Suliman et al. and Yilmaz et al. [18] [19]who concurred that individuals with diabetes and proteinuria displayed elevated serum levels of PTX3. Li et al. [22] and Tong et al. [21] discovered that PTX-3 levels were noticeably higher in chronic kidney disease sufferers compared to controls. Our findings are supported by Wu Dung et al. [23] who investigated PTX-3 levels in patients with varying degrees of DN. Interestingly, the PTX-3 concentration in group 2 (0.94 ± 0.26 ng/ml) was not vastly different from the control group's (1.35 ± 1.55 ng/ml). However, group 1 (0.81 ± 0.25 ng/ml) displayed noteworthy differences to the control group ($p = 0.009$ and $p = 0.012$, respectively). Our findings were corroborated by subsequent investigation. Kindly consider endorsing them. As stated by Zhou et al., the controls had lower levels of PTX3 compared to those with her DKD. A separate study conducted by Li et al. [25] supported this finding. In a related investigation by Dawood et al. (11), outcomes showed a concerning trend of increasing PTX3 levels as the disease progressed. In the DN group, PTX3 levels rose significantly when compared to both the control group and the diabetic groups lacking DN. Research conducted by Al-Kraity et al. [26] found that serum played a noteworthy role in these results.

In comparison to the control PTX3 levels, our findings align with Salcin et al.'s discovery[27] that the serum PTX3 level was higher in diabetic patients than in controls; however, their focus was only on cases of diabetes-related polyneuropathy. Wang et al. [9] conducted a study that examined the blood of 160 individuals with T2DM and 54 healthy individuals and reported that the PTX3 concentration in T2DM patients was lower than that of the control group, which was found to be more prevalent. Our findings are supported by various other studies as well. Reports from El-Naidani et al. [28] and El-Senosy et al. [29] indicate that PTX-3 concentrations were considerably elevated in the blood of T2DM patients in comparison to controls. An experiment conducted by XiaoYan et al. [30] demonstrated that patients experiencing microalbuminuria exhibited significantly higher serum PTX-3 levels than those without the condition. In our investigation, we uncovered that PTX3 plays a role in the creation of her DN, though we have yet to determine the exact process. A number of pathways, such as lowered endothelial cell activity and/or enduring mild inflammation, have been linked to the kidney failure stage of T2DM, as reported in previous research studies [31] . However, in contrast to Abu Seman et al.'s findings[32] , we found that patients with diabetes had less PTX3 in their serum compared to individuals without diabetes. Blood levels of PTX3 have been found to be lowered in Malaysian men with T2DM and DN, indicating that PTX3 has a possible role in the development of CKD and DN.

Different outcomes may be observed depending on ethnicity, age, and duration of illness in other research studies. In the present study, a modest correlation was detected between age and PTX-3 in DN patients ($r = 0.1$). Similar findings were reported by Mezier et al. [12], Suliman et al. [19], and El-Senosy et al. [29], which demonstrated a negligible positive correlation between the serum level of PTX-3 and the patient's age. Tong et al. [21]noted that although PTX-3 was positively correlated with age in healthy individuals, no such association was observed in patients with CKD ($r=-0.02$). Wang et al. [9] , Lee et al. [22] [25] , and Katakami et al. [35] however, found no linkage between age and PTX-3 serum levels. DN patients participating in the investigation showed a noteworthy inverse correlation between their PTX-3 and body mass index ($r = -0.14$). With findings comparable to that of Wang et al., the current outcomes are noteworthy. Valente et al. [14] , Witasp et al. [33] , and Miyazaki et al. [34] discovered a mutual link between BMI and PTX-3, an idea also supported by Mezil et al. [12] and El-Senosy et al. [29] whose research found a clear correlation between PTX-3 concentration in blood and BMI. However, the present findings are at odds with these prior studies and align more with the conclusions of Katakami et al. [35] and Li et al. [25] who found that PTX-3 levels and body mass index were not correlated. They all seem to concur regardless. In DN patients, there appears to be a link between an increase in PTX-3 levels and the progression of disease based on research. The current investigation highlights this trend, showing a significant positive association with an r-value of 0.58. Correspondingly, studies by Meligi et al. [20] and El-Senosy et al. [29] have also supported this connection, revealing a sizable association between PTX-3 concentration in serum and DN progression. These findings parallel the conclusions drawn from the present study. In regards to the correlation between serum PTX-3 and T2DM development, El Naidany et al. conducted a study [28] that revealed a weakening positive relationship. On the other hand, Katakami et al. [35] found no connection between PTX-3 levels and DM duration. Notably, our investigation revealed a significant positive correlation between PTX-3 levels and serum creatinine in DN patients ($r = 0.56$). In support of prior research, it has been discovered that there is a notable positive correlation between the PTX-3 level and the serum creatinine level in those with DN[9] [11] [12] [25] [28].

That being said, El Senusi and colleagues [26] brought to light a significant positive connection between creatinine and PTX-3 levels in the serum. Adding to this, Outinen et al.'s recent study[36] supported these conclusions. In the realm of kidney disease, studies have shown that individuals with heightened levels of PTX-3 also tend to have greater levels of creatinine while those with decreased levels have lower creatinine amounts. However, a recent research effort from

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Katagami et al. [35] flips current understandings on their head, as their findings display no correlation between the concentration of serum creatinine and PTX-3 levels in patients weighing 150 pounds or more. Further exploration revealed an insignificant rise in both PTX-3 and blood urea in those with DN (r = 0.22). In El Naidani's study, as well as in studies conducted by El Senusi and Ezzat, the findings indicated a minor rise in PTX-3 in patients with elevated blood urea levels. These results were inconclusive and did not reveal any significant changes. However, Mezil's analysis, which differed from these findings, suggested no link between serum creatinine and PTX-3 levels.. In DN patients, the investigation discovered a relationship between her PTX-3 and eGFR and apparently, it's negative with a value of -0.5. Research done by Wu Dung et al. [23] , Mezier et al. [12] , and Suliman et al. [33] have shown the same results. Interestingly, these researchers also observed a negative correlation between PTX-3 and eGFR in macroalbuminuria patients. Meanwhile, Tong et al. [18] found a similar link between PTX-3 and GFR. However, El Senusi et al. [29] failed to uncover any significant relationship between the serum level of PTX-3 and the eGFR. An observation by Katakami et al. indicated that PTX-3 levels had a noteworthy association with eGFR. Conversely, Li et al. found no connection between the two factors. The study[25] carried out by Katakami et al. showed a positive link between PTX-3 levels and eGFR, with [35] zero correlation reported in another study. It's anyone's guess why there are so many opposing findings, but it could be related to disease progression, various tests being utilized, or racial disparities. In fact, the notion that there are significant discrepancies between races is bolstered by one study that analyzed PTX-3 levels. But, it turns out that this doesn't apply to people of Hispanic, Chinese, or Caucasian descent. Interestingly,african Americans with elevated PTX-3 levels are more likely to experience decreased glomerular filtration rates.

Conclusion

Serum PTX3 correlated positively with age and B. urea but not significantly, positively with illness duration and S. creatinine, negatively with BMI but not significantly, and negatively with eGFR. In regard to this, PTX3 may be crucial for the development of diabetic ephropathy and its relationship to renal function.

Recommendations

For more effective use as a diagnostic tool for measuring the severity of DN in diabetic patients, larger samples and extended monitoring periods need to be explored through further research. This will allow for the potential to identify a successful biomarker.

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