Association Between Visceral Adiposity Marker with Diabetic Kidney Disease: An Analysis of Data from National Diabetes Registry Malaysia

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Abstract: Diabetic kidney disease (DKD) causes significant morbidity and mortality and an economic burden to the country. New visceral adiposity assessment and measurements have gained much attention as a surrogate marker to screen pathogenic visceral fat among patients with chronic kidney disease. This study aims to determine the association between visceral adiposity markers and DKD among T2DM patients. A cross-sectional study to analyze Putrajaya Diabetes Clinical Audit 2018 data from the National Diabetes Registry Malaysia was conducted. A universal sampling method was performed to include all T2DM patients in the dataset. Logistic regression analyses were utilized for three visceral adiposity markers, which were the hypertriglyceridemic waist (HW) phenotype, visceral adiposity index (VAI) and lipid accumulation product index (LAPI). A total of 1,297 T2DM patients were included in the analyses. The majority of them were of Malay ethnicity, male and aged between 40-64 years. The overall prevalence of DKD was 24.1%. VAI was significantly associated with DKD among males but not in females. Compared to males in the first VAI quartile group, both second and fourth quartile groups had increased odds of DKD [adjusted odds ratio (AOR) of 1.91 (95% confidence interval [CI]: 1.09, 3.34) and AOR 2.29 (95% CI: 1.03, 5.09) respectively)]. There was no significant association between HW phenotype and LAPI with DKD. VAI could predict DKD only in male T2DM patients. Thus, it might be a useful clinical indicator of DKD in male T2DM patients in primary care.

Keywords: Diabetic Kidney Disease, Marker, Visceral Adiposity Index, Lipid Accumulation Product Index, Hypertriglyceridemic Waist Circumference Value

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a worldwide public health problem. Diabetic kidney disease (DKD) is one of its serious complications affecting 30% to 50% of T2DM patients globally [1]. Studies have reported that the prevalence of DKD in Malaysia varies between 7.3% to 90.7% [2-4]. A study done among the primary care population gave a lower prevalence than among inpatients. DKD is a significant cause of morbidity and mortality in T2DM patients. In terms of morbidity, it has been shown to lead to end-stage renal disease (ESRD). Studies have also demonstrated DKD to be associated with high mortality rates [5], affects patients and their family's quality of life [6] and poses a substantial economic burden to the country [7].

T2DM and DKD have been associated with being overweight or obese [8-10]. Emerging evidence shows a relationship between three new visceral adiposity measures with chronic kidney disease (CKD). These measures were the hypertriglyceridemic waist (HW) phenotypes, visceral adiposity index (VAI) and lipid accumulation product index (LAPI), which had been developed as simple screening tools to measure visceral fat accurately. They subsequently enable the prediction of patients' risk of developing conditions such as cardiovascular diseases, cerebrovascular disease, hypertension and T2DM [11-13]. The predictive equations of visceral adipose tissue, together with anthropometric scales and biochemical indices of the blood, show high consistency with MRI in visceral obesity quantification [13]. Recent literature has demonstrated that VAI may be an alternative surrogate predictor of visceral obesity [14]. Lipid accumulation product index (LAPI) determines lipid overaccumulation in a body, which is better than BMI in predicting cardiovascular risk in the United States (US) adult population [15]. These new measures are also reported to be associated with CKD among the non-diabetic population [13] [16]. Hence, establishing their relationship with the DKD population is much needed. This study grouped these new visceral adiposity measures as a visceral adiposity marker.

The earliest concept of HW phenotype was proposed as a simple screening tool for identifying viscerally obese individuals at risk for cardiovascular disease (CVD) among men in Canada [17-19]. They used a cut-off point of TG ≥2.0 mmol/L for serum TG and waist circumference (WC) ≥90 cm for their male subjects [17]. Although WC is a better marker of abdominal fat accumulation than BMI, an elevated WC alone is insufficient to diagnose visceral obesity. Thus, it has been proposed that a high TG concentration and increased WC could represent a simple clinical marker of excess visceral or ectopic fat [19]. Since then, several studies have observed a positive relationship between HW phenotype and increased coronary risk factors or coronary artery disease and diabetes [20-24]. Its gender-specific association with CKD has been reported among the general population in Iran and China [25-29].

The lipid accumulation product index (LAPI) was initially formulated to describe lipid overaccumulation in a body, which was better than BMI in predicting cardiovascular risk [15]. Later, a growing body of evidence showed LAPI could be a potential indicator for risk of insulin resistance, T2DM, metabolic syndrome, cardiovascular disease, diabetic retinopathy and CKD [16] [30-32]. Its relationship with a decline in renal function and CKD has also been studied among the general population [16] [33-34]. Nevertheless, as far as we know, there is still a gap in the knowledge regarding the relationship between LAPI and kidney disease among the diabetes population.

Visceral adiposity index (VAI) was initially proposed as a diagnostic tool for cardiovascular and cerebrovascular events in Caucasian primary care patients [11] [35]. Association with several conditions such as cardiovascular disease, T2DM, hypertension, metabolic syndrome, liver disease and PCOS were studied in several works of literature [35-37]. Analyses among both general population and gender stratification reported VAI as a predictor for CKD in Japan, Iran and China communities [13-14] [16] [34] [36] [38]. There was a lack of studies that investigated the association between VAI and CKD in diabetes patients.

The higher prevalence of diabetes in Putrajaya compared to the national prevalence (19.2% vs 17.5%) and partnered with the highest burden of overweight (37.0%) and obesity (25.8%) in the country would eventually lead to increasing DKD burden in this government administrative city of Malaysia [39]. A large proportion (about 80%) of diabetes patients are managed at public primary health clinics [39-40]. Hence, the role of primary care in routine DKD screening and diagnosis cannot be further emphasized. The development of DKD complications is frequently first detected in a health clinic setting. Thus, early diagnosis is vital among those with risk factors, such as overweight or obese diabetic patients so that early intervention could be initiated. Hence, a simple screening tool feasible for daily use in a busy primary care setting is much needed to screen high-risk diabetic patients for developing DKD. Knowledge of the association between new visceral adiposity assessment measurements and DKD will enable the development of screening measures and targeted intervention programs for high-risk diabetes patients to prevent DKD. Thus, this study aims to determine the association between visceral adiposity markers with DKD among T2DM patients.

2. MATERIAL AND METHODS

2.1. Study design and setting

A cross-sectional study was conducted, which analyzed secondary data from an audit dataset of Putrajaya Diabetes Clinical Audit 2018 from the National Diabetes Registry (NDR). The NDR is a web-based national registry for diabetes patients managed at primary health clinics under the Ministry of Health, Malaysia. All T2DM patients aged 18 years and above, attending the government health clinics in the Federal Territory of Putrajaya, Malaysia, and registered in NDR with 'active status' were included in the study. A patient was considered 'active' if they had a record of a clinic visit for treatment at least once within one year from the audit date (from 2 June 2017 to 3 June 2018). This study considered the latest clinical examinations and laboratory tests performed within 12 months from the audit date. Patients without outcome data (DKD status) or non-Malaysian citizens were excluded from the analysis.

This study used a universal sampling method by selecting all 1301 patients in the 2018 audit dataset. Meanwhile, the sample for the audit dataset was autogenerated from the NDR web system done by the Kuala

Lumpur and Putrajaya State Health Department through a simple random sampling method [41]. The minimum sample size required for this study was 248 patients to ensure this study had enough power to give a statistically significant result. It was calculated using Open Epi version 3 open-source calculator using estimation for cross-sectional study by Kelsey et al. [42]. The odds ratio (OR) for exposure was selected from a study by Ma et al. in which the OR for the association between HW phenotype and DKD was 2.81 (95% CI: 1.36, 5.80) [12]. The percentage of unexposed samples with outcome was 10.6% and 24.5% for those exposed with the outcome. The significance level was set at 5% and a 95% confidence interval with a study power of 80%.

2.2. Variables' definition

This study's outcome variable was DKD, and the HW phenotype, LAPI, and VAI were the predictors. The patients were regarded as having a DKD when a specialist or a medical officer diagnosed them with nephropathy (DKD), as recorded in the medical records and the NDR. The diagnosis was based on the standard Malaysian clinical guidelines which defined DKD as either presence of albuminuria (microalbuminuria or proteinuria) or eGFR level <60 ml/min/1.73 m^2 or both, and persistent for more than three months [43].

Hypertriglyceridemic waist phenotype is defined as a simultaneous presence of serum TG concentrations ≥1.7mmol/L and WC ≥90cm (males) and ≥85cm (females) [12]. Visceral adiposity index (VAI) score was calculated using WC, BMI, TG and HDL values using the formula as below [11]:

$$\text{For male; VAI} = [\text{WC}/\ (39.68+(1.88 \times \text{BMI}))] \times (\text{TG}/1.03) \times (1.31/\ \text{HDL})\ (1)$$
$$\text{For female; VAI} = [\text{WC}/\ (36.58 + (1.89 \times \text{BMI}))] \times (\text{TG}/0.81) \times (1.52/\text{HDL})\ (2)$$

Lipid accumulation product index (LAPI) was calculated based on a combination of WC and TG concentration levels using the formula as below [15]:

$$\text{For male; LAPI} = (\text{WC-65}) \times \text{TG}\ (3)$$
$$\text{For female; LAPI} = (\text{WC-58}) \times \text{TG}\ (4)$$
$$(\text{WC in cm, TG concentration in mmol/L and LAPI in cm.mmol/L})$$

Any WC values of ≤65 cm in men were revised upward to 66 cm, and WC values of ≤58 cm in women were revised upward to 59 cm to avoid non-positive values for LAPI [15]. The LAPI and VAI values were categorized into four quartiles (1, 2, 3 and 4), with the fourth quartile having the highest LAPI and VAI value for further analysis.

The other independent variables were sociodemographic characteristics (age, gender and ethnicity), clinical characteristics including diabetes duration, WC, BMI, systolic blood pressure, diastolic blood pressure, serum TG concentration, serum high-density lipoprotein (HDL), serum low-density lipoprotein (LDL), total cholesterol level, HbA1c, serum creatinine, albuminuria status, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACE inhibitor/ARB) usage), comorbidities (hypertension, dyslipidemia and cardiovascular disease) and diabetes retinopathy. All continuous variables except serum creatinine were categorized for analyses according to clinical targets for diabetes patients in Malaysia [39] [44].

2.3. Data collection and analysis

Patients' data were obtained from the State Health Director in Kuala Lumpur and Putrajaya State Health Department in a Microsoft Excel file. Then, the data file was transferred into IBM-Statistical Package for the Social Sciences (IBM-SPSS) version 26. The initial number of diabetes patients in the 2018 NDR audit dataset was 1301 (Figure 1). All patients were having T2DM and aged 18 years and above. However, only 1297 patients were included in the analysis after excluding three patients without outcome data and a non-Malaysian patient. The data were explored, re-coded and cleaned for errors and outliers. We were unable to recheck the missing data in the health clinics since Malaysia was under Movement Control Order due to COVID-19 pandemic; hence permission to access the patients' medical record was not granted. Percentage of missing data was 8.3%, hence missing data were imputed using Expectation-Maximization technique. Then, the score for LAPI and VAI were computed.

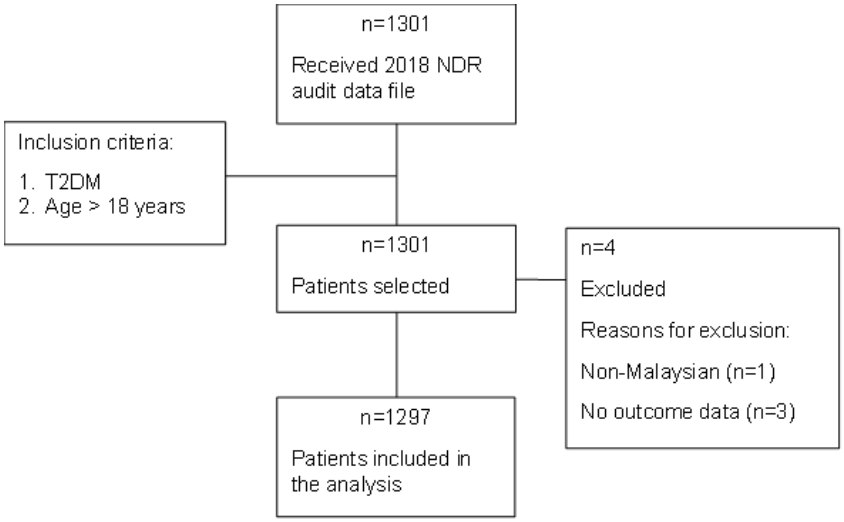

Figure 1. Patients flow diagram

Statistical analyses were performed using the IBM-SPSS version 26 for Windows according to gender since the mathematical formulas for the LAPI and VAI were gender-specific. Descriptive studies reported frequency and percentage for categorical data and mean (standard deviation [SD]) for continuous data. A chi-square test was performed to compare proportions between groups of categorical variables. Mean comparisons between groups of continuous variables were analyzed with independent t-test or one-way ANOVA. All continuous data were treated as normally distributed due to the large sample size in this study [45].

Further statistical analyses involved simple logistic regression in determining the association between independent variables and DKD, and the results were presented as a crude odds ratio (COR). Variables with a p-value of 0.10 or less in univariate analysis and based on clinical judgement were included in multiple logistic regression analysis by adjusting for confounders to determine significant association. The results were presented as an adjusted odds ratio (AOR). The significance level was set at a p-value of less than 0.05, with a 95% confidence interval.

3. RESULTS

3.1. General characteristics of study population

Table 1 shows the general characteristics of the study population according to gender. A total of 1297 T2DM patients were included in our analysis. The mean age was 55.59 years old. When categorized into 5-year age strata, the highest age group was between 40 and 64 (68.9%). A similar trend was seen among gender subpopulations. The majority of the participants were Malays (75.2%), with males (56.2%) slightly more than females (43.8%).

Table 1. Characteristics of the T2DM patients (n=1297) in the Putrajaya health clinics registered in the NDR by gender and DKD status

Characteristics	Total	Male (n=682)			Female (n=615)		
		DKD status		p-value[b]	DKD status		p-value[b]
		No[a]	Yes[a]		No[a]	Yes[a]	
Overall	1297	486 (71.3)	196 (28.7)		498 (81.0)	117 (19.2)	
Age (years)	55.59(11.09)[a]	53.18 (10.95)	55.98 (11.59)		57.05(10.59)	58.72 (11.10)	
18 - 39	137 (10.6)	70 (73.7)	25 (26.3)	0.001	34 (81.0)	8 (19.0)	0.093
40 - 64	894 (68.9)	354 (74.1)	124 (25.9)		346 (83.2)	70 (16.8)	
≥ 65	266 (20.5)	62 (56.9)	47 (43.1)		118 (75.2)	39 (24.8)	
Ethnicity							
Other	98 (7.6)	45 (81.8)	10 (18.2)	0.071	41 (95.3)	2 (4.7)	0.013
Malay	1199 (92.4)	441 (70.3)	186 (29.7)		457 (79.9)	115 (20.1)	
Diabetes duration (years)		6.01 (4.96)	7.14 (5.90)		6.28 (5.21)	7.64 (5.29)	
0 - 5	670 (51.7)	261 (73.1)	96 (26.9)	0.086	272 (86.9)	41 (13.1)	0.001
>5 - 10	360 (27.8)	131 (73.6)	47 (26.4)		134 (73.6)	48 (26.4)	
>10	267 (20.6)	94 (63.9)	53 (36.1)		92 (76.7)	28 (23.3)	
Waist circumference (cm)		99.52 (11.11)	98.48 (10.88)		95.04 (11.81)	97.12 (12.52)	
≤ 90 (male); ≤ 80 (female)	201 (15.5)	99 (68.8)	45 (31.3)	0.453	49 (86.0)	8 (14.0)	0.314
> 90 (male); > 80 (female)	1096 (84.5)	387 (71.9)	151 (28.1)		449 (80.5)	109 (19.5)	
Body mass index (BMI) (kg/m^2)		29.56 (4.90)	28.79 (4.36)		29.19 (5.71)	30.64 (6.04)	
Underweight/ Normal	211 (16.3)	70 (69.3)	31 (30.7)	0.638	91 (82.7)	19 (17.3)	0.605
Overweight/ Obese	1086 (83.7)	416 (71.6)	165 (28.4)		407 (80.6)	98 (19.4)	
SBP (mmHg)		135.39 (15.03)	135.39 (17.24)		135.52 (17.27)	138.39 (17.82)	
≤ 135	673 (51.9)	249 (72.2)	96 (27.8)	0.594	272 (82.9)	56 (17.1)	0.188
> 135	624 (48.1)	237 (70.3)	100 (29.7)		226 (78.7)	61 (21.3)	
DBP (mmHg)		83.79 (9.72)	82.66 (10.81)		80.43 (10.29)	81.12 (11.28)	
≤ 75	324 (25.0)	89 (65.9)	46 (34.1)	0.126	156 (82.5)	33 (17.5)	0.510
> 75	973 (75.0)	397 (72.6)	150 (27.4)		342 (80.3)	84 (19.7)	
Haemoglobin A1c (%)		7.47 (1.70)	7.76 (1.97)		7.19 (1.39)	7.69 (1.60)	
≤ 6.5	464 (35.8)	180 (75.9)	57 (24.1)	0.048	198 (87.2)	29 (12.8)	0.003
> 6.5	833 (64.2)	306 (68.8)	139 (31.2)		300 (77.3)	88 (22.7)	

3.2. Overall DKD prevalence and characteristics according to gender and DKD status

Diabetic kidney disease was present in 24.1% (313 patients) of the study population. Males had a higher prevalence (28.7%) of DKD compared with females (19.2%). Most of the DKD patients among both males and females were having larger WC, overweight/obese, uncontrolled diabetes (HbA1c more than 6.5%), serum TG at 1.7 mmol/L or less, hypertension, no retinopathy, a lower proportion of HW phenotype and higher LAPI score in quartile 3. However, most male patients had shorter diabetes duration (0-5 years), while most females had diabetes duration between 5-10 years.

3.3 Associations between DKD and visceral adiposity marker

The results for univariable analysis are presented in Table 2. Male diabetes patients with VAI score in quartile 2 were 1.74 times more likely having DKD than males in VAI quartile 1 [OR 1.74 (95% CI:1.08-2.79), p=0.022]. The other three VAI quartiles, all LAPI quartiles and HW phenotype did not show any significant association with DKD among males. Among female diabetes population, significant relationship with DKD was seen between HW phenotype and LAPI quartiles 3 and 4. Female diabetes patients with HW phenotype had 1.78 odds of developing

DKD compared with those without HW phenotype. When compared with diabetes female group with the lowest LAPI quartile score (Q1), both females in LAPI quartile 3 and 4 groups had 1.83-times and 1.89-times higher odds of having DKD, respectively.

Table 2. Univariate analysis on factors associated with DKD among T2DM patients (n=1297) in Putrajaya Health Clinics registered in NDR by gender

Variables	Male (n = 682)			Female (n = 615)		
	Wald (df)	Crude OR (95% CI)	p-value[a]	Wald (df)	Crude OR (95% CI)	p-value[a]
Age (years)						
18 - 39	12.72 (2)	1	ref	4.70 (2)	1	ref
40 - 64	0.01 (1)	0.98 (0.60-1.62)	0.939	0.13	0.86 (0.38-1.94)	0.715
≥ 65	6.18 (1)	2.12 (1.17-3.84)	0.013	0.61	1.41 (0.60-3.29)	0.434
Ethnicity						
Other		1	ref		1	ref
Malay	3.16 (1)	1.90 (0.94-3.85)	0.075	5.03 (1)	5.16 (1.23-21.64)	0.025
Diabetes duration (years)						
0 - 5	4.87 (2)	1	ref	14.51 (2)	1	ref
>5 - 10	0.01 (1)	0.98 (0.65-1.47)	0.905	13.29	2.38 (1.49-3.78)	<0.001
>10	4.17 (1)	1.53 (1.02-2.31)	0.041	6.61	2.02 (1.18-3.45)	0.010
Waist circumference (cm)						
≤ 90 (male); ≤ 80 (female)		1	ref		1	ref
> 90 (male); > 80 (female)	0.56 (1)	0.86 (0.58-1.28)	0.454	1.00 (1)	1.49 (0.68-3.23)	0.316
Body mass index (BMI) (kg/m²)						
Underweight/ Normal		1	ref		1	ref
Overweight/ Obese	0.22 (1)	0.90 (0.57-1.42)	0.638	0.27 (1)	1.15 (0.67-1.98)	0.606
SBP (mmHg)						
≤ 135		1	ref		1	ref
> 135	0.28 (1)	1.09 (0.79-1.53)	0.594	1.73 (1)	1.31 (0.88-1.96)	0.188
DBP (mmHg)						
≤ 75		1	ref		1	ref
> 75	2.32 (1)	0.73 (0.49-1.09)	0.127	0.43 (1)	1.16 (0.74-1.81)	0.511
Haemoglobin A1c (%)						
≤ 6.5		1	ref		1	ref
> 6.5	3.88 (1)	1.43 (1.00-2.05)	0.049	8.90 (1)	2.00 (1.27-3.16)	0.003
Serum TG (mmol/l)						
≤ 1.7		1	ref		1	ref
> 1.7	0.25 (1)	1.09 (0.78-1.52)	0.617	7.73 (1)	1.80 (1.19-2.72)	0.005
Serum HDL (mmol/l)						
> 1.0 (male), > 1.2 (female)		1	ref		1	ref
≤ 1.0 (male), ≤ 1.2 (female)	1.31 (1)	1.22 (0.87-1.71)	0.253	1.74 (1)	1.31 (0.88-1.97)	0.188
Serum LDL (mmol/l)						
≤ 2.6		1	ref		1	ref
> 2.6	0.26 (1)	0.91 (0.65-1.29)	0.608	0.76 (1)	0.83 (0.55-1.25)	0.383
Total cholesterol (mmol/l)						
≤ 5.2		1	ref		1	ref
> 5.2	1.40 (1)	0.81 (0.57-1.15)	0.236	2.45 (1)	1.39 (0.92-2.11)	0.118
Serum creatinine (μmol/l)	63.83	1.03 (1.02-1.04)	<0.001	63.01 (1)	1.05 (1.04-1.06)	<0.001
Albuminuria status						
No		1	ref		1	ref
Yes	52.86 (1)	4.96 (3.22-7.64)	<0.001	40.14 (1)	4.94 (3.02-8.11)	<0.001

Variables	Male (n = 682)			Female (n = 615)		
	Wald (df)	Crude OR (95% CI)	p-value[a]	Wald (df)	Crude OR (95% CI)	p-value[a]
ACE inhibitor/ARB usage						
Yes		1	ref		1	ref
No	25.13 (1)	0.36 (0.25-0.54)	<0.001	15.71 (1)	0.40 (0.26-0.63)	<0.001
Hypertension						
No		1	ref		1	ref
Yes	16.11 (1)	2.38 (1.56-3.65)	<0.001	21.64 (1)	5.83 (2.78-12.27)	<0.001
Dyslipidaemia						
No		1	ref		1	ref
Yes	6.96 (1)	1.85 (1.17-2.93)	0.008	1.91 (1)	1.47 (0.85-2.54)	0.167
Cardiovascular disease						
No		1	ref		1	ref
Yes	12.07 (1)	3.34 (1.69-6.59)	0.001	2.35 (1)	1.96 (0.83-4.62)	0.125
Retinopathy						
No		1	ref		1	ref
Yes	26.09 (1)	2.62 (1.81-3.79)	<0.001	18.15 (1)	2.80 (1.76-4.45)	<0.001
HW phenotype						
No		1	ref		1	ref
Yes	0.29 (1)	1.20 (0.78-1.54)	0.590	7.49 (1)	1.78 (1.18-2.70)	0.006
LAPI scores (cm.mmol/L)						
Quartile 1 (≤ 35.00)	1.25 (3)	1	ref	7.70 (3)	1	ref
Quartile 2 (35.01 - 53.30)	0.76 (1)	1.24 (0.77-2.00)	0.384	0.07 (1)	1.09 (0.58-2.03)	0.796
Quartile 3 (53.31 - 78.40)	0.93 (1)	1.26 (0.79-2.03)	0.334	4.27 (1)	1.83 (1.03-3.26)	0.039
Quartile 4 (≥ 78.41)	0.11 (1)	1.09 (0.67-1.75)	0.735	4.50 (1)	1.89 (1.05-3.39)	0.034
VAI scores						
Quartile 1 (≤ 1.37)	5.87 (3)	1	ref	7.21 (3)	1	ref
Quartile 2 (1.38 - 2.10)	5.27 (1)	1.74 (1.08-2.79)	0.022	0.21 (1)	0.86 (0.46-1.61)	0.646
Quartile 3 (2.11 - 3.03)	1.23 (1)	1.32 (0.81-2.14)	0.267	0.09 (1)	1.09 (0.60-1.99)	0.771
Quartile 4 (≥ 3.04)	3.24 (1)	1.56 (0.96-2.51)	0.072	3.67 (1)	1.74 (0.99-3.04)	0.055

Statistical test: [a]Simple logistic regression; Statistically significant at $p<0.05$ T2DM, type 2 diabetes mellitus; DKD, diabetic kidney disease; HW phenotype, hypertriglyceridemic waist phenotype; VAI, visceral adiposity index; LAPI, lipid accumulation product index, OR, Odds Ratio; CI, confidence interval

Further multivariable analysis showed an increased risk of developing DKD in males with the VAI quartile 2 [AOR 1.91 (95% CI: 1.09-3.34)], compared with VAI first quartile, adjusted for ethnicity, HbA1c, ACE inhibitor/ARB usage, hypertension and retinopathy among diabetes population (Table 3). While males with diabetes in VAI forth quartile had 2.29 odds more likely to have DKD compared with males in the VAI first quartile.

Table 3. Association between HW phenotype, LAPI and VAI with DKD among T2DM patients (n=1297) in Putrajaya Health Clinics registered in NDR by gender

Variables	Male (n=682)				Female (n=615)			
	B (S.E.)	Wald (df)	Adj. OR (95% CI)	p-value[a]	B (S.E.)	Wald (df)	Adj. OR (95% CI)	p-value[a]
HW phenotype								
No			1	ref			1	ref
Yes	0.16 (0.31)	0.26 (1)	1.17 (0.64-2.17)	0.611	-0.05 (0.36)	0.02 (1)	0.95 (0.47-1.92)	0.881
LAPI (cm.mmol/L)								
Q1 (≤ 35.00)		3.23 (3)		ref		1.74 (3)	1	ref
Q2 (35.01 - 53.30)	0.01 (0.29)	0.001 (1)	1.01 (0.57-1.79)	0.970	0.09 (0.40)	0.06 (1)	1.10 (0.50-2.41)	0.814
Q3 (53.31 - 78.40)	-0.16 (0.35)	0.21 (1)	0.85 (0.43-1.69)	0.650	0.52 (0.46)	1.28 (1)	1.68 (0.68-4.16)	0.259
Q4 (≥ 78.41)	0.63 (0.44)	2.09 (1)	0.53 (0.23-1.25)	0.149	0.42 (0.54)	0.59 (1)	1.51 (0.52-4.38)	0.444
VAI								
Q1 (≤ 1.37)		7.11 (3)	1	ref		2.55 (3)	1	ref
Q2 (1.38 - 2.10)	0.65 (0.29)	5.13 (1)	1.91 (1.09-3.34)	0.024*	-0.25 (0.40)	0.40 (1)	0.78 (0.36-1.69)	0.528
Q3 (2.11 - 3.03)	0.43 (0.37)	1.36 (1)	1.54 (0.77-3.15)	0.243	-0.30 (0.46)	0.43 (1)	0.74 (0.30-1.82)	0.511
Q4 (≥ 3.04)	0.83 (0.41)	4.1 (1)	2.29 (1.03-5.09)	0.043*	0.19 (0.52)	0.14 (1)	1.21 (0.44-3.35)	0.710

Statistical tests: [a]Multiple logistic regression (Enter method; B constant: -1.713 (male),-3.624 (female); R2=0.088 (male), R2=0.095 (female); Model assumptions were met; No interaction and multicollinearity between independent variables, no influential outlier); Statistically significant at p<0.05*. Adjusted for ethnicity, HbA1c, ACE inhibitor/ARB usage, hypertension and retinopathy, T2DM, type 2 diabetes mellitus; NDR, National Diabetes Registry; DKD, diabetic kidney disease; HW phenotype, hypertriglyceridemic waist phenotype; VAI, visceral adiposity index; LAPI, lipid accumulation product index, OR, Odds Ratio; Adj. OR, Adjusted OR; CI, confidence interval

Figure 2 shows the receiver operating characteristic curve (ROC curve) for males and females in the prediction of DKD. For males, the area under the curve (AUC) score was 68.5% (95% CI: 0.64-0.73), p-value <0.001. Hence, the model can discriminate 68.5% of the predicted of having DKD. For females, the AUC score was 71.9% (95%CI: 0.67-0.77), p-value <0.001. Thus, the model can discriminate 71.9% of the predicted DKD. Hence, this model was more capable of predicting DKD in females than males.

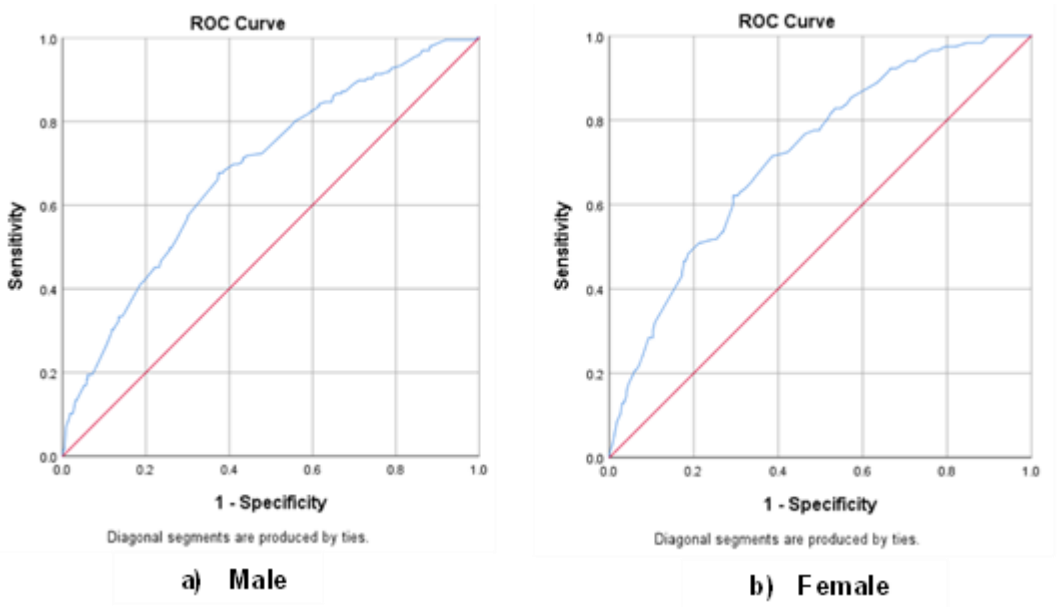

Figure 2. The discriminatory power of HW phenotype, VAI and LAPI, between subjects with or without DKD. The area under the receiver operating characteristic (ROC) curve of HW phenotype, VAI and LAPI to identify subjects with DKD according to gender.

4. DISCUSSIONS

This study identified sociodemographic and clinical characteristics of T2DM patients attending Putrajaya Health Clinics and registered in the NDR according to gender and determined the association between HW phenotype, VAI and LAPI with DKD in this population. Among the three visceral adiposity markers, only the male patients were significantly associated with DKD. The overall prevalence of DKD in our study was 24.1% (n=313) among T2DM patients in Putrajaya Health Clinics from 2018 NDR data. The DKD prevalence was found to be higher compared with the previous local study using the Malaysian diabetic registry database [Adult Diabetes Control and Management (ADCM)] in 2009 (7.3%) [46]. The DKD prevalence is consistent with the increasing trend in the overall prevalence of T2DM in Malaysia for the past two decades, as reported in the series of National Health and Morbidity Survey in 2006 (11.6%), 2011 (15.2%) and 2015 (17.5%)39 [47-48]. However, Malaysia's DKD prevalence was lower when compared with two studies done in a diabetes clinic in a teaching hospital in east coast Malaysia (90.7%) and among diabetes patients with diabetic complications admitted in a medical ward (34.9%) [2] [4]. The reason could be that hospital settings receive more complex diabetes cases, usually with complications such as DKD. The neighboring country, Singapore, had a higher DKD prevalence (53%) among primary care patients between 2011 and 2013 than our findings [49]. Although Singapore has almost similar ethnic groups to Malaysia, their study population had a higher proportion of Chinese ethnic, compared with predominantly Malay in our study.

Male diabetes patients with VAI scores in quartiles 2 and 4 were likelier to develop DKD than those in quartile 1. The association was more robust in the VAI fourth quartile than the VAI first quartile. It could be due to a higher VAI score for those in quartile 4 (3.04 or more) than quartile 2 (1.38 - 2.10). The non-significance finding between VAI quartile three and DKD could be explained by the lower proportion of males in this group compared with VAI quartiles 2 and 4. Meanwhile, our study found no relationship between all three VAI score groups and DKD among female diabetic patients, compared with the VAI group with the lowest score. The reason could be attributed to the lower proportion of female patients with DKD across all VAI quartile groups compared to males. However, several studies in Japan, Iran and China revealed different results.

The VAI could be a quick and reliable instrument for microalbuminuria assessment in newly diagnosed T2DM patients in Japan [50]. A possible reason could be the presence of high serum TG, and low serum HDL is commonly seen in T2DM [51]. However, our study population had low serum TG and high serum HDL concentrations. Several studies in the Chinese population showed that VAI had good prediction ability to detect CKD [14] [16] [38]. Another survey among the non-diabetic population revealed that the initial significant association found among females was abolished when adjusted for diabetes and hypertension in the model. VAI was dependent on diabetes and hypertension. However, VAI is not a useful indicator for CKD among males [29]. In a longitudinal study in Japan and Iran populations, VAI can predict incident CKD and renal function decline, respectively [34] [36]. This variation could be attributed to the difference in the study population and ethnicity. Our study was conducted among diabetes patients in primary care, predominantly Malay ethnicity, with the male proportion higher than females. In contrast, these studies were conducted among the general Chinese population, with the female proportion higher than males. VAI is associated with the emergence of metabolic syndrome and other metabolic disorders besides being a predictive indicator for visceral obesity [13].

Our study found that the HW phenotype did not predict DKD for both males and females with diabetes. Moreover, many studies showed a link between HW phenotype and CKD [12] [26] [29] [52]. A contrasting finding from one study reported that T2DM subjects with HW phenotypes were 2.8 times more likely to have early diabetic nephropathy than those with standard WC and TG in a study [12]. The difference in result could be due to an outcome where our study included DKD patients regardless of stages of the disease, while the study only considered an early stage of DKD. Ramezankhani et al. and Zeng et al. reported HW phenotype played a significant role as an indicator for CKD among males, while Huang et al. found positive results among females [26] [28-29]. Albuminuria may exhibit visceral fat [53]. The ability to predict CKD was still seen among relatively lean subjects (BMI <24 kg/m2) and older populations (aged 40 years and above) [25] [52]. The Asian population, including the Chinese, appear more prone to visceral fat accumulation despite having a generally low BMI [54]. Another reason for our study's different findings could be the variation in serum TG cut-off point. They used serum TG concentration

of 2.0 mmol/L or more for HW phenotype definition, which was higher than our study [25] [52]. Although the positive role of the HW phenotype was established, despite its simplicity, a possible limitation of this phenotype is its dichotomous nature of representation.

This study showed that LAPI had no significant role as a risk factor for DKD among male and female diabetes patients. A piece of contrasting evidence with our research showed that individuals with higher LAPI scores had two times the risk of developing CKD than those with a lower range LAPI score [33]. In Iran, although both LAPI and VAI outperformed other standard obesity measures as a reliable marker for CKD among non-diabetic subjects, VAI was far superior to LAPI [16] [34]. The possible explanation could be that the VAI formula consists of more indices than LAPI, which subsequently gives a more precise equation for pathogenic visceral fat prediction. However, more consideration should also be given to LAPI than other traditional adiposity measures since it appears to be a more reliable predictor of determining the relationship between visceral fat mass and diabetes and insulin resistance [55].

Visceral obesity could be related to renal damage in T2DM patients and non-diabetic subjects [56]. A study reported that larger waist circumference could also predict subsequent microalbuminuria development in type 1 diabetes [57]. Diabetes patients with higher BMI were more likely to have DKD than under/normal-weight individuals [58-59]. Thus, weight reduction was suggested as one of the solutions to protect the kidneys in diabetic patients [58]. Obesity is a risk factor for several interrelated conditions, such as metabolic disorders, diabetes and chronic kidney disease. Thus, the pathogenesis for obesity, specifically the pathogenic visceral adiposity leading towards DKD, is much more complex. Several works of the literature showed an association between visceral adiposity and diabetes [30] [60-62]. Diabetes could be a mediator for visceral adiposity and DKD. Thus, various factors may mediate the association between adiposity and CKD. There are several possible biological mechanisms to explain the study results.

Obesity induces renal impairment by increasing the deposition of fat in the kidney and liver, causing renal lipotoxicity in which excessive buildup of free fatty acids in the tissue and the high amounts of adipokines in the blood secreted by adipose tissue causing inflammation and hyperlipidemia as well as induce activation of the sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) [13]. Increased activation of RAAS leads to renal hyperfiltration, overburden the glomerulus and damages the filtration barrier podocytes, subsequently reducing the glomerular filtration rate [36]. Accumulation of visceral fat within the renal hilum and sinus causes compression of renal parenchyma and blood vessels, decreasing renal tubular flow rates and activating RAAS. This sympathetic nervous system stimulation subsequently causes hypertension and DKD independent of diabetes and BMI [34] [50]. Insulin resistance associated with obesity affects the podocyte cytoskeleton in the kidney by inducing apoptosis. Adipose tissue is more than just a storage site for excess energy in the form of TG. It is an endocrine organ which plays significant roles in glucose metabolism, insulin sensitivity and vascular disease and produces numerous proteins with broad biological activities, including adiponectin [36]. Excessive fat accumulation will increase proinflammatory cytokines such as factor-alpha tumor necrosis (TNF-α) and interleukin-6 (IL-6) and lower production of anti-inflammatory adipokines such as adiponectin. This pathway results in increased formation of macrophage chemotactic factors contributing to invasion of macrophage and excessive synthesis of TNF-α. Increased macrophage infiltration and synthesis of TNF-α will result in chronic inflammation and subsequent renal dysfunction [14].

This study's findings could also provide a foundation for future studies, as previous studies on visceral adiposity among patients with T2DM and DKD are still limited. The cross-sectional design of this study may not be able to infer causality between the factors being studied and the DKD. Findings from secondary data analysis from the registry need to be treated with precaution as the quality of record-keeping by the healthcare providers at the health clinics is beyond researchers' control. However, a quality control process was in place to ensure the NDR data accuracy. Misclassification bias could be possible in this study when dealing with secondary data. Findings from this study may contribute to the body of knowledge by adding new evidence on the association between new visceral adiposity assessments and DKD among T2DM, providing baseline data for future research, and providing evidence on local data on the proportion of DKD among T2DM patients in Putrajaya Health Clinics. The implication of this work in public health and clinical practice may be seen in increasing awareness among healthcare professionals of

the current burden of DKD in primary care. Subsequently, this will require an emphasis on routine screening, early diagnosis and intervention to slow the DKD progression among high-risk patients.

Furthermore, the data helps policymakers decide on resource allocation for DKD prevention and treatment. It contributes to evidence-based clinical practices for diabetes by proposing the possible use of new visceral adiposity assessment measurements for patients with DKD. Also, baseline information from this study can be used to formulate evidence-based healthcare policy and planning, effective prevention and control measures targeting modifiable risk factors for DKD.

CONCLUSIONS

Overall, the VAI predicts diabetic kidney disease in male patients with diabetes but not in females. However, no significant role was determined between hypertriglyceridemic waist phenotype and lipid accumulation product index with diabetic kidney disease in both genders. The VAI might be a useful clinical indicator for DKD in male T2DM patients in Putrajaya health clinics but not female patients. Thus, in clinical screening and intervention, more attention should be paid to waist circumference, body mass index, triglyceride and high-density lipoprotein concentration. Future primary research is needed to overcome the limitations of secondary data analysis. Furthermore, a large-scale longitudinal study for the uncertain gender-specific associations and the causality between factors is essential.

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