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Association of Angiopoietin Like Protein -4 and Fibroblast Growth Factor-23 in Different Stages of Diabetic Nephropathy For Early Detection and Progression.

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Abstract

Abstract: In many nations, diabetic nephropathy is the leading cause of renal failure and a major predictor of death and morbidity among diabetic patients. Preventing or early intervention to treat diabetes requires identifying the association between certain biomarkers and high protein levels in patients. Angiopoietin-like protein-4 (ANGPTL-4) and fibroblast growth factor-23 (FGF-23) were the most researched among these biomarkers. The participants depended on urine albumin–creatinine ratio (UACR) levels in classification of diabetic nephropathy. The study involved 176 individuals divided into four groups. The controls (44 as a healthy participant). Diabetic groups divided into three groups: Normoalbuminurea (no kidney disease and (UACR) levels within the normal range (<30 mg/g), Microalbuminuria (diabetic kidney disease patients with moderately increased UACR 30–300 mg/g), and Macroalbuminuria (diabetic kidney disease patients with severely increased UACR >300 mg/g).

Determination the levels of serum (ANGPLT-4, and FGF-23) and association with early detection and progression of diabetic nephropathy.

1.Introduction

Diabetic nephropathy, or DN, is a major global issue over the world. A common complication of Long-term effects of hyperglycemia on kidneys, including damage to their filtration units and blood vessels, lead to structural and functional problems, which in turn cause DN (1). As diabetes progresses, the kidneys naturally undergo glomerular hyperfiltration, albuminuria increases, and the estimated glomerular filtration rate (eGFR) gradually decreases. A clinical diagnosis of DN can be made when there are no symptoms or signs of other main causes of kidney disease (2). In the beginning, there are often no symptoms of DN. There is an increase in mortality and sickness rates, a decline in quality of life, and the need for dialysis or a kidney transplant for many individuals with renal failure (3). Worldwide, more than six million people die each year from complications related to diabetes mellitus (DM), making it the tenth most common killer of persons younger than 70 years old, according to the World Health Organization (WHO) (4). Twenty to thirty percent of people with T2D and twenty to forty percent of people with T1D develop DKD, according to epidemiological research (5). The cost-effectiveness can be greatly improved by early detection of DN and timely treatment of risk factors (6). The pathophysiology of DN is complex and involves multiple factors. One of these is oxidative stress, which plays a significant role in the metabolic inflammatory, hemodynamic, and other kidney-related pathologies caused by diabetes-induced hyperglycemia (7). These changes in hemodynamics also start and activate several vasoactive systems

in the kidneys, which speed up the development of DKD. The advancement of DN and an increase in glomerular perfusion and intraglomerular pressure are the results of these actions (8). Many rick factors can contribute to the development and progression of DN these risk factors fall into two categories: those that are modifiable such as(genetic factors, male gender, diabetic onset at 5-15 years, long duration of diabetes, increased age >65 years, and family history of diabetes and kidney disease), and non-modified such as(poor blood sugar and pressure control, poor lipid control, smoking, metabolic syndrome, and sedentary lifestyle (9). Early detection of DN, better treatments, and the development of new biomarkers are all necessary for risk prediction. Biomarkers employed in these investigations (Angiopoietin Like Protein-4(ANGPTL4), and Fibroblast Growth Factor-23 (FGF23)).

2.Materials and Methods

2.1Subjects: This case-control study will be executed in the Department of Chemistry and Biochemistry at the College of Medicine, Mustansiriyah University. The study was executed during the term from the first of December 2023 to the last of July 2024. A total of 176 subjects will be included in this study. Samples were collected from the Department of Nephrology and Diabetes Research Center of Mustansiriyah University. The participants divided into four groups' according to urine albumin to creatinine ratio (UACR), 44 healthy participants as control, and 132 patients with DM divided into three groups (44 patients with normoalbuminurea UACR values <30 mg/g), 44 patients with microalbuminuria, UACR values between 30-300 mg/g, and 44 patients with severe DKD (macroalbuminuria UACR >300mg/g). The DM patient's diagnosis according to (American Diabetes Association (ADA) guidelines), and DKD patients' diagnosis according to the guidelines for diagnosis and treatment of DKD and clinical practice guideline for diabetes management in chronic kidney disease (KDIGO-2024)(10). Informed consent was acquired from both patients and controls for participation in the study, which included a detailed explanation of the research aims.

2.2Inclusion and exclusion criteria: Subjects are adults of either sex. Confirmed DM, diagnosis based on a fasting blood glucose (FBG) level ≥ 126 mg/dl and (HbA1c) level of 6.5% or higher. Exclusion criteria infectious disease, presence of other renal or urinary tract illness confirmed by clinical or laboratory evidence, cerebrovascular disease, inflammatory diseases, cancer, tumor, recent surgery, pregnancy, and previous or current kidney replacement therapy.

2.3Blood and Urine Sample Collection: Approximately seven milliliters of blood samples were obtained from peripheral venous blood. Participants fasted for a minimum of 10 to 12 hours prior to collection. Approximately two milliliters of blood were obtained in an EDTA tube for HbA1C analysis, and five milliliters were collected in a gel tube and allowed to stand at room temperature for 20 minutes. Following coagulation, sera were isolated via centrifugation at 3000 r.p.m for 10 minutes and subsequently divided into small aliquots for the measurement of serum constituents, including uric acid, urea, fasting blood glucose, lipid profiles, creatinine, and albumin, utilizing a fully automated method with the Cobas C111 Biochemistry Analyzer from Roche, Germany. The remainder were preserved at -20°C until analyzed for serum human levels of ANGPTL-4 and FGF-23(Elabscience company USA). The analysis will be conducted with enzyme-linked immunosorbent assay (ELISA) kits. Urine samples are analyzed for albumin and creatinine levels using an automated urine chemical analyzer, based on measurements of urine microalbumin and urine creatinine. The estimated glomerular filtration rate (eGFR) was calculated for each patient utilizing a standardized serum creatinine formula: eGFR (ml/ min/1.73m^2) =194 x Cr$^{-1.094}$x age$^{-0.287}$(0.739 if female) (10).

3.Statistical Analysis: The gathered data were input into SPSS version 26.0 and Microsoft Excel 2020 for tabulation and analysis. Descriptive statistics were employed to encapsulate the demographic and clinical attributes of the study participants. Continuous variables were presented as mean ± standard deviation (SD). Categorical variables were expressed as frequencies and percentages. For parametric variables, Student's F test (ANOVA) was used to compare means of continuous variables across the four groups and Student's (t) test will be used to calculate individual p-value between each base pair, and between each of them and with the exogenous factor in patients with DKD using Pearson correlation test. P value < 0.05 is considered significant. Post-hoc comparisons were conducted using the Bonferroni test when the ANOVA brought p values of less than 0.05. When continuous variables did not meet the assumption of normality, the non-parametric Kruskal Wallis test was used supported by pairwise comparisons were performed using Dunn's test with Bonferroni correction. The Chi-squared test was used to seek association among the groups. ROC curve analysis was conducted to judge the diagnostic performance of the biomarkers.

4.Results and Conclusions

Demographic Characteristics of the Study Population

Table 1 displays the basic demographic and clinical characteristics of the sample under study. Male and female distribution did not significantly differ among the groups (p=0.237). The mean age ranged from 46.29±6.29 years in the control group to 66.08±8.04 years in the Macroalbuminuria group, with no significant difference (p=0.132). BMI values showed a significant difference among the groups (p=0.0001), with the highest mean BMI observed in the Normal group and the lowest in the Macroalbuminuria group. Fasting blood glucose (FBG) and HbA1c levels also showed significant differences (p=0.0001), with the highest mean values seen in

the Normal, Microalbuminuria, and Macroalbuminuria groups compared to the controls. Male and female distribution did not differ significantly among these groups (p=0.245).

Lipid profile parameters significantly differ across the four groups under study (P values <0.05) as shown in (Table 1). The total cholesterol level is only different between normal and control groups. Control group was significantly different from all other groups when TG levels are compared. Other groups did not show such differences. HDL followed TG in its differences plus a difference between patients with normal and microalbuminuria.

Biomarkers were significantly different among the four groups under study. However, all of the parameters showed a trend of increment from control group to macro passing through normal and micro groups as shown in (Table 1).

5.Discussion:

Diabetic nephropathy is clinically characterized by a progressive deterioration of renal function, with or without the presence of proteinuria, and is among the most common and serious chronic microvascular complications of diabetes (11). The results in (table1) of gender show there are no significant differences between females and males in the four groups. This implies that the DN is not affected by physiological changes for both sexes and can affect both genders with the same effect. These results were agreed upon by the studies conducted by (12), while these results disagreed with a study conducted by (13).

The range of age for this study was more than 40 years old for the four study groups, with no significant difference. These results were agreed upon by the studies conducted by (11), while disagreeing with a study conducted by (14). This implies that the groups included in the study were chosen based on their age within a narrow range to eliminate the potential issues associated with age differences that could potentially impact the levels of the markers used and, as a result, the nature of the study.

BMI values showed a significant difference among four groups. These results disagree with the study conducted by (11) show no significant differ between groups while agree with study conducted by (15). These findings indicate that the BMI of diabetic three groups is higher than that of control groups, which is consistent with the studies conducted by (16). When BMI is more than the optimal range, that means an individual may be overweight or increase the chance of obesity. The development of insulin resistance is strongly correlated with obesity, which is a significant risk factor for the development of hyperglycemia. As we are aware, obesity is one of the risk factors for DN (17). Other BMI values showed lower in the macro group compared with normo and microalbuminuria in diabetic groups. These results disagreed with a study conducted by (13) while agree with study conducted by (18) show in macro less than normo and microalbuminurea. One of the most important managements of DN reduce weight (19). Furthermore, patients experience a variety of symptoms, particularly dialysis patients who experience weight loss, which can result in a decrease in their BMI.

Significant differences were observed in FBG levels, and show the three diabetic groups higher compared with control these results agree with studies conducted by (20). Micro and macro show lower levels than normoalbuminurea these results disagree with studies conducted by (13) which show apposite that. The results of HbA1c levels were significantly different. These results showed the diabetic groups higher than control these results agree with studies conducted by (21). Macroalbuminuria groups show lower than micro group these results disagree with study conducted by (12).

Lipid profile parameters significantly differ across the four groups under study. The results show higher levels in patients groups compared with control for (TC, Tg, and LDL-C), and in macro lower than normo and micro this result agrees with study conducted by (22). For the serum TC and Tg levels the results show higher in normo than micro and macro this result disagrees with study conducted by (23) but in same time agreed between micro and macro. One of the most critical aspects of DN management is the adjustment of lipid profiles, particularly TC and Tg. During this stage of DKD, the medication is administered with great intensity. Results of high-density lipoprotein cholesterol show lower levels in patients' groups than control this result agrees with study conducted by (12). The current findings indicate that low HDL-C levels may be linked to an elevated risk of DKD, which is consistent with the hypothesis that high HDL-C levels may yield a protective effect (24).

ANGPTL-4, plays a significant role in energy metabolism (25). The current study groups show there are significant differences between four study groups. These results agree with those conducted by (23) in urine sample. FGF-23 is a hormone that is primarily produced by osteocytes and is a critical regulator of phosphate and vitamin D homoeostasis (20). Study groups show there are significant differences between four study groups. These results agree with those conducted by (26) when compared between diabetic and non-diabetic and agree with study conducted by (11) compared between patients' groups with T1DM. The elevated serum FGF23 concentration resulted from impaired renal function rather than diabetes, as diminished eGFR is associated with increased serum FGF23 levels. In another investigation, no significant difference in serum FGF23 concentration was found between patients with T2D and controls, although, similar to our study, elevated quantities were identified in those with diabetic kidney impairment (27). Biochemical parameters of serum (urea, albumin, uric acid, eGFR and creatinine) showed significant statistical differences across the four groups these results agree with study conducted by (28). In our study demonstrated a subsequent elevation in the AUC

from the normoalbuminuria, microalbuminuria, to the macroalbuminuria group, with optimal performance observed in the macroalbuminuria group. This means the (UACR, ANGPTL-4, and FGF23) have good sensitivity and specificity. Serum markers levels of (ANGPTL-4, and FGF23) increased in patients with normo, micro and macroalbuminurea diseases, and this cooperated in the pathophysiology of the disease. This agreed with studies conducted by (29)**.**

Conclusion: our study explains the correlation between serum ANGPTL4, and FGF23 levels and albuminuria in patients with diabetic nephropathy. The levels of ANGPTL4, and FGF23 increases significantly in different stage of patients with diabetic nephropathy compared with control and with the development of albuminuria state; therefore, it is possible to use ANGPTL4, and FGF23 as an early detection and progression of diabetic nephropathy.

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Recommendations:

1. It is possible to use the (Angiopoietin-Like Protein-4,and Fibroblast Growth Factor-23), and compare the results obtained in diabetic kidney disease with those in patients with chronic kidney disease, which result from non-diabetic causes.

2. It is possible to use the (Angiopoietin-Like Protein-4,and Fibroblast Growth Factor-23) in early detection of liver diseases such as fatty liver disease or in controlling and monitoring on this disease.

Table1: displays the basic demographic and clinical characteristics of the sample under study.

Variables		Non diabetic	Diabetic			p-value
		Controls	Normo Albuminuria	Micro albuminuria	Macro albuminuria	
Sex	Male	29 (65.9%)	28 (63.6%)	21 (47.7%)	23 (52.3%)	
	Female	15 (34.1%)	16 (36.4%)	23 (52.3%)	21 (47.7%)	0.237
Age, years Mean±SD		46.29±6.39	52.09±8.88	56.43±9.64	66.08±8.04	0.132
BMI, kg/m^2 Mean±SD		26.514±4.612	31.070±3.722	32.410±5.219	28.961±6.992	0.0001
FBG,mg/dl Mean±SD		97.909±10.000	154.889±15.578	148.676±9.817	146.946±9.447	0.0001
HbA1c% Mean±SD		4.811±0.350	8.275±1.491	8.777±1.533	8.556±1.353	0.0001
Duration/years		Not applicable	4.95 ± 2.69	9.20 ± 2.69	18.88 ± 6.73	0.0001
Medication	**Oral**	Not applicable	41 (93.2%)	26 (59.1%)	17 (38.6%)	0.0001
	Injection		3 (6.8%)	18 (40.9%)	27 (61.4%)	
TC mg/dl		154.67±33.501	186.990±28.494	175.790±42.715	171.898±51.159	**0.003**
TG mg/dl		132.746±38.518	167.335±27.364	173.432±34.990	159.135±33.440	**0.0001**
HDL-C mg/dl		45.971±4.711	39.818±4.309	36.682±6.816	34.452±4.619	**0.0001**
LDL-C mg/dl		92.621±23.728	119.564±25.103	123.736±30.983	101.877±17.864	**0.0001**
UACR mg/g		17.269±4.271	22.049±4.555	137.882±74.815	850.459±186.022	0.0001
ANGPTL4ng/ml		25.631±7.341	57.514±12.615	69.982±8.546	76.636±9.011	0.0001
FGF23pg/ml		169.193±48.537	393.976±68.564	504.495±80.224	695.597±114.232	0.0001

Urea mg/dl	22.455±6.125	31.432±9.503	51.455±28.188	130.045±29.759	0.0001
Creatinine mg/dl	0.840±0.144	1.015±0.170	1.383±0.356	5.195±1.283	0.0001
eGFR	101.727±9.478	80.545±13.827	54.614±13.650	10.886±2.830	0.0001
Uric acid mg/dl	4.986±1.107	5.252±1.820	6.242±1.340	7.919±4.111	0.0001
Albumin mg/dl	4.532±0.632	4.675±0.559	7.299±2.382	3.025±0.625	0.0001

BMI: body mass index, FBG: fasting blood glucose, HbA1c: glycated hemoglobin, TC: total cholesterol, TG: triglycerides, HDL-C: high density lipoprotein, LDL-C: low density lipoprotein, UACR: urinary albumin to creatinine ratio, eGFR: estimation of glomerular filtration rate.

Table 2: Post hoc tests for serum lipid profile, study biomarkers, and renal function tests:

Variables	Control vs Normal	Control vs Micro	Control vs Macro	Normal vs Micro	Normal vs Macro	Micro vs Macro
TC	0.001	0.084	1.000	0.466	0.466	1.000
TG	0.0001	0.0001	0.002	1.000	1.000	0.294
HDL-C	0.0001	0.0001	0.0001	0.032	0.227	0.277
LDL-C	0.0001	0.0001	0.495	1.000	0.006	0.0001
ANGPTL4	1.000	0.0001	0.0001	0.0001	0.0001	0.0001
FGF23	0.0001	0.0001	0.0001	1.000	0.0001	0.0001
UACR	0.0001	0.0001	0.0001	0.0001	0.0001	0.008
Urea	0.295	0.0001	0.0001	0.0001	0.0001	0.0001
Creatinine	1.000	0.001	0.0001	0.068	0.0001	0.0001
eGFR	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
Uric acid	1.000	0.093	0.0001	0.335	0.0001	0.008
Albumin	1.000	0.0001	0.0001	0.0001	0.0001	0.0001

Table 3: Diagnostic value in normoalbuminurea as compared to control group

Variables	Area under the curve (AUC) ROC	Confidence interval		p-value (AUC 0=0.5)	Best cut-off criterion	Sensitivity (%)	Specificity (%)	Efficiency
		Lower	**Upper**					
UACR mg/gm	0.809	0.717	0.900	0.0001	18.3200	93.2	63.6	78.4
ANGPTL4ng/ml	0.994	0.984	1.000	0.0001	42.2595	95.5	97.7	96.6
FGF23 pg/ml	0.994	0.983	1.000	0.0001	275.3070	97.7	97.7	97.7
CRP mg/dl	0.741	0.639	0.843	0.0001	4.9500	81.8	59.1	70.45

Table 4: Diagnostic value in microalbuminuria as compared to control group

Variables	Area under the ROC curve (AUC)	Confidence interval		p-value (AUC0=0.5)	Best cut-off criterion	Sensitivity (%)	Specificity (%)	Efficiency
		Lower	Upper					
UACRmg/g	1.000	1.000	1.000	0.0001	30.0210	100	100	100
ANGPTL-4 ng/ml	1.000	1.000	1.000	0.0001	49.3885	100	100	100
FGF23pg/ml	1.000	1.000	1.000	0.0001	313.9475	100	100	100
CRP mg/dl	0.933	0.886	0.980	0.0001	8.1200	79.5	90.9	85.2

Table 5: Diagnostic value in macroalbuminuria as compared to control group

Variables	Area under the ROC curve (AUC)	Confidence interval		p-value (AUC0=0.5)	Best cut-off criterion	Sensitivity (%)	Specificity (%)	Efficiency
		Lower	Upper					
UACR mg/g	1.000	1.000	1.000	0.0001	201.5810	100	100	100
ANGPTL-4 ng/ml	1.000	1.000	1.000	0.0001	55.0930	100	100	100
FGF23 pg/ml	1.000	1.000	1.000	0.0001	406.2060	100	100	100
CRP mg/dl	0.994	0.984	1.000	0.0001	8.7000	97.7	95.5	96.6

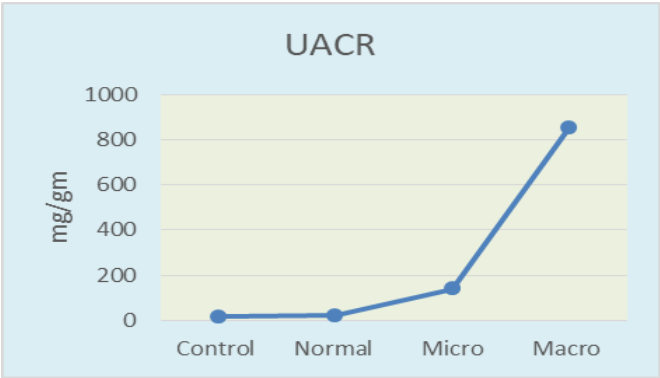

Figure1: UACR in four groups of the study

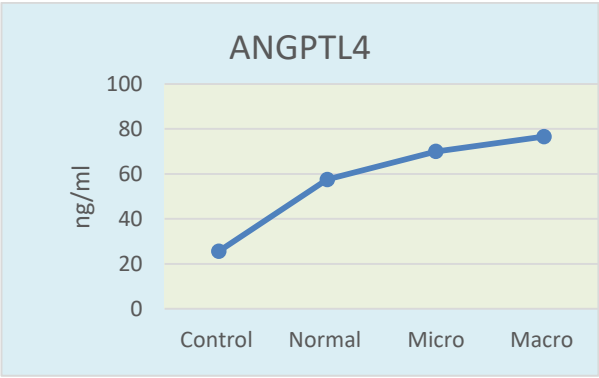

Figure 2: ANGPTL4 in four groups of the study

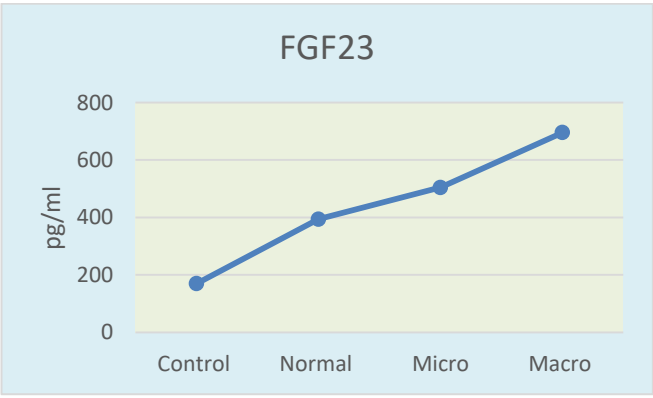

Figure 3: FGF23 in four groups of the study

REFERENCES:

١.Żołnierkiewicz O, Rogacka D. Hyperglycemia–A culprit of podocyte pathology in the context of glycogen metabolism. Arch Biochem Biophys. 2024;109927. https://doi.org/10.1016/j.abb.2024.109927

٢.Liang Y, Chen Q, Chang Y, Han J, Yan J, Chen Z, Zhou J. Critical role of FGF21 in diabetic kidney disease: from energy metabolism to innate immunity. Front Immunol. 2024; 15:1333429. https://doi.org/10.3389/fimmu.2024.1333429

٣.Hu S, Hang X, Wei Y, Wang H, Zhang L, Zhao L. Crosstalk among podocytes, glomerular endothelial cells and mesangial cells in diabetic kidney disease: an updated review. Cell Commun Signal. 2024;22(1):136. DOI:10.1186/s12964-024-01502-3

٤.van Olmen J. Evaluation of performance of diabetes care initiatives implemented in Cambodia [dissertation]. Antwerp: University of Antwerp; 2024. https://doi.org/ 10.63028/10067/2029940151162165141

٥.Liu J, Ren J, Zhou L, Tan K, Du D, Xu L, Zhang Y. Proteomic and lipidomic analysis of the mechanism underlying astragaloside IV in mitigating ferroptosis through hypoxia-inducible factor 1α/heme oxygenase 1 pathway in renal tubular epithelial cells in diabetic kidney disease. J Ethnopharmacol. 2024;118517. doi: 10.1016/j.jep.2024.118517. Epub 2024 Jul 5

٦.Wang N, Zhang C. Recent advances in the management of diabetic kidney disease: slowing progression. Int J Mol Sci. 2024;25(6):3086. DOI: 10.3390/ijms25063086

٧.Jha R, Lopez-Trevino S, Kankanamalage HR, Jha JC. Diabetes and renal complications: an overview on pathophysiology, biomarkers and therapeutic interventions. Biomedicines. 2024;12(5):1098. DOI: 10.3390/biomedicines12051098

٨.Abbate M, Parvanova A, López-González ÁA, Yañez AM, Bennasar-Veny M, Ramírez-Manent JI, Ruggenenti P. MAFLD and glomerular hyperfiltration in subjects with normoglycemia, prediabetes and type 2 diabetes: A cross-sectional population study. Diabetes Metab Res Rev. 2024;40(4):e3810. doi: 10.1002/dmrr.3810.

٩.Mallamaci F, Tripepi G. Risk factors of chronic kidney disease progression: between old and new concepts. J Clin Med. 2024;13(3):678. doi: 10.3390/jcm13030678.

10. Levin A, Ahmed SB, Carrero JJ, Foster B, Francis A, Hall RK, Stevens PE. Executive summary of the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease: known knowns and known unknowns. Kidney Int. 2024;105(4):684-701. doi: 10.1016/j.kint.2023.10.016.

11.Yan P, Yang Y, Zhang X, Zhang Y, Li J, Wu Z, Wan Q. Association of systemic immune-inflammation index with diabetic kidney disease in patients with type 2 diabetes: a cross-sectional study in Chinese population Front Endocrinol. 2024; 14:1307692. DOI: 10.3389/fendo.2023.1307692

12.Hirano T, Satoh N, Kodera R, Hirashima T, Suzuki N, Aoki E, Ito Y. Dyslipidemia in diabetic kidney disease classified by proteinuria and renal dysfunction: A cross-sectional study from a regional diabetes cohort. J Diabetes Investig. 2022;13(4):657-667. DOI: 10.1111/jdi.13697

13. Jin Q, Lau ES, Luk AO, Tam CH, Ozaki R, Lim CK, Hong Kong Diabetes Biobank Study Group. Circulating metabolomic markers linking diabetic kidney disease and incident cardiovascular disease in type 2 diabetes: analyses from the Hong Kong Diabetes Biobank. Diabetologia. 2024;67(5):837-849. DOI: 10.1007/s00125-024-06108-5

14.Alaidy IMM, Hasan FH, Ibrahim ESA, Alkhrsawy AMA. Serum erythropoietin hormone measurement for evaluation of anemia and red cell parameters in diabetes mellitus and diabetic kidney disease patients. Int J Med Arts. 2024;6(5):4426-4435. DOI: 10.21608/IJMA.2024.282217.1954

15.Chen YH, Lee JI, Shen JT, Wu YH, Tsao YH, Jhan JH, Geng JH. The impact of secondhand smoke on the development of kidney stone disease is not inferior to that of smoking: a longitudinal cohort study. BMC Public Health. 2023;23(1):1189. DOI: https://doi.org/ 10.1186/s12889-023-16116-6

16. Ahmed MH, Haddad NI, Nori E. Correlation between albuminuria levels and chitinase 3-like 1 protein in Iraqi patients with type 2 diabetes mellitus. Iraqi J Sci. 2022;21-32. DOI: https://doi.org/10.24996/ijs.2022.63.1.3

17. Gnudi L. Renal disease in patients with type 2 diabetes: magnitude of the problem, risk factors and preventive strategies. La Presse Médicale. 2023;52(1):104159. DOI: 10.1016/j.lpm.2022.104159

18.Yamanouchi M, Sawa N, Toyama T, Shimizu M, Oshima M, Yoshimura Y, Wada T. Trajectory of GFR decline and fluctuation in albuminuria leading to end-stage kidney disease in patients with biopsy-confirmed diabetic kidney disease. Kidney Int Rep. 2024;9(2):323-333. DOI: 10.1016/j.ekir.2023.11.004

19. Habiba, U. E., Khan, N., Greene, D. L., Shamim, S., & Umer, A. (2024). The therapeutic effect of mesenchymal stem cells in diabetic kidney disease. Journal of Molecular Medicine, 102(4), 537-570. DOI: 10.1007/s00109-024-02432-w

20. Méndez-Mancilla A, Turiján-Espinoza E, Vega-Cárdenas M, Hernández-Hernández GE, Uresti-Rivera EE, Vargas-Morales JM, Portales-Pérez DP. miR-21, miR-221, miR-29 and miR-34 are distinguishable molecular features of a metabolically unhealthy phenotype in young adults. PLoS One. 2024;19(4): e0300420. doi: 10.1371/journal.pone.0300420. eCollection 2024.

21. Kamal AL, Taher AY. Beta trace protein as a marker of eGFR as early prognostic stages of diabetic nephropathy. 2024. DOI:10.13140/RG.2.2.34059.91681

22.Wang H, Wu J, Lin M, Hu Y, Ma Y. High levels of high-density lipoprotein cholesterol may increase the risk of diabetic kidney disease in patients with type 2 diabetes. Sci Rep. 2024;14(1):15362. doi: 10.1038/s41598-024-66548-2.

23.Chagnac A, Friedman AN. Measuring albuminuria in individuals with obesity: pitfalls of the urinary albumin-to-creatinine ratio. Kidney Med. 2024;100804. DOI: 10.1016/j.xkme.2024.100804

24. Yuge, H., Okada, H., Hamaguchi, M., Kurogi, K., Murata, H., Ito, M., & Fukui, M. (2023). Triglycerides/HDL cholesterol ratio and type 2 diabetes incidence: Panasonic Cohort Study 10. Cardiovascular diabetology, 22(1), 308. DOI: 10.1186/s12933-023-01999-x

25. Ma, S., Qiu, Y., & Zhang, C. (2024). Cytoskeleton Rearrangement in Podocytopathies: An Update. International Journal of Molecular Sciences, 25(1), 647. DOI: 10.3390/ijms25010647

26. Fayed A, Mohamed A, Ahmed RM, Abouzeid S, Soliman A. Study of serum fibroblast growth factor 23 as a predictor of endothelial dysfunction among Egyptian patients with diabetic kidney disease. Saudi J Kidney Dis Transpl. 2023;34(4):305-312. DOI: 10.4103/1319-2442.374075

27. Zhang R, Wang Q, Li Y, Li Q, Zhou X, Chen X, Dong Z. A new perspective on proteinuria and drug therapy for diabetic kidney disease. Front Pharmacol. 2024; 15:1349022. DOI: 10.3389/fphar.2024.1349022

28. Nugnes M, Baldassarre M, Ribichini D, Tedesco D, Capelli I, Vetrano D, Bartolini M. Association between albumin alterations and renal function in patients with type 2 diabetes mellitus. Int J Mol Sci. 2024;25(6):3168. DOI: 10.3390/ijms25063168

29. Abinti M, Vettoretti S, Caldiroli L, Mattinzoli D, Ikehata M, Armelloni S, Messa P. Associations of intact and C-terminal FGF23 with inflammatory markers in older patients affected by advanced chronic kidney disease. J Clin Med. 2024;13(13):3967. DOI: 10.3390/jcm13133967