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RESEARCH ARTICLE

Association of High Levels of Spot Urine Protein with High Blood Pressure, Mean Arterial Pressure and Pulse Pressure with the Development of Diabetic Chronic Kidney Dysfunction or Failure among Diabetic Patients. Statistical Regression Modeling to Predict Diabetic Proteinuria

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ARTICLE HISTORY

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Abstract: ***Introduction*:** In research elevated Blood Pressure (BP) has been demonstrated to be a risk for the development of nephropathy and chronic renal disease (CKD) Or Diabetic Kidney Disease (DKD) among diabetics. However, no study has find correlation for the spot urine protein (UPr) excretion with elevated BP, Pulse Pressure (PP) and mean arterial pressure MAP). This technique was invented in the current study.

***Methods*:** 10,270 were recruited for more than 12 years. Demographically, 43%, 38%, and 16% showed hypertension, nephropathy and chronic renal disease, respectively. UPr demonstrated significant correlations with systolic BP (SBP) and diastolic BP (DPB), MAP and PP ($p < 0.0001$ for all). SBP, DBP, PP and MAP, UPr were observed to be higher among the groups with nephroaphty and CKD/DKD with highly significant p-values (all $p < 0.05$). With logistic regression, odds ratio of hypertension (HTN) with nephropathy was observed to be 2.99 (95% CI 2.44 to 3.7; $p < 0.0001$); and odds ratio of HTN with CKD/DK was 7.1 (95% CI 4.3 to 11.84; $p<0.0001$), indicating that HTN significantly contributes to the development of nephropathy and CKD/DKD in diabetics.

***Results*:** Invented regression models for the excretion of UPr from the kidney with elevated SBP, DBP, MAP and PP were highly significant ($p < 0.0001$ for all); UPr = -138.6 + [1.347 × SBP] ; UPr = -93.4 + [1.62 × DBP] ; UPr = -149.5 + [1.922 × MAP] ; UPr = -41.23 +[1.541 × PP].

***Conclusion*:** Current study is the first one to introduce this technique. These invented new equations can be used by physicians to estimate protein excretion in urine at bedside and outpatients departments for monitoring proteinuria and CKD/DKD.

Keywords: Blood pressure, diabetic kidney disease, mean arterial pressure, proteinuria, pulse pressure, spot urine protein.

1. INTRODUCTION

Diabetes mellitus is a chronic disease, which affects multiple human organs, causes complications such as neuropathy, retinopathy , nephropathy and diabetic septic foot and has an economic impact. Control of diabetic state with its comorbidities (such as dyslipidemia, high blood pressure and proteinuria) is an essential part of clinical diabetes management. Chronic renal failure or Chronic Kidney Disease (CKD) in the diabetic metabolic state, also called diabetic kidney disease (DKD), is a major cause of End-Stage Renal Disease (ESRD) among diabetics [1-3]. Similarly, Atherosclerotic Cardiovascular Disease (ASCVD) and Hypertension (HTN) are the risk factors and cause the development of CKD/DKD and End-stage Renal Disease (ESRD). Essential HTN or uncontrolled Blood Pressure (BP) and BP Variability (BPV) are also risk factors for target organ damage. In humans, atheroma formation is also associated with elevated BP and isolated systolic hypertension. This leads to hardening or stiffening of the aorta and other major arteries [4-12].

Recent research trials have demonstrated that proteinuria (either microalbuminuria or gross proteinuria) is an independent risk factor for cardiovascular mortality among the patients with diabetes and hypertension [13-16]. High blood pressure usually leads to renal impairment with the development of proteinuria over years and may lead to ESRD [17-26].

Elevated BP is damaging to the nephrons per se and causes filtration of micro- or macro-proteins (proteinuria) through the glomerulus and will cause nephropathy. Although microalbumin screening is recommended for the detection of incipient nephropathy, however, recently it has been proven that spot Urine Protein (UPr), or the ratio of spot Urine Protein to Creatinine UPr/Cr (PCR) can be also

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used to detect and monitor nephropathy or Diabetic Kidney Disease (DKD or CKD) [27-41].

In diabetic renal disease (or DKD) status, elevated BP and protein excretion are the major and modifiable risk factors for the progression of ESRD. The clinical research has demonstrated the benefits of reducing BP and proteinuria excretion between diabetics and non-diabetics [42-46].

Blood pressure is maintained by two components: a steady component called mean arterial pressure (MAP) and a pulsatile component, called pulse pressure (PP), which is a difference between systolic BP (SBP) and diastolic BP (DBP). The MAP is determined by ventricular ejection and peripheral vascular resistance. PP is determined by ventricular ejection interacting with the viscoelastic properties of the large arteries (direct) due to wave reflection (indirect). The elevated BP in middle and advanced age subjects is due to an increase in large-artery stiffness and an associated increase in wave reflection amplitude [47-53].

Furthermore, there is an increasing evidence that in older age groups, PP is also an independent predictor of risk of Coronary Artery Disease (CAD). Additionally, it is reported that older age groups which are not on antihypertensive management have age-related changes of PP and MAP; hence, DBP decreases, while SBP continues to rise. Ultimately, PP usually rises thereafter. However, the equation of MAP underestimates the peripheral vascular resistance in older subjects (age more than 60 years). Hence, PP is clinically important under these circumstances for CAD risk estimation [54-57]. Conversely, it has been demonstrated and proven that SBP, DBP, and MAP are strongly associated with Cardiovascular Disease (CVD) risk in younger age groups. Hence, MAP is clinically important as well [58]. High blood pressure (with elevated PP and MAP) when combined with proteinuria, is usually associated with cardiovascular risk, nephropathy, end-organ damage and ESRD [59-66].

Under this research evidence and background, this study was initiated and designed to investigate the development of proteinuria, nephropathy, Diabetic Kidney Disease (DKD/CKD), under the influence of elevated SBP, DBP, PP and MAP. Our objective was also to develop regression models for the SBP, DBP, PP and MAP with spot urine protein (UPr) excretion from the kidney nephrons, which previously had not been investigated in details.

2. MATERIALS AND METHODS

Current research is a prospective, cross-sectional and cohort study, conducted at the diabetology clinic of Aseer Endocrine and Diabetes Center of Aseer Central Hospital, Ministry of Health Saudi Arabia. The duration of study was 12 years and 10 months, from August 2005 until June 2018. The study included 10,270 diabetic patients. Both type-1 and type-2 diabetic patients were included. Pediatric age group or children (less than 13 years of age), patients with severe liver disease, those demonstrating urinary tract infection or inflammation, patients with proteinuria or nephrotic syndrome before the onset of diabetes, known cases of End-stage Renal Disease (ESRD) or dialysis and pregnant subjects were excluded from this study.

3. CLINICAL METHODS

Blood pressure was measured by standardized methodology with supine and resting position by electronic device, Mindray VS-800. Mean Arterial Pressure (MAP) and Pulse Pressure (PP) were calculated according to the clinical research literature review as follows [54, 67-70]:

$$MAP = (2 \times DBP + SBP)/3$$

$$PP = SBP - DBP$$

4. LABORATORY METHODS

Blood and urine samples were collected in a fasting state of 12 hours, in the morning. Serum creatinine (mg/dl) and urine creatinine (mg/dl) were quantitatively measured by CREA methodology by Dimension® clinical chemistry system and device (Siemens Healthcare Diagnostics Inc. Newark, DE 19714, USA) [71-73]. Patients demonstrating levels of serum creatinine ≥1.5 were defined as chronic kidney disease or diabetic kidney disease (CKD/DKD).

For the detection of nephropathy and the presence of albumin or protein in the urine, urine samples were examined for the presence of microalbuminuria, macroalbuminuria or proteinuria. All urine samples were first examined for the presence of gross proteinuria by QuikCheck™ urinalysis reagent strips (ACON biotech, Co., Ltd.) to rule out macroalbumin in urine. This technique is based on the phenomenon of pH indicators which release hydrogen ions to the protein. Samples which demonstrated macroalbuminuria (in mg/dl) or gross proteinuria by the color indicator of the reagent strips (ranging from 1+ to 4+) were defined/labeled as "nephropathy".

Samples with negative albumin were further examined for the presence of microalbumin in urine by MALB method used by Dimension® clinical chemistry system and device, *in vitro* diagnostic test for quantitative measurement of albumin (mg/L) in human urine by particle-enhanced turbidimetric inhibition immunoassay (PETINIA) methodology (Siemens Healthcare Diagnostics Inc. Newark, DE 19714, USA). Samples demonstrating microalbuminuria (albumin excretion in urine in the range of 30-300 mg/L) were also labeled and defined as nephropathy. Collectively, patients demonstrating urinary protein excretion such as microalbuminuria or gross proteinuria were labeled as "nephropathy".

Spot urine protein was measured by UCFP (Urinary/ Cerebrospinal Fluid Protein) method on Dimension® clinical chemistry system (Siemens healthcare diagnostics Inc. Newark, DE 19714, U.S.A). This is *in vitro* diagnostic test intended for the direct quantitative determination of total protein in human urine and cerebrospinal fluid, which is an adaptation of pyrogallol red molybdenum method by Y. Fujita, I. Mori and S. Kitano [74]. In the reaction sequence, pyrogallol red combined with sodium molybdate to form a red complex with maximum absorbance at 470 nm. The protein in the sample reacted with this complex in an acid solution to form a bluish-purple colored complex, which absorbs at 600 nm. The absorbance at 600 nm was directly proportional to the concentration of protein in the sample. The analyte concentration was determined by the calculation using a logit curve fit on a previously stored calibration curve. PCR (pro-

tein to creatinine ratio) was measured by spot urine protein / spot urine creatinine.

All laboratory sample requests were entered in a computer software and results were retrieved by Natcom Hospital Information System (NATCOM HIS; National Computer System Co. Ltd [75].

5. STATISTICAL METHODS

IBM® SPSS® statistics version 20 was used to analyze the data. Data were summarized as percentages with mean ± SD and 95% CI. Independent t-test was used to test the significant differences between the group of variables (nephropathy and CKD/DKD). For Pearson's correlation and regression model construction and all statistical and mathematical assumptions considered that variables must show a linear relationship. Logistic Regression and Odds Ratio were used to measure associations of HTN with nephropathy and DKD/CKD. Predictive regression model analysis was used to develop a relationship of blood pressure with spot urine protein, and it was then estimated by mathematical linear equations to confirm that how blood pressure values (SBP, DBP, PP, and MAP) can contribute to the development of increased levels of spot urine protein or proteinuria. Statistical power of 90% was built for the detection of significance and p-values (two-sided) of less than 0.05 that were considered significant.

6. PATIENT CONSENT

This study was reviewed and approved by the research committee of Aseer Diabetes Center, and all methodologies on subjects reported in the current study were in accordance with the Helsinki Declaration of 1975 (revised in 2008).

7. RESULTS

Demographic data for the patients are presented in Table **1**. Nephropathy was observed in 38% of patients, while 16% demonstrated DKD/CKD. Descriptive statistics for variables are shown in Table **2**.

Table 1. Demographic data of diabetic patients.

Parameters	Description with N (%); Totals = 10,270	
Gender	Male	Female
	6162 (60%)	4108 (40%)
Type of Diabetes	Type-1	Type-2
	1541 (15%)	8270 (85%)
Hypertension	Positive	Negative
	4416 (43 %)	5854 (57%)
Nephropathy	Positive	Negative
	3903 (38%)	6367 (62%)
Diabetic Kidney Disease (DKD/CRD/CKD) status	Positive	Negative
	1643 (16%)	8627(84%)

Table 2. Descriptive statistics for the variables with mean ± SD.

Variables	Mean ± SD
Age (years)	53 ± 13.9
Diabetes duration (years)	16 ± 7.8
Serum creatinine (mg/dl)	0.953 ± 0.682
Systolic blood pressure (mmHg)	128.8 ± 16.4
Diastolic blood pressure (mmHg)	79.2 ± 9
Mean arterial pressure	95.8±10.43
Pulse pressure	49.5±12.7
Spot urine protein (UPr)	52.9 ± 141
Spot urine creatinine (UCr)	120±143
Spot urine protein / creatinine ratio (PCR)	0.6±2

Table 3. Correlations of variables.

Variables	Pearson Correlation (r)	p-value
Systolic BP and UPr	0.47	< 0.0001
Diastolic BP and UPr	0.31	< 0.0001
MAP and Spot urine protein and	0.43	< 0.0001
PP and Spot urine protein	0.45	< 0.0001

Table 4. Significant statistical tests between groups of variables (with and without nephropathy) with mean±SD and p-values.

Variables and Indicators	Patients Variable Values With or Without Nephropathy				
	Mean ± SD 95 % CI		F-value	T-Value	P-values
Systolic blood pressure (mmHg)	With Nephropathy	Without Nephropahty	11.1	14.6	< 0.0001
	135.5 ± 16.9 134.3 to 136.8	124 ± 14.5 123 to 125			
Diastolic blood pressure (mmHg)	With Nephropathy	Without Nephropathy	4.86	10.4	0.028
	81.93 ± 9.2 81.3 to 82.7	77.4 ± 8.4 76.8 to 77.9			
Mean arterial pressure (MAP)	With Nephropathy	Without Nephropathy	10.75	13.74	< 0.0001
	99.8 ± 10.7 98.6 to 100.9	92.8 ± 9.4 92.3 to 93.5			
Pulse pressure (PP)	With Nephropathy	Without Nephropathy	24.85	11.2	< 0.0001
	53.6 ± 13.63 52.5 to 54.7	46.7 ± 11.2 46 to 47.4			
Spot urine protein (UPr)	With Nephropathy	Without Nephropathy	122.5	8	< 0.0001
	150.8 ± 98.5 98.7 to 259	23.8 ± 20.7 14.7 to 29.8			
PCR	With Nephropathy	Without Nephropathy	89.4	6.8	< 0.0001
	1.1±2.78 0.842 to 1.39	0.19 ± 1 0.11 to 0.21			

Table **3** shows Pearson's correlations between the variables. Correlations for spot urine protein with SBP, DBP, MAP and PP were significant (p-values < 0.0001 for all variables).

Table **4** shows significant t-test among the variables (SBP, DBP, MAP, PP, spot urine protein (UPr) and spot urine protein to creatinine ratio (UPr/Cr or PCR) and nephropathy status. All blood pressure values were elevated between the groups with nephropathy (p-values < 0.0001 for all variables).

Similarly, Table **5** demonstrates significant differences of variables (SBP, DBP, MAP, PP, spot urine protein (UPr) and spot urine protein to creatinine ratio, PCR) between the groups with and without DKD. It is evident that the levels of these variables are elevated between the patients with DKD (p-values < 0.0001 for all variables).

Table **6** demonstrates Pearson's (χ^2) and logistic regression with odds ratio. It is evident from this table that HTN and nephropathy were significantly associated; odds ratio 2.99 (95% CI 2.44 to 3.7; p < 0.0001). Similarly, HTN was significantly associated with the development of DKD/CKD; odds ratio 7.1 (95% CI 4.3 to 11.84; p < 0.0001).

Table **7** demonstrates the significant correlation and regression models among different variables. The regression models were significantly associated, p-values < 0.0001 for all variables.

Table 5. Significant statistical tests between groups of variables (with and without CKD and HTN) with mean ± SD and p-values.

Variables and Indicators	Patients Variable Values with or Without CKD				
	Mean ± SD 95 % CI		F-value	T-Value	P-values
Systolic BP	With CKD	Without CKD	26.8	9.4	< 0.0001
	142 ± 21.3 139 to 146	128 ± 15.6 127 to 128.6			
Diastolic BP	With CKD	Without CKD	2.74	6.2	0.023
	84 ± 9.2 82.5 to 85.85	78.9 ± 8.93 78.5 to 79.4			
Mean arterial pressure (MAP)	With CKD	Without CKD	6	8.5	0.014
	103.5 ± 11.8 101.4 to 105.7	95.2 ± 10 94.7 to 95.8			
Pulse pressure (PP)	With CKD	Without CKD	38	7.6	< 0.0001
	58 ± 17.6 54.8 to 61.3	48.8 ± 11.98 48.3 to 49.5			
Spot urine protein (UPr)	With CKD	Without CKD	224.5	12.7	< 0.0001
	258.2 ± 247 157 to 359	34.57 ± 79.21 29.2 to 39.95			
Spot urine creatinine (UCr)	With CKD	Without CKD	7	-3.65	< 0.0001
	90.7 ± 46 80 to 101.3	122.3 ± 73.4 117.2 to 127.3			
PCR	With CKD	Without CKD	205	12.4	< 0.0001
	3.2 ± 5.4 1.96 to 4.4	0.37 ± 1.18 0.3 to 0.46			

Table 6. Significant pearson's (χ^2) results for the variables HTN, nephropathy, and CKD/DKD.

Variables	Pearson's (χ^2) ; p-value	Fisher's Exact Test p-value	Linear-by-linear Association p-value	Logistic Regression and Odds Ratio (95% CI)
HTN and nephropathy	< 0.0001	< 0.0001	< 0.0001	2.99 (2.44 to 3.7)
HTN and DKD/CKD	< 0.0001	< 0.0001	< 0.0001	7.1 (4.3 to 11.84)

This data demonstrated that elevated blood pressure values significantly contribute to the elevated levels of spot urine protein.

8. DISCUSSION

Elevated BP or HTN exhibits a risk for nephropathy or proteinuria, ESRD, CAD and Cerebrovascular Disease (CVD) with high diabetic complications rate. According to the recent guidelines, BP should be minimized to the required target to prevent complications [76-90].

Mean Arterial Pressure (MAP) gives an average of pressure during the cardiac cycle and provides a measure of the average perfusion pressure of the systemic circulation and tissues or organs. SBP and DBP may have variations and one of them may be normal and other abnormal or high. Under these situations, MAP can be helpful to determine average blood pressure. Framingham Heart Study and other research trials have demonstrated that MAP and pulse pressure are better associated with CAD, elderly patients and those on hemodialysis [91-94]. Data from these and recent trials have also demonstrated that SBP usually rises with age; and once increased, continue to rise. However, SBP usually increases until age 55-60 and then decreases or remains constant. Hence, under these circumstances, PP is an important tool for estimating mean blood pressure, and can provide cardiovascular risk assessment as well [95-101].

Table 7. Correlation and regression models for the different variables.

Data and Variables	Pearson's Correlation (r)	P-Value For Pearson's Correlation	Regression Analysis				
			R^2	F-Statistic	ANOVA Model P-Value	T-Statistic	P-Value
Systolic BP and pot urine protein	0.47	<0.0001	0.145	150	<0.0001	-9.72	<0.0001
Diastolic BP and pot urine protein	0.31	< 0.0001	0.058	54.92	<0.0001	-5.4	< 0.0001
Mean arterial pressure (MAP)	0.43	< 0.0001	0.115	115	<0.0001	- 8.7	<0.0001
Pulse pressure (PP)	0.45	<0.0001	0.110	109.74	<0.0001	-5.52	<0.0001
Mathematical / Statistical Regression models and equations							
Systolic BP and pot urine protein		Spot urine protein = -138.6 + [1.347 × systolic BP]					
Diastolic BP and pot urine protein		Spot urine protein = -93.4 + [1.62 × diastolic BP]					
Mean arterial pressure and spot urine protein		Spot urine protein = -149.5 + [1.922 × mean arterial pressure]					
Pulse pressure and spot urine protein		Spot urine protein = -41.23 +[1.541 × pulse pressure]					

However, in previous studies, PP or MAP has not been studied in detail especially for the risk of development of proteinuria / nephropathy. We conducted this study to estimate the relation of blood pressure to the protein excretion in the urine (proteinuria); and to develop regression models that how elevated blood pressure can contribute to the development of nephropathy or CKD/DKD. This was achieved by measuring spot urine protein (UPr), which has not been studied in the past.

According to our data analysis and Table **1**, 38% (3903) of patients demonstrated nephropathy and 16 % (1643) CKD or DKD (serum creatinine > 1.5). Table **3** demonstrates Pearson's correlations among variables. Significant associations were found for the blood pressure values (SBP, DBP, PP and MAP) and spot urine protein excretion (p-values < 0.0001 for all variables). Highest correlation was observed between SBP and spot urine protein (Pearson's correlation 0.47; $p < 0.0001$).

Patients with the status or with and without nephropathy were compared for the levels of BP values (SBP, DBP, MAP , PP), spot urine protein and spot urine protein to creatinine ratio (PCR), Table **4**. Subjects with nephropathy demonstrated elevated values of these variables with significant differences (p-values < 0.0001 for all variables tested; DBP p-value = 0.028). It was evident from the data and table-4 that elevated BP values significantly contribute to the to the raised protein excretion and development of nephropathy. Similarly, data for CKD/DKD (serum creatinine > 1.5 mg/dl) were also analyzed to observe the significant differences of variables (SBP, DBP, PP, MAP, spot urine protein, and PCR) between the group with and without CKD. It is evident for table-5 that blood pressure values and urinary protein excretion were observed to be increased inthe patients labeled CKD (all p-values < 0.0001 ; for MAP p-value 0.014). Hence, it was demonstrated by our data that elevated SBP, DBP, MAP, and PP significantly contribute to the development of CKD/DKD. Furthermore, it was observed that spot urine protein (UPr) and PCR values were also raised between the groups with CKD/DKD. In summary, it can be stated that elevated BP leads to the development of nephropathy and thereafter leads to the elevation of serum creatinine and ultimately DKD/CKD.

Essential hypertension, isolated systolic hypertension and raised diastolic BP have been demonstrated to be associated with risk of cardiovascular disease, myocardial infarction, arterial distensibility and left ventricular hypertrophy [102-106]. Furthermore, it was demonstrated that increased pulse pressure is also associated with heart failure [107]. Additionally, elevated BP values are a risk for nephropathy and associated with albumin or protein excretion in the urine. These filtered proteins are considered early markers of nephropathy. Recently it has been demonstrated that filtered proteins through the glomerulus are nephrotoxic intrinsically, will cause progression of renal injury and eventually may lead to chronic renal failure (CKD/DKD) [108-116]. This phenomenon was also demonstrated and confirmed from current study data; Table **6** demonstrates the odds ratio of HTN with nephropathy and DKD/CKD with significant p-values ($p<0.0001$ for all tested variables). Hence, HTN or elevated BP caused the development of nephropathy and chronic renal insufficiency among the studied diabetic subjects. Such histological pathology, if untreated, may lead to an increase in creatinine over time and eventually chronic renal insufficiency and irreversible renal damage, in type-1 and type-2 diabetics and even non-diabetics [117-126].

Hence there is a need to develop a methodology by which physicians can estimate protein excretion by the kidney under the influence of elevated BP. Until date, Research trials are lacking to demonstrate this relationship and phenomenon and regression models. However, this was invented in the current study. Hence, Regression models and mathematical equations were developed to estimate protein excretion from the kidney nephrons under the influence of increased BP. Table **7** demonstrates regression analysis and developed mathematical equations. All regression models were significantly correlated with significant p-values (p<

0.0001 for all tested models). Hence, for example, if SBP is 150 mmHg, then estimated spot urine protein excretion will be approximately 67.5 mg/dl. If SBP is considered 110 mmHg, then the given value of spot urine protein will be 12 mg/dl. Similarly, if MAP is 110, the spot urine protein will be approximately 63 mg/dl. However, if MAP is 120, then spot urine protein excretion will be more of about approximately 81.6 mg/dl. According to our data, pulse pressure can be used also to estimate spot urine protein; hence, if PP is 40 (within normal limits), the spot urine protein will be 20 mg/dl. Conversely, if PP is high of about 80, for example, then spot urine protein excretion will be 82 mg/dl. Interestingly, the current study has developed and invented significant associations and mathematical equations of BP values with protein excretion from the kidney. These mathematical equations can be used to estimate protein excretion by kidney under given BP values, for monitoring proteinuria and diabetic kidney disease.

Past and current guidelines for the diagnosis and management of hypertension have demonstrated that elevated SBP and DBP carry a significant cardiovascular risk [79], [127-129]. Blood pressure control also requires a good compliance from the patient, diet control and regular walk as well. Additionally, moderate salt reduction of 5 to 10 g per day is required to prevent BP elevation and urine protein excretion; benefits of low to moderate salt intake has been demonstrated also in non-diabetics [130-134].

CONCLUSION AND RECOMMENDATIONS

We have invented a new method for the estimation of proteinuria excretion from the kidney based on the blood pressure values. This method will assist cardiologists, nephrologists, diabetologists, and other physicians for proteinuria estimation at bedside and in OPDs (outpatient department).

Blood pressure control is essential to prevent kidney damage in the diabetic state, and to slow down the progression of DKD/CKD. Diabetes management requires not only to control glycemic status, but also HTN, dyslipidemia and other co-morbid conditions. Hyperlipidemia (elevated total cholesterol, low-density lipoproteins, and triglycerides) isalso the independent risk factor for the ASCVD and nephropathy or renal failure. Serum lipids also per se contribute to the elevated BP. Large-scale clinical trials have shown that retinopathy is usually associated with nephropathy and HTN with poor prognosis. At tertiary care diabetes centers, all diabetic patients should be screened for HTN, dyslipidemia, nephropathy and retinopathy. Evidence-based medicine and guidelines should be used for the management of diabetic patients to prevent complications [135-172].

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was reviewed and approved by the research committee of Aseer Diabetes Center, Saudi Arabia.

HUMAN AND ANIMAL RIGHTS

No animals were used in this study. All the methodology on subjects reported in the current study were in accordance with the Helsinki Declaration of 1975 (revised in 2008).

CONSENT FOR PUBLICATION

Informed consent was obtained from each participants.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from third party. Restrictions apply to the availability of these data, which were used under licence for this study.

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CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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