Scoring System Development and Added Value of Albuminuria to Estimate Carotid Intima-media Thickness (CIMT) in Type 2 Diabetes Mellitus Patients

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ABSTRAK

Tujuan: mengembangkan sistem skor dan menentukan nilai tambah diagnostik albuminuria dalam mengestimasi carotid intima-media thickness (CIMT). Metode: studi potong lintang dilakukan di poliklinik endokrin RSCM bulan Maret-Mei 2012 pada pasien DMT2 tanpa komplikasi serebrokardiovaskular, penyakit ginjal kronis (PGK) stadium ≥ III, dan tidak merokok. Kami melakukan analisis statistik yang dilanjutkan dengan pembuatan sistem skor. Hasil: dari 71 subjek, didapatkan CIMT dan albuminuria masing-masing sebesar 67,6% dan 73,3%. Dari 48 subjek dengan CIMT, sebanyak 87,5% mengalami albuminuria. Pemeriksaan albuminuria memiliki sensitivitas sebesar 87,5%. Penambahan nilai albuminuria akan meningkatkan AUC sebesar 2,3%. Skor estimasi untuk variabel lama terdiagnosis DM, hipertensi, dislipidemia berturut-turut sebesar 1, 2, 1. Skor probabilitas CIMT pada skor <2, 2, dan >2 sebesar 15%, 57%, dan 90%. Kesimpulan: pemeriksaan albuminuria meningkatkan nilai tambah diagnostik CIMT. Sistem skor dapat digunakan sebagai alat skrining terhadap CIMT pada pasien DM tipe 2 tanpa komplikasi serebrokardiovaskular, PGK stadium ≥ III, dan tidak merokok.

Kata kunci: carotid intima-media thickness (CIMT), diabetes melitus tipe 2, albuminuria.

ABSTRACT

Aim: to develop a scoring system and measure the diagnostic added value of albuminuria to estimate CIMT. Methods: cross-sectional study was done in Endocrine Outpatient Clinic Cipto Mangunkusumo Hospital between March-May 2012 in T2DM patients without history of cerebrocardiovascular event, CKD stage ≥ III, and smoking. Bivariate analysis and multivariate (logistic regression) analysis was done, followed by developing the scoring system. Results: from 71 subjects, there were 67.6% with increased CIMT and 73.3% with albuminuria. From 48 subjects with increased CIMT, 87.5% had albuminuria. Albuminuria measurement had high sensitivity (87.5%). Adding albuminuria measurement will increase the AUC as 2.3%. Estimation score for duration of DM, hypertension, dyslipidemia were as follows 1, 2, 1 respectively. Probability score of increased CIMT for score <2, 2, and >2 was as follows 15%, 57%, and 90%. Conclusion: albuminuria measurement increase the diagnostic value of CIMT. Scoring system can be used as a screening tool to estimate the increased of CIMT in type 2 DM patients without history of cerebrocardiovascular event, CKD stage ≥ III, and smoking.

Keywords: carotid intima-media thickness (CIMT), type 2 diabetes mellitus, albuminuria.

INTRODUCTION

Cardiovascular event in patient with Type 2 Diabetes Mellitus (T2DM) are significantly related to vascular calcification. Studied by Lavranos et al. showed that vascular calcification, marked by increasing of Intima Media Thickness (IMT) in carotid artery, reach 71% in T2DM patients.[1]

Some studies such as Cardiovascular Health Study (CHS)[2], Atherosclerosis Risk in Communities Study (ARIC)[3], the Insulin Resistance Atherosclerotic Study (IRAS)[4], and Carotid Atherosclerosis Progression Study (CAPS)[5] showed that significant risk factors in Carotid Intima Media Thickness (CIMT) are diabetes, hypertension, and dyslipidemia, but albuminuria has not been measured in those studies.

Albuminuria has long been recognized as a systemic endothel dysfunction marker and a strong determinant for vascular calcification. In PREVEND Study (Prevention of Renal and Vascular End Stage Disease), albuminuria is known to be correlated with cardiovascular event, increasing the relative risk in patients with albuminuria about 29,1%.[6]

One of the objective diagnostic test for detecting vascular calcification is measuring the carotid intima media thickness using carotid ultrasound which has sensitivity of 93.4% and spesificity of 94%. It has some limitations such as operator dependent, limited availability in health care facilities, expensive, time-consumed, and still not been done as routine investigation in general health care facilities.[3] Because of the limitations and limited application in Indonesia, we need other diagnostic method which is not invasive, sensitive, spesific, applicable, and not expensive. One of the method that can be applied generally is scoring system.

Studies on vascular calcification and the usage of carotid ultrasound in Indonesia are still limited, and there are differences in studies about the correlation of albuminuria with carotid IMT, so we try to access it with different method. This is a diagnostic study by developing scoring system which is never been conducted before and also we measure the added diagnostic value of albuminuria for estimating vascular calcification in T2DM patients.

METHODS

This is a cross-sectional study to measure albuminuria examination as estimator and developing a scoring system, conducted in Endocrine Outpatient Clinic Cipto Mangunkusumo Hospital in February-May 2012. Inclusion criteria in this studies are T2DM patient. Exclusion criterias are coronary heart disease, history of cerebrovascular disease, chronic kidney disease stage ≥III, acute infection, heart disease, smoking, and anatomical neck defect which make difficulty in carotid ultrasound examination. There are 71 eligible subjects in this study, by using rule of thumb (prevalence of CIMT in T2DM from previous study was 70.5%).

Carotid ultrasound measurement was conducted in RCCA (right communis carotid artery), LCCA (left communis carotid artery), right bulb carotis, and left bulb carotis. CIMT is defined as the length between border of intima lumen and border of tunica media-adventitia. Thickening CIMT is defined as the mean CIMT of CCA is higher than normal CIMT, with equation: CIMT = 0,4 mm + {(age-21) x 0,01 mm} or mean CIMT in carotid bulb >0.8 mm.

Statistical analysis was performed by using SPSS, with student t-test and Chi-square test. Diagnostic power of 5 risk factors were measured by area under receiver operating characteristic curve (AUC) from estimated probability to CIMT from logistic regression multivariate analysis and 95% confidence interval.

This studies got Ethical Clearance from Ethical Committee of Faculty of Medicine in University of Indonesia No.114/PT02.FK/ETIK/2012.

RESULTS

There are 71 eligible subjects in this study and the measuring of carotid intima-media thickness (CIMT) was presented on **Table 1**.

In bivariate analysis, the significant risk factors related to increased CIMT are duration of DM, hypertension, dyslipidemia, and albuminuria. Odds ratio with confidence interval (CI) 95% was found on **Table 2**.

Table 1. Subjects's characteristics

Characteristic	n (%)
Gender - male	31 (43.7)
Age – y.o, mean (SD)	56.3 (9.5)
DM Duration	
- ≥5 years	47 (66.2)
- <5 years	24 (33.8)
Hypertension	
- Yes	43 (60.6)
- No	28 (39.4)
HbA1c	
- ≥7%	39 (54.9)
- <7%	32 (45.1)
Dyslipidemia	
- Yes	55 (77.5)
- No	16 (22.5)
Albuminuria	
- Yes	50 (70.4)
- Microalbuminuria	23 (32.4)
- Macroalbuminuria	27 (38)
- No	21 (29.6)
Carotid IMT	
- Increased	48 (67.6)
- plaque (+)	23 (32.4)
- plaque (-)	25 (35.2)
- Not Increased	23 (32.4)
- plaque (+)	10 (14.1)
- plaque (-)	13 (18.3)
RCCA, median (range)	0.81 (0.41-1.10)
Right bulb carotis, median (range)	1.04 (0.40-1.80)
LCCA, median (range)	0.76 (0.44-1.32)
Left bulb carotis, median (range)	1.04 (0.40-1.80)

Fifty-two subjects (73.3%) have albuminuria. Sensitivity of albuminuria is 87.5%, but the specificity is not high (65.2%). Albuminuria have significance in detecting increased carotid IMT (p=0.034, OR: 5.385; CI 95%: 1.141-25.43).

Variables included in multivariate analysis are variabels in bivariate analysis which give significance statistical analysis (p<0.25) which are duration of DM, hypertension, HbA1c, dyslipidemia, and albuminuria.

The comparison of two analysis models with and without albuminuria variable are followed by logistic regression to evaluate the added value of albuminuria in estimating the increase of CIMT.

**Table 2.** Analysis of factors related to increase CIMT

Variables	CIMT		OR (CI 95%)	p
	(-)	(+)		
Duration of DM				
- ≥5 years	37	10	4.37	0.005
- <5 years	11	13	(1.5-12.7)	
Hypertension				
- Yes	38	5	13.68	<0.001
- No	10	18	(4.1-16.9)	
HbA1c				
- ≥7%	29	10	1.98	0.179
- <7%	19	13	(0.73-5.43)	
Dyslipidemia				
- Yes	41	14	3.76	0.021
- No	7	9	(1.81-12.0)	
Albuminuria				
- Yes	42	8	13.13	<0.001
- No	6	15	(3.91-11.1)	

Comparison of these two model analysis can be seen in ROC curve on **Figure 1**.

Discrimination quality is measured through ROC analysis. AUC (area under the curve) in analysis with albuminuria is 0.894 (CI 95%: 0.811-0.977), and AUC value in analysis without albuminuria is 0.871 (CI 95%: 0.774-0.969).

Table 3. Multivariate analysis of related factors

Variables	OR (CI 95%)	p
Duration of DM	3.4 (0.828-13.963)	0.089
Hypertension	7.728 (1.628-36.680)	0.01
Dyslipidemia	7.381 (1.425-38.217)	0.017
Albuminuria	5.385 (1.141-25.426)	0.034
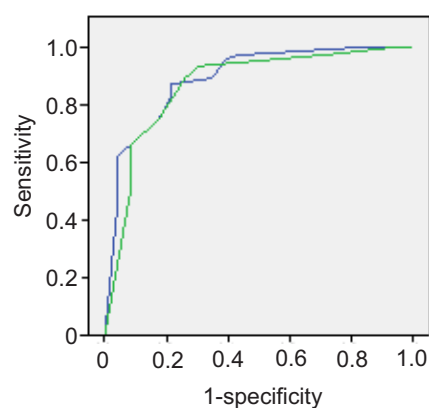
Figure 1. ROC curve analysis of albuminuria in estimating the increase of CIMT

Scoring System and Carotid Intima-media Thickness Probability

Determinant probability of increased CIMT is calculated from multivariate analysis (logistic regression) to determine the regression coefficient, using three determinant variables. According to the analysis, probability of CIMT can be defined through formula with variable value as 0 when negative and as 1 when positive:

$$P = \frac{1}{1 + e^{-2,898+1,368 \, DM +2,741.HT+1,999 \, Dyslipidemia}}$$

Probability range value subject score is 0-4. Probability total score from the result of logistic regression analysis to total score showed constanta -2,491 with regression coefficient 1,389, so the equation is y = -2,491 + (1,389 x score total), so the risk class can be classified. Estimation score for the duration of DM, hypertension, and dyslipidemia are 1, 2, and 1, respectively. The probability of increased carotid IMT in score <2, 2, and >2 are: 15%, 57%, and 90%. (**Table 4**)

Table 4. Estimation score and probability of increased carotid IMT

Patient score	Risk class	Probability of carotid IMT thickness
<2	Low	15%
2	Medium	57%
>2	High	90%

In analysis to subject score, the sensitivity and specificity are 94% and 70%, means if score > 2, it's a high probability for increased carotid IMT.

DISCUSSION

Prevalence of microalbuminuria in this study (30.9%) is similar to some studies like HOPE, NHANES III, PREVEND, EPIC, Ausdiab Kidney, and CHS, whereas the prevalence of microalbuminuria is 30-40% in diabetes mellitus population.[6]

The result of carotid ultrasound in this study is 48 subjects (67.6%) have increased carotid IMT and 23 subjects (32.4%) do not have increased carotid IMT. In 23 subjects (32.4%) with no increased of carotid IMT, 10 subjects (14.1%) has carotid plaque. This study showed the high prevalence of increased CIMT in TDM2 with no/minor complication.

Study measuring carotid IMT in patient with TDM2 in Cipto Mangunkusumo Hospital have been conducted previously by Mulya in 106 subjects without measuring chronic complication. He found the median value of RCCA IMT is 0.95 mm (0.520-0.382) and LCCA IMT is 0.93 mm (0.040-0.257).[7] This value is higher compared to our result. This is caused by exclusion criterias for study samples which excluded subjects with chronic complications.

Determinant Factors

Duration of DM is clinically proven to estimate increased of carotid IMT (p=0.089, OR: 3.4; CI 95% 0.828-13.963) and in this scoring system, the score of duration of DM ≥ 5 years is 1. Hypertension is statistically and clinically correlated with increased CIMT (p=0.01, OR 7.728; CI 95% 1.628-36.680) and the score of hypertension is 2.

Dyslipidemia also statistically and clinically correlated with increased CIMT (p=0.017, OR 7.381; 95% CI 1.425-38.217) and have score 1 in subject having LDL ≥100 mg/dL and/or dyslipidemia history or using statin or listed in medical report as having dyslipidemia. Other study from Viswanathan et al.[8] also found that LDL cholesterol is statistically and clinically significant risk factor for increased CIMT.[8] Contradictory with the pathophysiology, glycemic control represented by glycated hemoglobin (HbA1c) do not correlated with increased CIMT, so it is not further analyzed.

Albuminuria

Albuminuria has been known as a surrogate marker for systemic endothelial dysfunction. It can be used as one of determinants of CIMT. Albuminuria have significance in detecting increased carotid IMT (p=0.034, OR 5.385; CI 95% 1.141-25.43). IRAS study (The Insulin Resistance Atherosclerosis Study) has showed that albuminuria increases cerebrocardiovascular risk by increased carotid IMT. Albuminuria and increased carotid IMT are also related to insulin resistance.[4]

This result is linear with Chin-Hsun Chu et al.[9] who found that albuminuria correlated significantly with CIMT. Matsagoura et al.[10] also showed that albuminuria has a positive correlation with CIMT and as an independent predictor for CIMT.

Added Value of Albuminuria to CIMT

Result of AUC in analysis model without albuminuria is 0,871 and addition of albuminuria examination increase the discrimination to AUC 0,894. Addition of albuminuria to estimate carotid IMT is only 2,3%, therefore it is not included in the final model because is not cost-effective. In the scoring system, we only use three determinants (duration of DM, hypertension, and dyslipidemia).

Scoring System to Estimate CIMT

Scoring system is developed to help clinicians in screening for CIMT. From statistical analysis, probability range value is 0-4. Total score probability can be calculated with equation: $y = -2,491 + (1,389 \text{ x total score})$. Total score are classified to probability low, medium, and high. In sensitivity and specificity analysis to subject score, sensitivity is 94% and specificity is 70% to score higher than 2, means score higher than 2 have high probablity to increased CIMT.

Validation of Scoring System

Scoring system validation is conduct in minimum of 8 T2DM patients. This scoring system is applied to 15 T2DM out of study subjects according to inclusion and exclusion criteria with the result as **Table 5**.

Table 5. Table 2x2 scoring system with carotid IMT

Scoring system	Carotid IMT		Total
	Yes	No	
> 2	10	0	10
≤ 2	3	2	5
Total	13	2	15

From the result of analysis validation test, the sensitivity and specificity scoring system are 77% and 100%. By this good sensitivity and specificity, this scoring system can be applied as diagnostic screening tools.

Scoring System Cost-effectiveness

Cost-effectiveness comparison of scoring system and carotid ultrasound is showed on **Table 6**.

Table 6. Cost-effectiveness comparison of scoring system to carotid ultrasound

	Scoring system	Carotid ultrasound
Sensitivity	77%	93.4%
Specificity	100%	94%
Cost	USD 13	USD 80
Operator	Independent	Dependent
Time	Fast - Flexible	Slow
Application	Easy	Difficult

The comparison show that scoring system is more cost-effective compare to carotid ultrasound in clinical setting.

Scoring System Clinical Application

Scoring system that has been developed is a new diagnostic method that can be use as screening tools for detecting CIMT in T2DM patients which have not developed cerebrocardiovascular disease, CKD stage <3, and non-smoker. Patient with total score >2 could be followed up with carotid ultrasound for confirmation, atherosclerosis plaque examination, and carotid stenosis level.

Benefit and Limitation of the Study

Benefit of this research is to value the diagnostic estimation to carotid IMT. Study analysis for albuminuria added value have not been done before. In this study, we also make validation of scoring system to estimate increased carotid IMT in T2DM patients without major chronic complication. The main limitation in this study is limited sample and specific T2DM patients with no or early complication, so the result of this study can not be generalized into all T2DM population (especially to T2DM patients without history of cerebrocardiovascular event, CKD stage ≥ III, and smoker).

CONCLUSION

This study shows that the added value diagnostic albuminuria examination is only

2.3%. Determinant score for duration of DM, hypertension, and dyslipidemia are 1, 2, and 1, respectively. The probability of increased CIMT in score < 2, 2, and > 2 are 15%, 57%, and 90%.

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