Role of Retinol Binding Protein-4 as well as Procollagen III N-Terminal Peptide as Nephropathy Markers in Type 2 Diabetes

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Abstract

Background: Retinol-binding protein 4 (RBP4) is the primary circulatory carrier of retinol. Procollagen type III N-terminal peptide (PIIINP) increase suggested the substitution of muscles by additional fibrotic tissues.
Purpose: To identify RBP-4 + PIIINP as a distinct marker for nephropathy in type 2 diabetes
Methods: This case-control research involved 100 participants was carried out at El Mansoura Military Hospital from January 2019 and December 2021. Fifty individuals with a clinical and laboratory T2DM as well as nephropathy investigation made up the case group (group A). The control group (group B) comprised 50 non-diabetic people.
Results: There were highly substantial distinction among group A as well as group B ($p<0.01$) regarding RBP-4 ($p<0.01$) (9.40 ± 2.76 versus 7.06 ± 1.74), and PIIINP ($p<0.001$) (250.35 ± 2.97 versus 880.80 ± 4.99). With an AUC of 0.784, 80.1% sensitivity, and 76.2% specificity, RBP-4 showed a strong diagnostic ability to distinguish between groups A and B. Also, PIIINP demonstrated good performance with an AUC of 0.756 and produced 74.0% sensitivity and 76.0% specificity, successfully detecting nephropathy in type 2 diabetes.
Conclusion: RBP-4 and PIIINP are helpful biomarkers. Their complementary ability to represent tubular dysfunction as well as renal fibrosis, respectively, aids in diabetic nephropathy management.

Key Words: Nephropathy, Procollagen type III N-terminal peptide, Retinol-binding protein 4, Type 2 diabetes.

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Introduction:

Global wellness and economic performance is being impacted by diabetes mellitus (DM) along with its related repercussions, which had reached the stage of a pandemic. Globally, the quantity of people suffering from diabetes is predicted to become 642 millions in 2040. The urban resident populations of low-to-middle-income countries are expected to see the most alterations; of these, more than ninety percent of type II diabetes people (Zheng et al., 2018).

Type 2 diabetes mellitus has been a diverse etiology illness manifested via increased blood sugar levels, caused by malfunctions of insulin metabolism, releasing insulin, or both. Prolonged diabetes was linked to microvascular disorders like retinal damage, neurological disorders, and kidney problems. Diabetic nephropathy (DN), the most known adverse effect of DM, is a main trigger of advanced renal problem globally, that is linked to crucial deaths and morbidity. Type I DM cases were less likely to suffer from DN (30%) than Type 2 DM (40%) (Thipsawat, 2021).

Retinol-binding protein 4 (RBP4) is an adipokine primarily generated in liver as well as mature fat cells (between twenty to forty percent). It is a member of the lipocalin superfamily, attaches particularly to vitamin A, as well as moves tiny hydrophobic substances (Steinhoff et al., 2021). Multiple diseases as well as metabolic disorders, such as the insulin resistance in type 2 DM, coronary artery disorders, overweight, as well as macular degeneration, had been associated with RBP4 (Kim & Priefer, 2021). Individuals with DM, the insulin resistance, and lowered tolerance to glucose have elevated the serum RBP4 levels (Olsen & Blomhoff, 2020). By activating the

retinol transport receptor STRA6, RBP4 influences insulin signalling. This has a cascading effect on JAK2/STAT3 signalling pathways as well as increases expression of genes which impede the action of insulin (Huang et al., 2021; Perumalsamy et al., 2021). Additionally, variations in estimated glomerular filtration rate as well as serum creatinine were linked to serum RBP4, indicating its association with the kidney condition (Masaki et al., 2008).

Procollagen type III N-terminal peptide (PIIINP) is a result of manufacturing of type III collagen, a crucial protein via extracellular matrix remodelling as well as linked to accumulation of fibrotic tissues within the liver, kidneys, plus additional organs. As a result, PIIINP is a qualitative indicator of the collagen synthesis and has demonstrated the potential for use as a biomarker for fibrosis, especially liver fibrosis (Pettersson-Pablo et al., 2021), heart muscle (Agarwal et al., 2014), as well as the lungs (Su et al., 2017). Increased amounts of PIIINP could suggest the substitution of muscles by additional fibrotic tissues (Curcio et al., 2016). Adults had different phases of long-term renal illness have also been shown to have a role for PIIINP in renal disease (Ghoul et al., 2010).

The goal of the current work had been to identify RBP-4 + PIIINP as a distinct marker for nephropathy in type 2 diabetes

Patients and methods:

This case-control research involved 100 participants was carried out at El Mansoura Military Hospital from January 2019 and December 2021. Fifty individuals with a clinical and laboratory T2DM as well as nephropathy investigation made up the case group (group A). The control group (group B) comprised 50 non-diabetic people whose body mass index (BMI), age, as well as gender matched those of diabetes. Patients were excluded if they had type 1 diabetes, if they were pregnant, had malignancy, advanced kidney disease, cardiovascular disorders, and hepatic problems.

Baseline characteristics were gathered from the study groups including age, gender, body mass index, co morbidities as well as the medical history. Results from the lab included fasting blood sugar as well as the blood test measuring average blood sugar over 2-3 months for every diabetic patient. Venous blood samples had been taken from everyone in the sodium heparin tubes as well as tubes containing no anticoagulants; subsequently, left for resting half hour as well as centrifugation at 1100×g for twenty minutes at twenty five degree. Divisions retrieved in supernatant had been distributed as well as then saved till the chemical estimation was performed. Subsequent standards of lipid profile had been implemented: low density lipoprotein cholesterol (LDL-C) equal or more than one hundred mg/dl, and/or high density lipoprotein cholesterol (HDL-C) equal or less than fifty mg/dl, and/or triglycerides equal or more than 150 mg/dl, and/or consumption of medications that lower lipid (American Diabetes Association, 2012). In order to estimate creatinine and albuminurea ; urine samples had been gathered from the study population. Albumin-to creatinine ratio (ACR), kidney disease marker had been categorized as normal less than 30 mg/g; microalbuminurea 30 to 299 30 mg/g and macroalbuminurea if equal or more than 300 mg/g.

For estimating RBP-4 and PIIINP in serum samples had been done through calorimetric method by ELISA technique (Elabscience®, Houston, US)

Statistical analysis

The statistical package for social sciences, version 23.0 (SPSS Inc., Chicago, Illinois, USA), was used to analyze the information that was collected. Whenever the statistical pattern of the quantitative information had been parameterized (normal), it was shown as mean± standard deviation as well as ranges; whenever the statistical distribution had been non-parametric, it had been displayed as median with inter-quartile range (IQR). The qualitative factors had been displayed as ratios as well as numbers. The Kolmogorov-Smirnov and Shapiro-Wilk tests had been employed to examine the results for normalcy.

Results:

As shown in Table (1), the average age of patients in group A had been (52.86 ± 12.54) years and (54.39 ± 11.95) years in group B with none substantial distinction among both groups (p=0.950). Group A patients' mean BMI was (30.50 ± 6.11) and (20.82 ± 1.82) kg/m2 in group B with highly substantial distinction among both

groups (p<0.001). There was none substantial distinction among both groups regarding gender (p=0.131), hypertension (p=0.470) and smoking (p=0.107). There were highly substantial distinction among group A as well as group B (p<0.01) regarding fasting blood sugar (224.23 ± 13.10 versus 80.45 ± 1.44), HbA1c (%) (p<0.001) (9.45 ± 1.71 versus 5.28 ± 0.91), total cholesterol (p<0.001) (260.46 ± 8.04 versus 160.12 ± 3.62), HDL (p<0.01) (30.5 ± 6.11 versus 39.38 ± 9.93), LDL (p<0.01) (150.87 ± 3.05 versus 110.10 ± 1.85), HOMA-IR (p<0.001) (14.41 ± 3.48 versus 2.72 ± 0.73), eGFR (p<0.001) (50.29 ± 11.57 versus 123.28 ± 11.27), and ACR (p<0.001) (260.90 ± 6.13 versus 25.64 ± 4.36).

As shown in Table (2), there were highly substantial distinction among group A as well as group B (p<0.01) regarding RBP-4 (p<0.01) (9.40 ± 2.76 versus 7.06 ± 1.74), and PIIINP (p<0.001) (250.35 ± 2.97 versus 880.80 ± 4.99).

Table (1): Comparison of the baseline and biochemical characters between the two study groups

	Group A (n=50)	Group B (n=50)	p- value
Age (years)	52.86 ± 12.54	54.39 ± 11.95	0.950
BMI (kg/m^2)	30.50 ± 6.11	20.82 ± 1.82	<0.001
Male (n, %)	20 (40.0%)	19 (38.0%)	0.131
Female (n, %)	30 (60.0%)	31 (62.0%)	
Hypertension	3 (26.0%)	11 (22.0%)	0.470
Smoking	24 (48.0%)	18 (36.0%)	0.107
Disease duration	4.52 ± 0.81	---	
Fasting blood sugar (mg/dl)	224.23 ± 13.10	80.45 ± 1.44	<0.01
HbA1c (%)	9.45 ± 1.71	5.28 ± 0.91	<0.001
Total cholesterol (mg/dl)	260.46 ± 8.04	160.12 ± 3.62	<0.001
HDL (mg/dl)	30.5 ± 6.11	39.38 ± 9.93	<0.01
LDL (mg/dl)	150.87 ± 3.05	110.10 ± 1.85	<0.01
HOMA-IR (µU/ml)	14.41 ± 3.48	2.72 ± 0.73	<0.001
eGFR ml/min/1.73m^2	50.29 ± 11.57	123.28 ± 11.27	<0.001
ACR (mg/dl)	260.90 ± 6.13	25.64 ± 4.36	<0.001

Table (2): Comparison of RBP-4 and PIIINP between the two study groups

	Group A (n=50)	Group B (n=50)	p- value
RBP-4	9.40 ± 2.76	7.06 ± 1.74	<0.01
PIIINP	250.35 ± 2.97	880.80 ± 4.99	<0.001

The receiver-operating characteristic (ROC) curve analysis showed that RBP-4 had a excellent diagnostic effectiveness for differentiating between group A and group B, with the area under the curve (AUC) of 0.784 (95% CI: 0.661-0.872, P<0.001). RBP-4 had a sensitivity of 80.1%, specificity of 76.2%, positive predictive value (PPV) of 76.9%, and negative predictive value (NPV) of 79.2%, indicating that RBP-4 can be a distinct marker for nephropathy in type 2 diabetes (Figure 1).

The receiver-operating characteristic (ROC) curve evaluation showed that PIIINP had a outstanding diagnostic effectiveness for differentiating among group A as well as group B, with AUC of 0.756 (95% CI: 0.672-0.819, P<0.001). PIIINP had a sensitivity of 74.0%, specificity of 76.0%, PPV of 75.5%, and NPV of 74.5%, indicating that PIIINP 4 can be a distinct marker for nephropathy in type 2 diabetes (Figure 2).

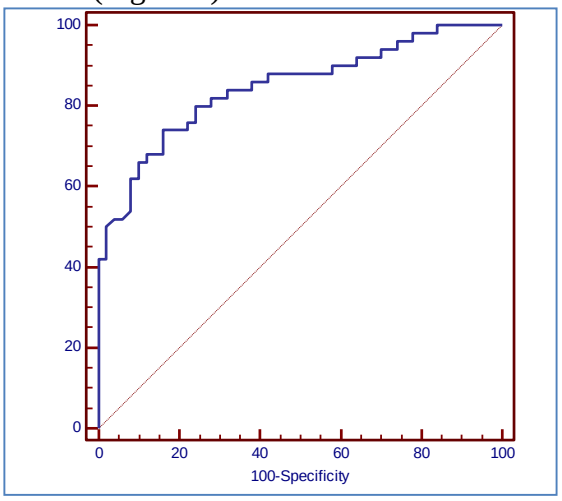


Figure (1): Receiver-operating characteristic (ROC) curve showing the diagnostic performance of RBP-4.

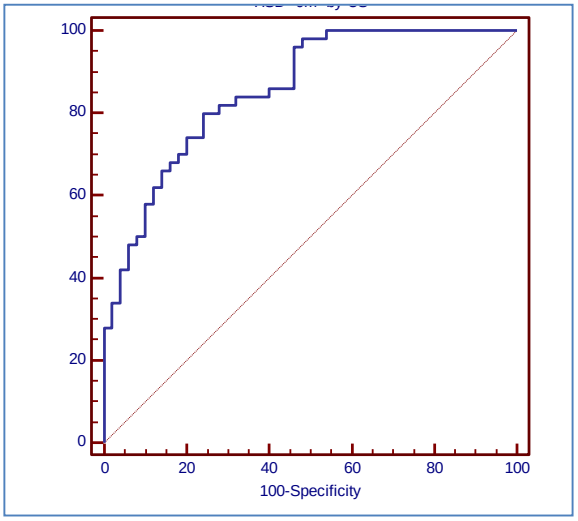


Figure (2): Receiver-operating characteristic (ROC) curve showing the diagnostic performance of PIIINP.

Discussion:

The current study results revealed highly substantial increase in body mass index, HbA1c percentage, the fasting glucose levels, total cholesterol, LDL, HOMA-IR and ACR among group A than group B. Also, there had been highly substantial reduction in HDL and eGFR in group A than group B. These results were consistent with Ahmad Khan, (2007), they reported substantially elevated LDL as well as cholesterol in both male and female individuals suffering from poorer glycaemic control (HbA(1c) > 9%).

Kawamoto et al., (2008) proposed that a graded decline in eGFR had been continually and considerably linked to increase BMI, microalbuminuria and proteinuria can result from a decrease in rate of the glomerular filtration along with elevation in rate of excretion of urine albumin that could speed up the onset of diabetic kidney disorder (de Jong et al., 2002). Another study conducted by Hu & Zhang, (2020) found that between individuals with diabetes as well as overweight, diabetes duration, glycated HbA1c, and BMI were distinct factors for diabetic nephropathy. Abdominal obesity, elevated triglycerides, low HDL-C, hypertension, as well as elevated fasting glucose are indicators of risk for chronic kidney disease, according to earlier research (Kurella et al., 2005).

An increasing amount of research suggested that renal haemodynamic alterations were linked to the insulin resistance. Glomerular hydrostatic pressure, renal vascular permeability, hyperfiltration of the glomerulus, and sodium renal absorption can all be exacerbated by hyperinsulinemia. These changes could impair haemodynamic balance as well as kidney endothelial processes, which could explain the relationship between the HOMA-IR score as well as the microalbuminuria onset (Hsu et al., 2011).

Our results showed highly substantial distinction regarding RBP-4 as well as PIIINP among group A as well as group B ($p<0.01$, $p<0.001$).

With an AUC of 0.784, 80.1% sensitivity, and 76.2% specificity, RBP-4 showed a strong diagnostic ability to distinguish between groups A and B in our study, making it a relevant marker for nephropathy in type 2 diabetes. In a similar vein, PIIINP demonstrated good performance with an AUC of 0.756 and produced 74.0% sensitivity and 76.0% specificity, successfully detecting nephropathy in type 2 diabetes.

In order to examine the relationships between RBP4 level as well as clinical markers of kidney operations as well as albuminuria within T2DM individuals, Zhang et al., (2020) meta-analysis demonstrated that RBP4 concentrations had been substantially greater in the micro plus macroalbuminuria group of T2DM individuals than within normal albuminuria group.

Lower catabolism as well as the insulin resistance could be the pathogenic process responsible for the variations in RBP4 quantities between patients had diabetes and those had no impaired kidney function. First, glomerular filtration as well as the following reabsorption of RBP4 into the proximal tubular tissues control retinol homeostasis, which is maintained across the body by the kidneys (Marinó et al., 2001). As a result, DN patients have inceased concentrations of RBP4 than T2DM patients with no renal disorder due to renal function disorders (Masaki et al., 2008). In patients with DN, increased levels of RBP4 could be linked to deteriorating resistance of insulin. This may result from the liver producing more sugar due to a greater development of gluconeogenic enzymes in hepatic cells, a disruption in insulin signalling, as well as decreased uptake of glucose in the skeletal muscles (Yao-Borengasser et al., 2007).

Serum and urine PIIINP levels could be helpful in evaluating renal fibrosis in both native as well as transplanted kidneys, according to two prior investigations (Soylemezoglu et al., 1997; Teppo et al., 2003). Elevated urinary PIIINP concentrations could be a sign of the initial kidney damage in solitary functioning kidney (Taranta-Janusz et al., 2019). Patients with type 2 diabetes who had nephropathy additionally had elevated serum PIIINP (Ishimura et al., 1996).

Conclusion:

RBP-4 and PIIINP had been helpful indicators. Their complementary ability to represent tubular malfunction as well as renal fibrosis, respectively, aids in diabetic nephropathy management.

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