

# Impact of Procollagen III Amino Terminal Peptide and Laminin on Nephropathy in Pre-Diabetic and Type 2 Diabetic Patients

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**Abstract-** Chronic hyperglycemia is one of the most prevalent causes of the development of type 2 diabetes mellitus (T2DM) worldwide, with diabetic nephropathy (DN) being the principal microvascular complication. Laminin is a major non-collagenous glycoprotein that is an important component of all basement membranes. Serum PIIINP is a precursor of collagen III associated with several inflammatory disorders and tissue fibrosis, including liver and kidney fibrosis. The aim of this study was to assess and compare the concentrations of Laminin (LM), Procollagen III N-terminal Peptide (PIIINP), and various biochemical parameters in individuals diagnosed with type 2 diabetes, both with and without nephropathy, alongside control subjects, in order to explore the potential of LM and PIIINP as predictive biomarkers for early detection in these patients. A case-control study was conducted from March 2024 to October 2024. The study included 180 participants (93 females and 87 males) consisting of four groups: Group 1 (45) healthy participants, Group 2 (45) participants with prediabetes, Group 3 (40) T2DM patients with normoalbuminuria, and Group 4 (50) T2DM patients with nephropathy (microalbuminuria and macroalbuminuria). The study was conducted at Al-Imamin Al-Kadhimeen City Hospital. Our study showed that the serum concentration of laminin in patients with type 2 diabetes mellitus with nephropathy ( $560.60 \pm 66.85$  pg/ml) was significantly elevated compared with individuals with type 2 diabetes without nephropathy ( $359.60 \pm 29.83$  pg/ml), prediabetes ( $140.00 \pm 19.72$  pg/ml), and healthy subjects ( $113.90 \pm 29.65$  pg/ml) ( $P < 0.001$ ). Additionally, the mean serum PIIINP value was significantly higher in type 2 diabetes patients with nephropathy ( $660.90 \pm 47.67$  pg/ml) compared to those without nephropathy ( $521.60 \pm 80.00$  pg/ml), prediabetes ( $437.80 \pm 75.00$  pg/ml), and controls ( $360.30 \pm 57.50$  pg/ml) ( $P < 0.001$ ). There was no correlation between LM and PIIINP in prediabetes; however, there was a substantial positive correlation between laminin and PIIINP in type 2 diabetes with nephropathy ( $r = 0.67$ ,  $P < 0.001$ ) and in type 2 diabetes without nephropathy ( $r = 0.36$ ,  $P < 0.014$ ).

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## Introduction

Prediabetes is defined as blood glucose levels that are above the normal range but below the threshold for diabetes; it is commonly known as impaired fasting serum glucose or impaired glucose tolerance (IGT) (1).

In 2012, diabetes mellitus was the eighth leading cause of death, responsible for 4% (1.5 million) of all

deaths among individuals under 70 years of age worldwide. Furthermore, the most recent data from the WHO indicate that 422 million adults worldwide have been diagnosed with diabetes mellitus (2).

The main cause and clinical manifestation of type 2 diabetes is hyperglycemia, which usually results from insulin deficiency (complete absence of insulin) and/or the inability of the body's cells to respond properly to

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insulin (i.e., insulin resistance), which is produced in the pancreas. Both conditions can lead to chronically high blood glucose levels, and insulin resistance can also result in disturbances in lipid and protein metabolism (3).

Uncontrolled diabetes results in prolonged hyperglycemia and excessive glucose excretion in the urine. In most cases, it is associated with both microvascular and macrovascular complications in peripheral tissues, including the kidneys, blood vessels, cardiovascular system, retina, brain, and liver (4,5).

Diabetic kidney disease (DKD), also known as diabetic nephropathy, manifests as a microvascular complication of diabetes, with a prevalence of 30-40%. DKD is a leading cause of end-stage renal disease (ESRD), accounting for 30-47% of ESRD cases and representing a major cause of diabetes-related deaths (5).

Procollagen III amino-terminal peptide (PIIINP) is an important indicator of collagen production, specifically type III collagen. It consists of three identical peptide chains with an approximate molar mass of 42 kDa and is released during the maturation of type III collagen (6,7). Type III collagen is a crucial component of the extracellular matrix (ECM) and plays an important role in tissue remodeling (8).

The serum level of Procollagen type III N-terminal peptide (PIIINP) serves as a reliable indicator for assessing active fibrosis in different tissues and organs of the body. Elevated PIIINP levels indicate increased collagen synthesis and are associated with fibrotic processes in chronic liver diseases, respiratory disorders, and cardiac fibrosis, including ischemic heart disease and congestive heart failure (9,10).

Elevated concentrations of PIIINP have also been reported in several inflammatory conditions, including pulmonary fibrosis, acromegaly, and rheumatoid arthritis (RA) (11). The increase in PIIINP levels during skeletal muscle repair and growth is associated with collagen production, which is essential for muscle regeneration and remodeling after injury or intense exercise. Treatments involving growth hormone and testosterone may also increase collagen production, leading to elevated PIIINP levels (12).

Laminins are the main non-collagenous, high-molecular-weight glycoproteins, typically approximately 850 kDa, and are vital components of the basement membrane. They comprise three subunits:  $\alpha$ ,  $\beta$ , and  $\gamma$  polypeptide chains, which bind to form cross- or T-shaped heterotrimers (13). This distinctive structure is essential for their function in the extracellular matrix, which has a broad regulatory role in many cellular

biological processes, including cell adhesion, apoptosis, proliferation, migration, growth, inflammatory responses, and differentiation (14). Laminins are essential for providing structural support and influencing cell behavior in nearly all body tissues (15).

Laminin maintains the structure of the basement membrane, which is crucial during embryogenesis; improper cell adhesion or differentiation can lead to defects in the kidney, eye, muscle, peripheral nerve, brain, and skin (16). Additionally, laminin is involved in fibrogenesis, with elevated levels being strongly correlated with hepatic fibrosis (17). Laminin isoforms serve distinct functions in the development, maintenance, and operation of specific metabolic cells, including those located in muscle, liver, adipose tissue, and other metabolically active organs (18).

This research aimed to evaluate serum levels of LM and PIIINP in individuals with nephropathy associated with prediabetes and type 2 diabetes mellitus, and to compare these levels with those of healthy individuals. Additionally, it aimed to identify the interrelationship among these components in healthy controls and in patients with type 2 diabetes mellitus with and without nephropathy.

## Materials and Methods

### Subjects and design of the study

A total of 180 participants were classified into four groups

- 45 healthy controls (**Group 1**).
- 45 participants with pre-diabetes (**Group 2**) (HbA1c >5.7% and <6.5%),
- 40 patients with diabetes mellitus type 2 (T2DM) showing normal albuminuria (**Group 3**), (HbA1c >6.5% and UACR <30 mg /g,
- 50 patients with diabetic albuminuria (**Group 4**) including those with microalbuminuria (UACR 30 to 299 mg albumin/g creatinine) and macroalbuminuria (UACR  $\geq$ 300 mg/g).

Each participant completed a survey that collected demographic and baseline data, including age, sex, clinical history, smoking status, blood pressure, BMI, height, and blood test results, all of which were recorded and reviewed. The assessment was performed for both patients and the experimental groups, and consent was obtained.

This research received approval from the Medical Ethics Committee of the College of Medicine, Al-Nahrain University. All data used in the investigation

were anonymized; therefore, the requirement for informed consent was waived.

**Inclusion criteria:** - Patients aged between 40 and 70 years with type 2 diabetes.

#### Exclusion criteria

The exclusion criteria for the research study included persons possessing the following conditions or characteristics:

- Type 1 diabetes mellitus
- A background of extended use of toxic to the kidney's medications
- Laboratory indicators of urination or urinary system infections
- End-stage renal disease (ESRD), hepatic disease, and cardiac failure.
- Individuals diagnosed with any form of cancer or carcinoma.

#### Serum and urine collection

Venous fasting blood samples (about six to eight milliliters) were collected from each subject in the morning after a 12- hour fast using a disposable syringe and were immediately stored at  $-20^{\circ}\text{C}$  from March 2024 to November 2024. The whole blood samples were divided into two parts. In the first part, two milliliters of blood were collected in EDTA tubes for HbA1c analysis. Additionally, six milliliters of whole blood were collected in a gel tube and allowed to stand for 20 minutes at room temperature. After coagulation, the clot was separated by centrifugation at 2,000-3,000 rpm for 20 minutes.

Urine samples were immediately collected from patients and controls and placed into sterile containers. The current research included assays to measure the concentrations of albuminuria and creatinine in urine. Participants in the study were evaluated using the urine albumin- to- creatinine ratio (ACR), an indicator of kidney disease, which was categorized as normal ( $<30$  mg albumin/g creatinine), microalbuminuria (30-299 mg albumin/g creatinine), and macroalbuminuria ( $\geq 300$  mg albumin/g creatinine) (19).

Serum concentrations of glucose, urea, creatinine, and lipid profile were rapidly assessed in serum samples using the Cobas Roche 311. Serum concentrations of insulin and biomarkers, including PIIINP (SunLong Biotech, China) and Laminin (SunLong Biotech, China), were determined in serum samples stored at  $-20^{\circ}\text{C}$  using the ELISA technique.

#### Statistical study

Statistical analysis was performed using SPSS 26.0,

GraphPad Prism 9.0, and MedCalc. Data were presented as (mean $\pm$ SD). The Pearson correlation coefficient was calculated to evaluate the strength of the relationship between two numerical variables. A  $P$  of  $P<0.05$  was considered statistically significant. The area under the receiver operating characteristic (ROC) curve analysis was used to determine the diagnostic value of the indicators (20).

## Results

#### Characteristic of the study population

Table 1 presents the mean $\pm$ SD data for demographic characteristics and parameter levels across the different groups. No statistically significant differences in age or sex were observed among the study groups compared with the normal group. Individuals with prediabetes and type 2 diabetes mellitus, with or without albuminuria, had elevated levels of BMI and hypertension. The clinical characteristics of the study population are illustrated in Table 2.

Significant differences in PIIINP and LM levels were observed among the groups ( $P<0.001$ ). The results indicated that the mean serum PIIINP levels in patients with type 2 diabetes with and without nephropathy were significantly elevated at (660.90 $\pm$ 47.67) pg/ml and (521.60 $\pm$ 80.00) pg/ml, respectively, compared with the control group (360.30 $\pm$ 57.50) pg/ml and the prediabetes group (437.80 $\pm$ 75.00) pg/ml ( $P<0.001$ ) (table 2).

The mean LM levels in type 2 diabetic patients with nephropathy (560.60 $\pm$ 66.85 pg/ml) and without nephropathy (359.60 $\pm$ 29.83 pg/ml) were significantly higher compared with the control group (113.90 $\pm$ 29.65 pg/ml) and the prediabetes group (140.00 $\pm$ 19.72 pg/ml) ( $P<0.001$ ).

In addition, higher levels of HbA1c, total cholesterol, triglycerides, VLDL- C, LDL- C, HOMA- IR, LM, PIIINP, and UACR were observed, as illustrated in Table 2 and Figures (1-4), while lower levels of HDL- C and eGFR were reported. There were highly significant differences in LM, PIIINP, FBS, HbA1C, TC, TG, HDL- C, LDL- C, and VLDL- C among the four groups ( $P<0.001$ ).

#### Relationship between serum PIIINP and LM levels and clinical and laboratory parameters

The subsequent stage of this research involves determining the correlation between blood PIIINP and LM levels and various characteristics across all demographic subgroups using Pearson correlation coefficient analysis (as shown in Table 3).

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Serum PIIINP showed a positive and significant correlation with LM ( $P=0.0066$ ,  $r=0.38$ ), FBS ( $P=0.004$ ,  $r=0.275$ ), HbA1C ( $P=0.019$ ,  $r=0.185$ ), total cholesterol ( $P=0.007$ ,  $r=0.378$ ), LDL ( $P=0.0094$ ,  $r=0.341$ ), VLDL-C ( $P=0.0053$ ,  $r=0.313$ ), HOMA ( $P=0.0027$ ,  $r=0.283$ ), and UACR ( $P<0.001$ ,  $r=0.551$ ), and a significant negative correlation with eGFR ( $P=0.009$ ,  $r= -0.302$ ).

Serum LM exhibited a positive and significant correlation with age ( $P=0.0022$ ,  $r=0.363$ ), PIIINP ( $P=0.0066$ ,  $r=0.38$ ), BMI ( $P=0.01$ ,  $r=0.254$ ), FBS ( $P<0.001$ ,  $r=0.818$ ), HbA1C ( $P<0.001$ ,  $r=0.675$ ), total cholesterol ( $P=0.0013$ ,  $r=0.487$ ), triglycerides ( $P=0.002$ ,  $r=0.377$ ), LDL ( $P=0.0024$ ,  $r=0.335$ ), VLDL-C ( $P=0.0019$ ,  $r=0.381$ ), HOMA ( $P<0.001$ ,  $r=0.834$ ), and UACR ( $P<0.001$ ,  $r=0.563$ ), and a significant negative correlation with HDL ( $P=0.0018$ ,  $r= -0.452$ ) and eGFR

( $P<0.001$ ,  $r= -0.547$ ).

Due to the substantial disparity in LM and PIIINP levels between prediabetic patients and type 2 diabetes cohorts, both with and without albuminuria, a receiver operating characteristic (ROC) curve analysis was conducted. The results indicated a cutoff value of  $>8.37$  pg/mL, with an area under the curve (AUC) of 91.6, sensitivity of 96.7%, and specificity of 80.0% (table 4).

The Pearson correlation coefficient test was used. A  $P$  less than 0.05 was considered significant, and the correlation coefficient ( $r$ ), which quantifies the relationship between two variables, ranges from  $-1$  to  $1$ . An  $r$  value from  $0$  to  $1$  indicates a positive correlation, while an  $r$  value from  $-1$  to  $0$  indicates a negative correlation.

**Table 1. Outlines the socioeconomic features of the subject of the study population**

Variables	Group 1	Group 2	Group 3	Group 4		P
	Control (n=45)	Pre-diabetes (n=45)	T2DM.W. A (n=40)	T2DM.Mi (n=25)	T2DM.Ma (n=25)	
Age, years Mean±SD Range	51.63±5.46 44 - 65	53.09±7.18 (48-65)	52.80±5.00 49-66	56.31±6.38 52-67	57.98±3.66 48-70	0.255
BMI, k/m <sup>2</sup> Mean±SD Range	24.4±1.93 18.8-26.1	27.6±3.84 20.5-28.6	29.14±3.75 21.0-36.3	30.6±2.86 25-33	34.28±3.8 30-37	<0.01
Duration years Mean±SD Range	-----	-----	10.69±2.69 7.0-17	14.2±3.91 8.0-21	17.18±3.70 11.0-23	<0.05
Hypertension						
No	45(100%)	34(75.5%)	23(57.5%)	7(28%)	2(8%)	<0.001
Yes	0(0%)	11(24.5%)	17(42.5%)	18(72%)	23(92%)	

**Table 2. Lists the clinical and biochemical characteristics of each research participant**

Parameters	Group1 (n=45)	Group2(n=45)	Group3(n=40)	Group4 (n=50)	P
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
PIIINP (pg/ml)	360.3±57.5	437.8±75.0	521.6±80.0	660.9±47.67	<0.001
LM (pg/ml)	113.9±29.65	140.0±19.72	359.6±29.83	560.6±66.85	<0.001
FBS (mg/dl)	96.9±6.98	110.8±5.58	200±50.16	259±41.43	<0.001
HbA1C (%)	5.18±0.28	5.9±0.27	7.7±1.42	9.22±1.01	<0.001
TC (mg/dl)	169.00±11.5	186.80±19.5	205.4±25.5	208.70±28.0	<0.001
TG (mg/dl)	114.00±11.1	139.40±28.6	162.6±32.96	191.2±41.84	<0.001
HDL (mg/dl)	49.70±8.03	40.00±5.42	41.00±7.05	33.16±4.00	<0.01
LDL (mg/dl)	91.07±7.00	103.10±9.21	109.30±18.81	124.1±13.39	<0.01
VLDL (mg/dl)	22.79±2.23	27.88±5.72	31.75±7.22	38.24±8.39	<0.01
HOMA-IR (μU/ml)	2.03±0.27	4.11±0.59	8.80±2.36	15.77±3.38	<0.001
eGFR ml/min/1.73m <sup>2</sup>	122.0±28.71	108.10±26.59	102.90±18.72	48.81±10.96	<0.001
UACR (mg/g)	15.24±7.524	14.15±7.084	19.37±5.163	355.6±34.06	<0.001

Group 1. Control individual, Group2: Pre-diabetes, Group3: T2DM without albuminuria, Group4: T2DM with albuminuria n: number of cases; SD: Standard deviation; data were expressed as mean and standard deviation; One-way ANOVA; Post hoc Tukey's test; \*very significant at  $P\leq 0.00$  or  $0.01$ ; significant at  $P\leq 0.05$ ; P1: Control vs. pre-diabetic; P2: Control vs. T2DM.WA; P3: Control vs. T2DM.WA

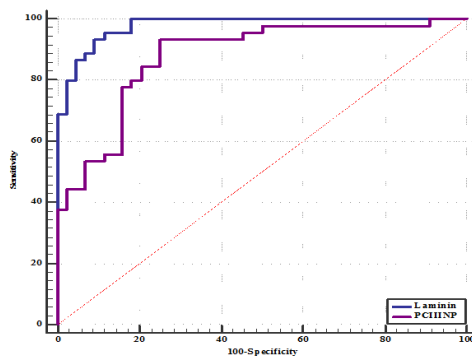
**Table 3. Shows the relationship between PIIINP, LM, and the laboratory and clinical indicators.**

Parameters	PIIINP		LM	
	P	r	P	r
Age (years)	0.84	0.015	0.0022	0.363
PIIINP	-	1.00	0.0066	0.380
LM	0.0066	0.380	-	1.00
BMI (Kg/m <sup>2</sup> )	0.130	0.12	0.010	0.254
FBS (mg/dl)	0.004	0.275	<0.001	0.818
HbA1C (%)	0.019	0.185	<0.001	0.675
TC (mg/dl)	0.007	0.378	0.0013	0.487
TG (mg/dl)	0.31	0.08	0.002	0.377
HDL (mg/dl)	0.853	-0.015	0.0018	-0.452
LDL (mg/dl)	0.0094	0.341	0.0024	0.335
VLDL (mg/dl)	0.0053	0.313	0.0019	0.381
HOMA-IR (μU/ml)	0.0027	0.283	<0.001	0.834
eGFR ml/min/1.73m <sup>2</sup>	0.0097	-0.302	<0.001	-0.547
UACR (mg/g)	<0.001	0.551	<0.001	0.563

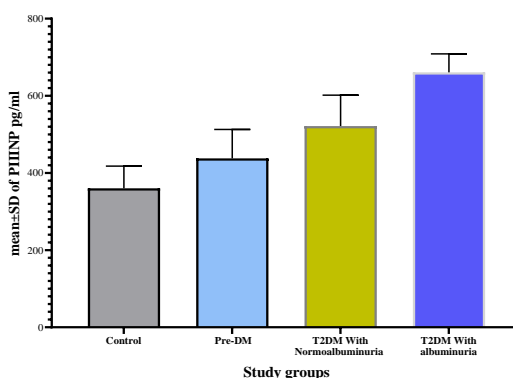
Significant difference  $P < 0.05$

**Table 4. Shows the ROC and cutoff values for procollagen III amino terminal peptide and laminin in each study groups nephropathy, pre-diabetic and type 2 diabetic patients**

Marker	AUC	SE	95%CI	Cutoff	Sensitivity	Specificity
LM	0.978	0.011	0.922 to 0.997	>204	93.30	90.90
PIIINP	0.878	0.037	0.791 to 0.938	>481	93.30	75.0



**Figure 1. ROC curve and cutoff values for LM and PIIINP in the study groups nephropathy, pre-diabetic and type 2 diabetic patients**



**Figure 2. Serum levels of procollagen III N-terminal peptide in each study groups nephropathy, pre-diabetic and type 2 diabetic patients**

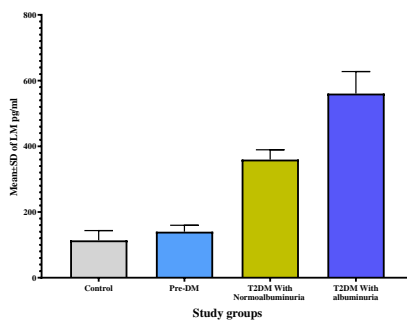


Figure 3. Serum levels of laminin in each study groups nephropathy, pre-diabetic and type 2 diabetic patients

## Discussion

Laminin is an essential glycoprotein present in the extracellular matrix (ECM) and is crucial for supporting cells and tissues. It significantly influences the regulation of insulin signaling and its activity in metabolic tissues, including muscle, liver, and adipose tissue. Procollagen III N-terminal peptide (PIIINP) acts as a biomarker indicating type III collagen formation, an essential component of the extracellular matrix (ECM).

The interactions between extracellular matrix proteins and cells are essential for preserving the structural and functional integrity of tissues, while also affecting metabolic pathways, especially insulin sensitivity and glucose homeostasis. Diabetes mellitus is classified as a metabolic illness that impacts the metabolism of carbohydrates, lipids, and proteins. In recent years, chronic diseases such as diabetes and hypertension have become recognized as significant contributors to global mortality (21).

The prevalence of type 2 diabetes mellitus and its associated nephropathy as a complication in developed countries has reached significant levels, constituting a major public health issue. The current study demonstrates a strong positive association between LM and both insulin resistance and blood glucose levels. Additionally, both PIIINP and LM exhibit a correlation with UACR that is more pronounced in individuals with type 2 diabetes and nephropathy.

This investigation showed elevated concentrations of serum PIIINP and LM in subjects diagnosed with prediabetes, type 2 diabetes mellitus without albuminuria, and type 2 diabetes mellitus with albuminuria, compared with healthy individuals. Significantly increased levels of LM were found to be closely correlated with kidney function tests. The findings of this study indicate that PIIINP may serve as a promising biomarker for diagnosing type 2 diabetes mellitus with nephropathy. Consequently, it is essential to further examine the

potential involvement of LM and PIIINP in the etiology of type 2 diabetes mellitus.

Procollagen III N-terminal peptide (PIIINP) underscores the peptide’s function in signaling the synthesis of type III collagen, an essential element in tissue healing, fibrosis, and various processes related to extracellular matrix remodeling in organs such as the liver, pancreas, and kidneys.

Although direct studies examining the correlation between PIIINP levels and type 2 diabetes or prediabetes are scarce, some research has investigated the potential association of PIIINP with broader metabolic processes, particularly glucose metabolism, insulin secretion, and pancreatic beta- cell function. Ionin and Baranova’s research indicates that PIIINP concentrations are elevated in patients with atrial fibrillation (AF) and metabolic syndrome (MS). Metabolic syndrome encompasses a constellation of disorders such as insulin resistance, dyslipidemia, hypertension, and central obesity, which are significant risk factors for type 2 diabetes (22).

Elevated blood PIIINP levels in patients with type 2 diabetes, both with and without nephropathy, may indicate increased collagen turnover and fibrosis, potentially associated with insulin resistance and other metabolic abnormalities observed in prediabetes and type 2 diabetes.

This work suggests that high PIIINP levels may not only indicate collagen formation but may also play a role in the complex pathological changes affecting insulin production and function. Additional research is required to determine the direct role of PIIINP in these pathways and its potential as a therapeutic target for diabetes and metabolic diseases.

The study demonstrated that patients diagnosed with nephropathy associated with type 2 diabetes mellitus (T2DM) and those with prediabetes had elevated levels of PIIINP and LM in their blood. These levels were associated with abnormalities in glucose and renal function tests and effectively differentiated between

prediabetes and type 2 diabetes mellitus, both with and without nephropathy.

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