

# Thyrotropin Hormone Is Directly Associated with Diabetic Nephropathy in Euthyroid T2DM Patients: A Case-Control Study

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## ABSTRACT

**Background & Aim:** To investigate the association between diabetic nephropathy and thyrotropin in euthyroid T2DM patients.

**Methods:** A retrospective study in T2DM patients. It included 107 healthy control subjects, 100 diabetes patients with albuminuria and 117 without albuminuria. Nephropathy was defined as urine albumin creatinine ratio (UACR) > 30 mg/gm in at least 2 urine samples with at least 3 months in between. All patients were euthyroid with TSH levels within the normal reference range (0.27-4.2 uIU /ml). **Results:** TSH was significantly higher in diabetes patients compared with the control group ( $p=0.032$ ). No significant difference in TSH between patients with or without nephropathy ( $p=0.75$ ). TSH significantly and directly correlated with UACR ( $p<0.0001$ ). Compared with diabetes without nephropathy, patients with nephropathy showed: longer diabetes duration ( $p=0.004$ ), higher systolic and diastolic blood pressure, heart rate, body mass index, fasting plasma glucose, HbA1c, total cholesterol, triglycerides, and white blood cell count ( $p=0.001, 0.001, 0.021, 0.026, <0.001, 0.001, 0.001, 0.008, 0.002$  respectively) with more

prevalence of metabolic syndrome, hypertension, and diabetic retinopathy ( $p=0.003, 0.001, <0.001$  respectively). Diabetic nephropathy showed a significant and direct correlation with age, diabetes duration, body mass index, metabolic syndrome, systolic and diastolic blood pressure, diabetic retinopathy, hypertension, fasting plasma glucose, HbA1c, triglycerides and white blood cell count ( $p=0.001, 0.013, 0.02, <0.0001, <0.0001, <0.0001, 0.001, 0.007, <0.0001, <0.0001, 0.001, 0.001$  respectively), and inverse correlation with estimated glomerular filtration rate and high-density lipoprotein cholesterol ( $p=0.048, 0.001$  respectively). **Conclusion:** Thyrotropin hormone is directly and significantly associated with diabetic nephropathy in T2DM and is one of its significant risk factors.

**Keywords:** Diabetes, nephropathy, thyrotropin, urine albumin, creatinine

## INTRODUCTION

Diabetic kidney disease (DKD) describes either albuminuria or reduction in renal function due to progressive kidney damage in diabetes patients.<sup>(1)</sup> About 20%–40% of patients with diabetes, mostly with

T2DM develop DKD, and 40% of them pass to end-stage renal disease (ESRD).<sup>(2-4)</sup> Albumin creatinine ratio (ACR) measurement in a first-morning spot urine collection is adequate for the detection and diagnosis of albuminuria.<sup>(5)</sup>

Thyroid dysfunction is more prevalent in T2DM patients as compared with a healthy population.<sup>(6,7)</sup> Authors found an association between high levels of thyrotropin hormone (TSH) and low levels of free triiodothyronine (FT3) within the normal range and the higher risk of chronic kidney disease (CKD).<sup>(8,9)</sup> Thyroid hormones have direct effects on glomerular function, tubular absorptive and secretory capacities and the functioning of different electrolyte pumps and indirect actions due to influences on the cardiovascular system which ultimately affects renal blood flow.<sup>(10)</sup> The kidneys influence the synthesis, secretion, metabolism, and elimination of thyroid hormones. Thyroid dysfunction and albuminuria are both associated with endothelial dysfunction and microvascular disease.<sup>(11)</sup>

TSH was found to be independently associated with renal function and CKD in normoglycemic euthyroid adults. Some studies found an independent association between microalbuminuria and subclinical hypothyroidism in prediabetes and type 2 diabetes<sup>(12,13)</sup>.

### **AIM OF THE WORK**

We conducted this cross-sectional case-control study to investigate the association between albuminuria as defined in our study by UACR > 30 mg/gm and TSH in euthyroid patients with T2DM.

### **PATIENTS & METHODS**

Our study included 324 patients. 107 healthy controls aged more than 18 years. 217 patients with diabetes visited the endocrine clinic at Zulaikha Hospital, Sharjah, during the period from May 2018 to May 2019. The diabetes patients were divided into two groups: 100 patients with albuminuria and 117 patients without albuminuria. Diabetes patients were T2DM with age > 18 years. Exclusion criteria: other types of DM; chronic and acute illness; severe cardiac disease, urinary tract infections,

hematuria (including menstrual period), pregnancy; non-diabetic kidney disease; history of thyroid disease, or any thyroid medication or biochemical evidence of thyroid disease; elevated serum creatinine, use of drugs that can affect any of the measured variables.

The present study protocol was reviewed and approved by the MOHAP Research Ethics Committee, Sharjah, UAE. The ethics committee waived the need for informed consent for the study.

**Statistical analysis:** Variables with a normal distribution were expressed as the mean  $\pm$  standard deviation (SD). The categorical variables were expressed as proportions. Differences in history, clinical and laboratory values between the three groups were assessed by a Pearson chi-square test, and Wilcoxon test. One-way analysis of variance, followed by the LSD multiple comparison test, was used for comparisons between groups. Multivariate regression analysis was used to estimate the odds ratio (OR) for assessing the independent risk factors of DN. We initially adjusted for age and sex (model 1), and in addition, for hyperlipidemia, diabetes duration, BMI, SBP, HbA1c, and eGFR (model 2). The statistical tests were two-sided, and a *P* value less than 0.05 was considered statistically significant. All statistical analysis was carried out using SPSS 25.0 for Windows (Chicago, IL, USA).

Information including gender, duration of diabetes, history of hypertension, hyperlipidemia, micro and macrovascular complications, and medication was obtained from patient files and available standard questionnaires in hospital records. Hypertension was defined as systolic blood pressure (SBP)  $\geq$  140 mmHg and/or diastolic blood pressure (DBP)  $\geq$  90 mmHg or if the patient was already taking anti-hypertensive drugs. Dyslipidemia was defined according to NCEP-Panel III or if the patients were being treated with lipid-lowering agents. Metabolic syndrome was diagnosed as per the NCEP panel III definition.<sup>(14)</sup>

Albuminuria was confirmed by repeat testing over 3 to 6 months; a minimum of two elevated albumin creatinine ratio (ACR) levels more than 3 months apart were required for the diagnosis.<sup>(15)</sup>

**Laboratory blood assay:** Laboratory workup and its results were available in patients' records. All laboratory work was done as per hospital protocol. Blood samples were collected after overnight fasting for 8–12 hours, using plain ethylenediamine tetra-acetic acid (EDTA) and lithium heparin vacutainers. Sera/plasma was separated by centrifuging blood at 3500 rpm for 10 min.

Using the Cobas 6000, Roche Diagnostics, modular autoanalyzer, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs) were measured by using an enzymatic colourimetric method. Low-density lipoprotein cholesterol (LDL-C) was directly measured, blood glucose was tested by enzymatic hexokinase method, serum creatinine concentrations were determined by kinetic Jaffe method & serum TSH was determined by electrochemiluminescence immunoassay (ECLIA). HbA1c concentrations were measured by turbidimetric inhibition immunoassay using the COBAS INTEGTRA 400 plus machine, Roche Diagnostics. Complete Blood count was done using UniCel DxH 800 Coulter Cellular Analysis System. WBCs & platelets were measured by the Coulter Principle, Hemoglobin was measured photometrically, and Hematocrit, MCH & MCHC were calculated (Beckman Coulter).

UACR was determined by immunoturbidimetry and kinetic Jaffe methods for urine albumin & urine creatinine, respectively, on the COBAS INTEGTRA 400 plus machine, Roche Diagnostics. CKD-EPI equation was used for the calculation of eGFR.<sup>(16)</sup>

## RESULTS:

The age and gender of the healthy control group were comparable to the study group of diabetes with and without nephropathy ( $p= 0.13, 0.201$  respectively). TSH was significantly higher in the diabetes group as a whole and in the nephropathy and non-nephropathy subgroups when compared with the control group ( $p= 0.032, 0.018, 0.037$  respectively). However, no significant difference in TSH between the 2 groups of

diabetes with and without nephropathy ( $p=0.75$ ).

Compared to diabetes without nephropathy, patients with nephropathy showed: longer duration of diabetes ( $p=0.004$ ), higher SBP, DBP, and HR ( $p= 0.000, 0.000, 0.021$  respectively), more prevalence of metabolic syndrome, hypertension, hyperlipidemia, and diabetic retinopathy ( $p=0.003, 0.001, 0.002, <0.001$ ) and higher BMI ( $p= 0.026$ ), higher FPG and HbA1c ( $p=0.000, 0.000$ ), higher TC, TG and WBC count ( $p=0.001, 0.008, 0.002$  respectively). No observed significant difference between the two groups as regards serum creatinine, eGFR, LDL-C, HDL-C, Hb or RDW ( $p= 0.552, 0.13, 0.16, 0.117, 0.936, 0.493$  respectively). (Table I, II)

No significant difference in the use of antidiabetic medications apart from pioglitazone and glucagon-like peptide -1 analogues (GLP-1 analogues) which were more in use in patients with albuminuria ( $p <0.001, 0.018$  respectively). Antihypertensive medications: angiotensin-converting enzyme inhibitors (ACEi), Angiotensin receptor blockers (ARBs), calcium channel blockers (CCB), beta-blockers (BB), thiazide-like diuretics (indapamide) were also more in use in the nephropathy group ( $p=0.013, 0.049, 0.006, 0.001, 0.000$ ). (Table II)

TSH showed a statistically significant positive correlation with UACR ( $r 0.241, p <0.0001$ ). A positive association was also found between TSH and FPG ( $r 0.176, p=0.033$ ). A statistically significant negative association between TSH and HR and HDL-C was observed ( $r -0.141, -0.185, p= 0.04, 0.007$  respectively). It was also noticed that the use of GLP-1 analogues was associated with lower TSH levels ( $r -0.177, p=0.035$ ). (Table III)

Diabetic nephropathy as defined in our study by albumin /creatinine ratio of  $> 30$  mg/gm showed a significant and positive correlation with age of patients, duration of diabetes, BMI, metabolic syndrome, SBP and DBP, diabetic retinopathy and hypertension ( $r 0.233, 0.209, 0.158, 0.269, 0.388, 0.349, 0.271, 0.228$  respectively,  $p= 0.001, 0.013, 0.02, <0.0001, < 0.0001, < 0.0001, 0.001, 0.007$

respectively). It also showed a strong positive correlation with FPG, HbA1c, estimated average plasma glucose (APG), TG and WBC count ( $r$  0.373, 0.388, 0.34, 0.242, 0.241,  $p$  <0.0001, 0.0001, 0.001, 0.001, 0.001 respectively) and inverse correlation with eGFR, HDL-C ( $r$  -0.135, -0.219,  $p$ =0.048, 0.001 respectively). (Table III)

Use of calcium channel blockers, indapamide, sulfonylurea and long-acting insulin was directly and significantly associated with UACR ( $r$  0.298, 0.194, 0.18, 0.306,  $p$ <0.0001, 0.022, < 0.001, <0.001). Use of statins ( $r$  -0.270,  $p$ =0.001). (Table III)

The univariate analysis entailed the age, TSH, presence of metabolic syndrome, DM duration, SBP, DBP, HbA1c, triglyceride, HDL, WBCs, BMI, intake of (SU, Insulin, statin, ACE, ARBS, CCB, indapamide) as well as presence of DR as risk factors for diabetic nephropathy. A binary logistic regression analysis after adjustment for age and sex, showed that high DBP & HbA1c levels remained as independent risk factors for DN [OR:0.86, (95% CI: 0.75-0.95), 0.3 (95% CI: 0.13-0.7)  $p$ =0.02, 0.005; respectively]. On the other hand, the use of ACEi showed to be independent and significantly protective against DN (OR: 11.595% CI: 1.32 - 101.49,  $p$ =0.027).

Table (I): Comparison of baseline variables between the control group and both groups of diabetes:

	Diabetes with Nephropathy (n=100)		Diabetes without Nephropathy (n=107)		Control Non-Diabetes (n=117)		PALL	P1	P2	P3
	Mean	SD	Mean	SD	Mean	SD				
Age (yrs)	46.88	7.91	46.53	9.16	44.76	7.56	0.13	0.76	0.07	0.15
Duration (years)	7.90	6.09	5.59	5.41	NA	NA	0.004	0.004	NA	NA
SBP (mmHg)	133.20	16.862	124.53	11.909	118.00	11.327	0.000	0.000	0.000	0.004
DBP (mmHg)	85.98	10.334	80.65	7.869	76.72	7.362	0.000	0.000	0.000	0.000
HR (bpm)	84.14	9.017	81.18	4.608	81.49	7.427	0.034	0.021	0.001	0.693
TSH (uIU/mL)	1.80	1.01	1.80	0.91	1.702	0.733	0.032	0.750	0.018	0.037
FPG (mg/dL)	183.46	83.882	140.68	39.350	97.98	8.041	0.000	0.000	0.000	0.000
HbA1C (%)	8.27	2.078	6.78	1.173	5.28	0.225	0.000	0.000	0.000	0.002
Scr (mg/dL)	0.81	0.214	0.79	0.163	0.72	0.135	0.008	0.552	0.004	0.016
eGFR (CKD-Epi)	98.99	19.909	103.14	14.592	110.86	13.911	0.000	0.130	0.000	0.004
UACR (mg/g)	174.35	211.236	10.82	6.753	12.26	5.682	0.000	0.000	0.000	0.939
Total Cholesterol (mg/dL)	186.83	47.225	171.93	49.411	194.47	37.015	0.056	0.001	0.321	0.002
Triglycerides (mg/dL)	223.55	275.220	149.15	82.287	117.86	52.570	0.001	0.008	0.000	0.236
HDL (mg/dL)	42.68	9.869	44.73	9.900	51.75	12.701	0.000	0.117	0.000	0.000
LDL (mg/dL)	116.58	41.032	107.19	43.932	128.72	31.299	0.004	0.160	0.069	0.000
Hb ((g/dL)	14.85	1.873	14.72	1.440	15.40	11.876	0.996	0.936	0.966	0.985
RDW CV (%)	12.20	1.209	12.14	0.987	11.91	1.093	0.408	0.493	0.564	0.181
WBC (x103/uL)	9.33	2.295	7.74	2.310	7.30	1.904	0.000	0.002	0.000	0.237
Body weight (Kg)	95.19	21.252	89.85	15.215	86.95	16.943	0.031	0.077	0.009	0.228
BMI (mL/min/1.73m <sup>2</sup> )	33.12	6.417	30.98	4.731	30.39	5.870	0.013	0.026	0.005	0.493

*P* all: significance anova for all groups, *P1*: significance of diabetes with nephropathy vs diabetes without nephropathy, *P2*: significance of diabetic nephropathy vs healthy control, *P3*: significance of diabetes without nephropathy versus healthy control

*SBP*: systolic blood pressure, *DBP*: diastolic blood pressure, *bpm*: Beat per minutes, *HR*: Heart Rate, *TSH*: Thyroid stimulating hormone, *FPG*: Fasting

*plasma glucose*, *HbA1c*: glycated haemoglobin, *Scr*: serum creatinine, *GFR*: glomerular filtration rate, *Ucr*: Urine creatinine, *UACR*: Urine Albumin Creatinine ratio, *HDL*: High-density Lipoprotein, *LDL*, Low-density Lipoprotein, *Hb*: Hemoglobin, *RDW*: Red cell distribution width, *WBC*: White blood cell count, *BMI*: body mass index, *SD*: Standard Deviation, *NA*: Not applicable,

Table (II): Comparison of baseline variables between the control group and both groups of diabetes (continued):

		Diabetic with Nephropathy			Diabetic without Nephropathy			Control Non-Diabetic			PALL	P1	P2	P3
		Count	Column N %	Column Valid N %	Count	Column N %	Column Valid N %	Count	Column N %	Column Valid N %				
GENDER M1, F2	M	71	71.0%	71.0%	88	75.2%	75.2%	39	64.0%	64.0%	0.201	0.505	0.064	0.062
	F	29	29.0%	29.0%	29	24.8%	24.8%	6	94.4%	94.4%				
MS	Non-MS	40	61.5%	61.5%	61	80.3%	80.3%	73	96.1%	96.1%	0.000	0.003	0.000	0.021
	MS	25	38.5%	38.5%	15	19.7%	19.7%	3	3.9%	3.9%				
HTN	Non-HTN	32	49.2%	49.2%	54	71.1%	71.1%				0.001	0.001		
	HTN	33	50.8%	50.8%	22	28.9%	28.9%							
CAD	Non-CAD	62	95.4%	95.4%	72	94.7%	94.7%				0.781	0.781		
	CAD	3	4.6%	4.6%	4	5.3%	5.3%							
DR	Non-DR	42	64.6%	64.6%	68	89.5%	89.5%					0.000		
	DR	23	35.4%	35.4%	8	10.5%	10.5%				0.442	0.442		
Metformin	No	5	7.7%	7.7%	8	10.5%	10.5%							
	yes	60	92.3%	92.3%	68	89.5%	89.5%				0.066	0.066		
SGLT2i	No	29	44.6%	44.6%	45	59.2%	59.2%							
	yes	36	55.4%	55.4%	31	40.8%	40.8%				0.066	0.066		
DPP4i	No	19	29.2%	29.2%	28	36.8%	36.8%							
	yes	46	70.8%	70.8%	48	63.2%	63.2%				0.403	0.403		
GLP-1A	No	55	84.6%	84.6%	69	90.8%	90.8%							
	yes	10	15.4%	15.4%	7	9.2%	9.2%				0.018	0.018		
SU	No	46	70.8%	70.8%	66	86.8%	86.8%							
	yes	19	29.2%	29.2%	10	13.2%	13.2%				0.307	0.307		
TZDs	No	62	95.4%	95.4%	74	97.4%	97.4%							
	Yes	3	4.6%	4.6%	2	2.6%	2.6%				0.000	0.000		
LAI	No	54	83.1%	83.1%	75	98.7%	98.7%							
	Yes	11	16.9%	16.9%	1	1.3%	1.3%				0.059	0.059		
SAI	No	62	95.4%	95.4%	76	100.0%	100.0%							
	Yes	3	4.6%	4.6%	0	0.0%	0.0%				0.050	0.050		
Statin	NO	39	60.0%	60.0%	33	43.4%	43.4%							
	Yes	26	40.0%	40.0%	43	56.6%	56.6%				0.125	0.125		
FF	NO	63	96.9%	96.9%	75	98.7%	98.7%							
	Yes	2	3.1%	3.1%	1	1.3%	1.3%				0.264	0.264		
Aspirin	No	61	93.8%	93.8%	73	96.1%	96.1%							
	Yes	4	6.2%	6.2%	3	3.9%	3.9%				0.055	0.055		
ACEi	No	46	70.8%	70.8%	64	84.2%	84.2%							
	Yes	19	29.2%	29.2%	12	15.8%	15.8%				0.013	0.013		
ARBs	No	53	81.5%	81.5%	68	89.5%	89.5%							
	yes	12	18.5%	18.5%	8	10.5%	10.5%				0.049	0.049		
BB	No	59	90.8%	90.8%	72	94.7%	94.7%							
	yes	6	9.2%	9.2%	4	5.3%	5.3%				0.001	0.001		
CCB	No	46	70.8%	70.8%	71	93.4%	93.4%							
	yes	19	29.2%	29.2%	5	6.6%	6.6%				0.006	0.006		
Indapamide	No	56	86.2%	86.2%	74	97.4%	97.4%							
	yes	9	13.8%	13.8%	2	2.6%	2.6%				0.000	0.000		

*P all: significance anova for all groups, P1: significance of diabetes with nephropathy vs diabetes without nephropathy, P2: significance of diabetic nephropathy vs healthy control, P3: significance of diabetes without nephropathy versus healthy control*

HTN: hypertension, CAD: Coronary artery disease, DR: diabetic retinopathy, MS: metabolic syndrome, SGLT2i: Sodium Glucose Transporter 2 Inhibitors, DPP4i: Dipeptidyl Peptidase Inhibitors, GLP1A: Glucagon like peptide 1 receptor agonist, SU: Sulphonyl

urea, TZDs: Thiazolidinedione, ACEI: Angiotensin converting enzyme inhibitor, ARBs: Angiotensin II Receptor Blockers, BB: Beta Blockers, CCB: Calcium Channel blockers, LAI: long acting insulin, SAI: short acting insulin, FF: fenofibrate, Cr: creatinine

Table (III): Correlation between TSH and UACR with different variables

		TSH1	UACR			TSH1	UACR
TSH1	R	1.000	.241**	WBCs	R	0.130	.241**
	P		0.000		P	0.074	0.001
	N	217	216		N	190	189
UACR	R	.241**	1.000	BW	R	-0.029	.153*
	P	0.000			P	0.670	0.025
	N	216	216		N	217	216
eGFR-Epi	R	-0.046	-.135*	BMI	R	-0.033	.158*
	P	0.502	0.048		P	0.631	0.020
	N	217	216		N	217	216
GROUP DN1,NONDN2, C3	R	-.148*	-.617**	metformin	R	-0.059	-0.053
	P	0.029	0.000		P	0.487	0.536
	N	217	216		N	141	140
MS	R	0.049	.269**	SGLI	R	-0.157	0.066
	P	0.473	0.000		P	0.064	0.436
	N	217	216		N	141	140
GENDER	R	-0.003	-0.024	DPP4	R	-0.003	0.015
	P	0.961	0.731		P	0.971	0.862
	N	217	216		N	141	140
age	R	0.048	.233**	GLP1	R	-.177*	0.051
	P	0.485	0.001		P	0.035	0.546
	N	217	216		N	141	140
DM duration	R	-0.060	.209*	SU	R	-0.046	.180*
	P	0.479	0.013		P	0.587	0.0
	N	140	139		N	141	140
SBP	R	0.086	.388**	pioglitazone	R	-0.072	0.038
	P	0.213	0.000		P	0.396	0.655
	N	213	212		N	141	140
DBP	R	0.005	.349**	LAI	R	0.073	.306**
	P	0.937	0.000		P	0.387	0.000
	N	213	212		N	141	140
HR	R	-.141*	0.115	SAI	R	-0.082	0.139
	P	0.040	0.095		P	0.333	0.103
	N	212	211		N	141	140
FPG	R	.176*	.373**	statin	R	-0.115	-.270**
	P	0.033	0.000		P	0.174	0.001
	N	147	147		N	141	140
A1c	R	0.098	.388**	FF	R	0.048	0.074
	P	0.152	0.000		P	0.569	0.386
	N	215	215		N	141	140
APG	R	-0.159	.340**	aspirin	R	-0.062	0.018
	P	0.132	0.001		P	0.464	0.831
	N	91	91		N	141	140
Cr	R	0.027	0.050	ACEi	R	-0.042	0.162
	P	0.693	0.468		P	0.624	0.057
	N	217	216		N	141	140

TC	R	-0.007	0.070	CCB	R	-0.005	.298**
	P	0.924	0.314		P	0.954	0.000
	N	209	208		N	141	140
triglyceride	R	0.031	.199**	indapamide	R	-0.160	.194*
	P	0.655	0.004		P	0.057	0.022
	N	212	211		N	141	140
HDL-C	R	-.185**	-.219**	HTN	R	-0.091	.228**
	P	0.007	0.001		P	0.283	0.007
	N	210	209		N	141	140
Hb	R	-0.019	0.000	CAD	R	-0.153	0.039
	P	0.798	0.996		P	0.070	0.651
	N	190	189		N	141	140
RDW	R	0.112	0.022	DR	R	-0.043	.271**
	P	0.123	0.767		P	0.613	0.001
	N	190	189		N	141	140

*SBP: systolic blood pressure, DBP: diastolic blood pressure, bpm: Beat per minutes, HR: Heart Rate, BW: body weight, TSH: Thyroid stimulating hormone, FPG: Fasting plasma glucose, HbA1c: glycated hemoglobin, APG: average plasma glucose, Scr: serum creatinine, GFR: glomerular filtration rate,*

*Ucr: Urine creatinine, UACR: Urine Albumin Creatinine ratio, HDL: High density Lipoprotein, LDL, Low density Lipoprotein, Hb: Hemoglobin, RDW: Red cell distribution width, WBC: White blood cell count, BMI: body mass index, SD: Standard Deviation, NA: Not applicable.*

Table (IV): Multivariate Regression analysis showing the independent risks of diabetic nephropathy

Variable	B	Sig.	Exp(B)	95% C.I.	
				Lower	Upper
DBP	-0.156	0.022	0.856	0.749	0.978
A1c	-1.192	0.005	0.304	0.131	0.703
ACEi	2.448	0.027	11.570	1.319	101.494

DBP: diastolic blood pressure, A1c: glycated haemoglobin, ACEi: angiotensin-converting enzyme inhibitors

Figure 1: ROC curve analysis of the sensitivity and specificity of HbA1c as an independent risk for nephropathy

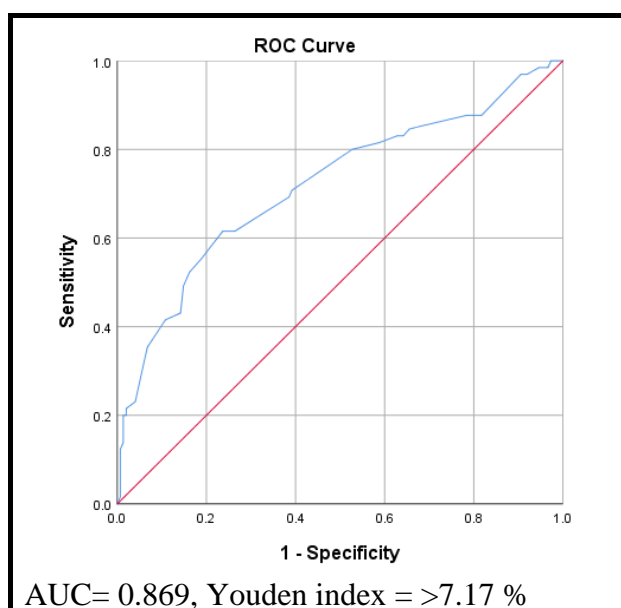
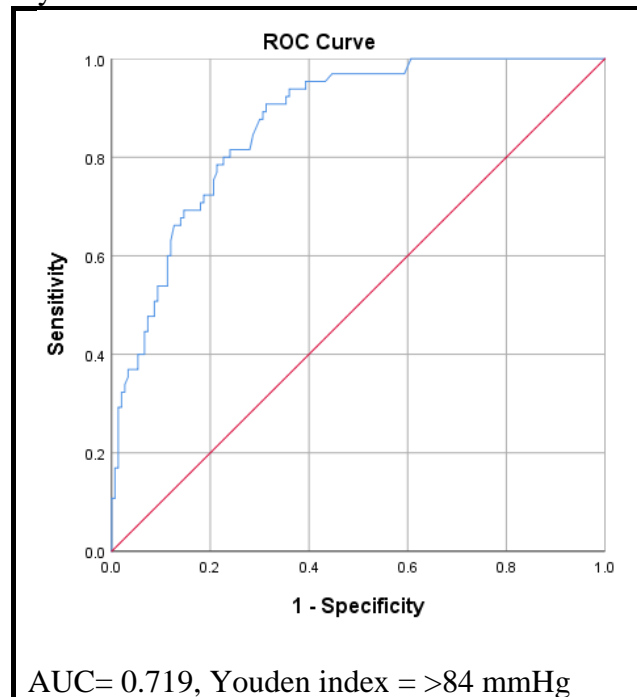


Figure (2): ROC curve analysis of the sensitivity and specificity of diastolic blood pressure as an independent risk for nephropathy



## DISCUSSION

Contrary to Wang's report (17), TSH in our study population did not show significant difference between T2DM with and without nephropathy but was significantly higher in both groups of diabetes together and in each group in comparison with the healthy control. Also, we did not find significant differences between patients with and without nephropathy as regards age, serum creatinine, eGFR, LDL-c, HDL-c, Hemoglobin or RDW.

Like Wang's report, compared to patients with normoalbuminuria, patients with high UACR in our study had significantly longer diabetes duration, higher SBP and DBP, heart rate, triglycerides, and total cholesterol. We also found higher FPG, HbA1c, BW, BMI, and WBC counts in the nephropathy group. Metabolic syndrome and diabetic retinopathy were significantly more frequent in the nephropathy group.

In agreement with our observation, Zou (18) did not find a significant difference in the TSH level between the DKD and non-DKD groups. His study, similarly, showed that subjects with DKD were older with a prolonged duration of diabetes with a higher prevalence of hypertension, more use of ARBs

or ACEi medication and higher SBP, DBP, HbA1c, FPG and TG. But, in contrast to our findings, there was no significant difference concerning BMI and TC and there was more use of insulin in patients with nephropathy. In our report, no significant difference in age was noticed although there was a significant positive association between age and UACR and no significant difference in the use of insulin between the two groups.

Zhu mentioned a significant positive correlation between UACR and BMI, FPG, HbA1c that agrees with our observation. (19) But contrary to our report, he did not find an association between UACR and thyrotropin hormone or the measured variables of SBP, DBP, TG, metabolic syndrome, eGFR and HDL-c.

In his research, Zou also found that BMI was independently associated with UACR. This is consistent with our report of a significant and positive correlation between BMI and UACR and being one of the risk factors for diabetic nephropathy on univariate regression analysis. (18) One possible hypothesis is obesity-induced glomerular hyperfiltration and increased urinary albumin excretion rate. (20) Moreover, adipocytes

secrete inflammatory factors such as TNF- $\alpha$  and C-reactive protein. These factors are toxic to glomerular podocytes and mesangial cells. (21, 22) Other mechanisms include insulin resistance, excessive lipid deposition oxidative stress caused by obesity. (23, 24) Like our study, Zhu found no difference in gender or age between patients who had albuminuria and those who did not. The nephropathy patients had longer diabetes duration and higher TC. (19) Higher serum creatinine, lower eGFR and higher TSH in the DN group could not be elucidated in our patients.

In the Gautam study, the prevalence of microalbuminuria increased according to TSH quartiles and in a fully adjusted logistic regression model, higher TSH concentrations were associated with a higher prevalence of microalbuminuria, compared with the lowest quartile of TSH. In his study, multiple linear regression analysis showed an independent association between serum TSH and urine albumin creatinine ratio ( $P = 0.04$ ). Serum TSH even in the euthyroid range was positively associated with microalbuminuria in euthyroid patients with diabetes independent of traditional risk factors. This relationship was strongest in patients with components of the metabolic syndrome. (25) Patients with microalbuminuria and overt proteinuria have increased plasma levels of very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and triglycerides. However, the plasma level of high-density lipoprotein (HDL) is lower than those of patients with normoalbuminuria. (26) This agrees with our observation of higher TC and TG in albuminuria patients than in non-albuminuria. We also found that UACR was significantly and directly associated with high TG and inversely with HDL-C, and both were significant risk factors for high UACR.

The results of Russo's study supported the independent role of TG and HDL-C in the development and progression of DKD and showed that, although LDL-C levels were well controlled, TG above 150 mg/dL and HDL-C below 40 mg/dL in men and 50 mg/dL in women increased this risk of kidney failure/eGFR reduction. (27) In the ACCORD

Lipid Trial, a median of 4-year follow-up, fenofibrate treatment lowered the rate of eGFR decline and the incidence of micro- and macro-albuminuria. (28)

Diabetes and hyperlipidemia cause renal lipid accumulation. At the same time, lipid toxicity due to the accumulation of lipids in the mesangium may accelerate the progression of DN. (29) Several studies have shown that peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ) agonists could inhibit renal inflammation and fibrosis and prevent renal oxidative stress. (30) The Diabetes Atherosclerosis Intervention Study (DAIS) showed a reduction of albumin excretion after fenofibrate treatment. (31) This effect of fenofibrate was also suggested by the FIELD study with slowing of progression to diabetic nephropathy. (32) Similar reports about such effect of fibrates are also available. (33)

GLP1 analogues were more in use in patients with albuminuria ( $p=0.018$ ). GLP-1RA may exert a beneficial action on the kidneys through blood glucose and BP-lowering effects, reduction of insulin levels and weight loss as well as possible direct cardio-nephroprotective mechanisms through actions on endothelial dysfunction and inflammation. (34,35)

Like previous reports, diabetic nephropathy patients in our study had a higher prevalence of hypertension. (36) In our study high diastolic blood pressure was an independent risk factor for diabetic nephropathy. The use of ACEi and ARBs was similar in all diabetes patients indicating its priority in treating hypertension in diabetes. CCBs were significantly more used in patients with nephropathy and mostly in combination with ACEi and ARBs indicating the higher blood pressure and the need for more medication for control of hypertension in nephropathy patients. The antiproteinuric effects of thiazide-like diuretics, such as chlorthalidone and indapamide, have also been studied. A 12-week pilot study tested the effects of chlorthalidone in 12 patients with moderate to advanced CKD and found a 40–45% albuminuria reduction. Indapamide was

significantly more used in nephropathy patients. (37)

In hypertension patients with CKD, RAAS inhibitors were recommended as a first-line drug as they reduce albuminuria in addition to BP control, while CCBs and diuretics were considered as add-on medications after initiation of RAAS inhibitors. (38)

## CONCLUSION

Thyrotropin hormone even within the normal range in euthyroid T2DM patients is significantly associated and is considered as a risk factor for diabetic nephropathy as presented by albuminuria and elevated UACR.

Further prospective interventional studies are required to assess the effect of thyroxine intake in euthyroid T2DM patients with nephropathy. New cut-off values for thyrotropin in T2DM with and without nephropathy may be considered in further studies.

## Conflict of interest:

The authors declare no conflict of interest.

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