CORRELATION OF HEMOGLOBIN A1c AND DIABETES RISK USING THE THAI DIABETES RISK SCORE

Wyn Parksook, Preamrudee Chaisuwirat **, Apussanee Boonyavarakul**

***Division of Endocrinology, Department of Internal Medicine, Phramongkutklao Hospital, Bangkok, Thailand**
**** Blood Bank, Army Institute of Pathology, Phramongkutklao Medical Center, Bangkok, Thailand**

Abstract

Background: Early detection of diabetes allows prompt access to interventions that can improve microvascular and macrovascular disease outcomes. Multiple strategies have been employed, i.e., the use of diabetes risk scores including blood testing.

Objective: The study aimed to evaluate the correlation between point-of-care hemoglobin A1c (POC HbA1c) and Thai diabetes risk score.

Methods: A cross-sectional study was conducted consisting of 252 individuals without diabetes over the age of 35. Demographic data and anthropometric measures were recorded and the blood test for POC HbA1c including plasma glucose were performed.

Results: Of 252 participants, the mean HbA1c was 5.56 ± 0.73%, the median Thai diabetes risk score was 7 [5-10] and American Diabetes Association (ADA) risk score was 3 [2.3-4]. Males had higher risk scores than females. Weak positive correlations were observed between POC HbA1c and both Thai and ADA risk score (r = 0.226 and 0.279, respectively, p<0.001). The predictors of higher HbA1c among males were high BMI and waist circumference.

Conclusion: A weak correlation of POC HbA1c and Thai diabetes risk score suggested that POC HbA1c may not be beneficial in screening diabetes in out-of-clinic situations; however, male participants with WC >100 cm and BMI >27.5 kg/m^2 were associated with highest HbA1c.

Keywords: Type 2 diabetes, Diabetes risk score, HbA1c, Point-of-care, Screening

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Correspondence to:
Parksook W, Department of Internal Medicine, Phramongkutklao Hospital, Bangkok, Thailand
E-mail: wynparksook@hotmail.com

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Introduction

Type 2 diabetes mellitus is one of more prevalent noncommunicable diseases with increasing prevalence yearly. The International Diabetes Federation (IDF) estimated that diabetes affected 463 million individuals globally.[1] In Thailand, the prevalence of diabetes among adults is 7.0% and is estimated to increase to 8.0% by 2045.[2] Of those affected, 43.6% remain unaware of their diabetic conditions.

Due to the silent nature of the disease, diabetes often goes undetected. The lack of adequate interventions and monitoring until late into the disease progression results in microvascular and macrovascular complications.[3] These include diabetic retinopathy, neuropathy, nephropathy and cardiovascular atherosclerosis. The chronic and additive clinical progression of diabetes means that cost of care increases over time, as demonstrated in a recent UK Prospective Diabetes Study (UKPDS) 84.[4] It would be prudent; therefore, to detect diabetes at the earliest phase so intervention result could reduce complications and mortality.

High risk screening for diabetes has been the mainstay strategy for early detection and has been adopted in a number of guidelines. The Thai Clinical Practice Guidelines for Diabetes 2017 has endorsed a risk score system devised by Aekplakorn et al.[5] This cohort study has good accuracy in predicting 12-year risk of new-onset diabetes (**Table 1**).[6] The maximum score is 17. When the score is 6 or more, further diabetes evaluation is warranted. Waist circumference and BMI are classified according to WHO definitions.

In the absence of risk factors, Thai guidelines also suggested blood tests for diabetes among individuals over the age of 35 with these following conditions: BMI ≥25 kg/m^2, increased waist circumference, first degree relatives having diabetes, hypertension, dyslipidemia, prior gestational diabetes (GDM) or when delivering a child >4 kg, cardiovascular disease or polycystic ovarian syndrome. [5] Studies in other countries validated diabetes risk scores that correlate to their specific populations. The American Diabetes Association (ADA) is one of the major guidelines in the US having its own risk score.[7]

Table 1. Type 2 diabetes risk score

Risk Factor	Diabetes Risk Score
Age	
34-39 years	0
40-44 years	0
45-49 years	1
≥50 years	2
Gender	
Female	0
Male	2
Body mass index (BMI)	
< 23 kg/m^2	0
23-27.5 kg/m^2	3
> 27.5 kg/m^2	5
Waist circumference	
Males<90 cm, Females <80 cm	0
Males ≥90 cm, Females ≥80 cm	2
Hypertension	
No	0
Yes	2
Family history DM	
No	0
Yes	4

Screening of diabetes requires elevated fasting plasma glucose (FPG) or fasting capillary blood glucose (FCBG) ≥126 mg/dL, which has to be repeated once.[7] However, hemoglobin A1c (HbA1c) has not yet been implemented in the Thai guidelines.[5] Alternatively, 75 g oral glucose tolerance test (OGTT) can be used which has higher sensitivity than fasting glucose.[8] However, due to its invasive and time-consuming nature, OGTT is not routinely practiced.

Diagnostic cut off points are similar in all guidelines, requiring two abnormal values for diagnosis. However, the accuracy of HbA1c can vary as over 300 different protocols are available to measure HbA1c.[9,10] The heterogeneity of HbA1c has been addressed and a number of organizations have endeavored to standardize HbA1c. This includes the National Glycohemoglobin Standardization Program (NGSP), International Federation of Clinical Chemistry (IFCC), Mono-S, and Japanese Society of Clinical Chemistry/Japanese Diabetes Society (JSCC/JDS). The IFCC-NGSP master equation is the current accepted standards for HbA1c.[11, 12] The limitation of diabetes screening and risk score use is they are usually evaluated at a doctor's clinic. Even when individuals have routine check-ups, not evaluating other risks and lifestyle, diabetes diagnosis can be missed.

The aim of this study was to evaluate the correlation between POC HbA1c and diabetes risk score, endorsed by the Thai diabetes clinical practice guidelines among blood donors. Additionally, the correlation between ADA diabetes risk score and the measured POC HbA1c was also investigated.

Methods

This study was approved by the Institutional Review Board, Medical Department, Royal Thai Army. Informed consent was signed by all study participants. Individuals, donating blood at the Blood Bank, Pathology Institute, Phramongkutklao Medical Center, were asked to participate in this study. According to the published IDF Diabetes, the prevalence of impaired glucose tolerance (IGT) was 15.5.[13] To calculate the sample size powered to include diabetes and IGT, a minimum of 202 individuals were necessary to provide a 95% confidence interval at the margin of error of 5%. The inclusion criteria were individual blood donors without type 2 diabetes, and aged 35 years or older who had given inform consent. Those who had prior diabetes, hemoglobinopathy, untreated hypothyroidism, chronic liver, chronic kidney diseases, prior splenectomy, received blood transfusion in the past four months, or routinely took supplements of iron, folic acid, vitamin B12 or vitamin E in the past three months were excluded.

All participants were asked to fill in a questionnaire designed to assess individual demographics, anthropometric and lifestyle measures. Blood collection was taken at the time of blood donor screening. Aside from the blood tests required for routine blood donation, hemoglobin, serum creatinine and POC HbA1c (cobas b 101, Roche Diagnostics) were also collected. The Thai diabetes risk score was derived from the study using Aekplakorn et al.[6] In addition, the ADA diabetes risk score was also used for comparison.

Definitions

Diabetes is defined as FPG ≥126 mg/dL,75 g OGTT ≥200 mg/dL, and HbA1c ≥6.5%. Prediabetes is defined as FPG 100-125 mg/dL, 75 g OGTT 140-199 mg/dL, and HbA1c 5.7-6.4%. Dietary control is defined as the self-perceived attitude in an individual's diet in glycemic and hypertensive control. Regular exercise is defined as regular physical activity for at least 30 minutes daily for three to five days weekly.

Statistical analysis

Statistical analysis was performed using SPSS Software, Version 23.0 (SPSS Inc, Chicago, USA) with significance at $p<0.05$. Normality of data was assessed using the one-sample Kolmogorov -Smirnov test. Normally distributed data were expressed as mean ± standard deviation (SD) and nonnormal data were expressed as median (interquartile range). Correlations were evaluated using two-tailed Pearson's tests. The Mann -Whitney test was used to analyze the differences between risk categories of the diabetes risk scores.

Results

A total of 273 individuals agreed to participate in the study. After excluding 21 participants having type 2 diabetes, 252 people were recruited in the study. Of these, 137 (54.4%) were male. The majority of participants (86.1%) did not fast before blood collection. None reported having chronic kidney disease, cardiovascular disease or stroke. No significant differences between sexes were found; however, male participants had higher diabetes risk according to both Thai and ADA scores. Baseline characteristics of participants are shown in **Table 2**.

Table 2. Baseline clinical characteristics of enrolled participants

	All Individuals (n = 252)	**Female Individuals (n = 115)**	**Male Individuals (n = 137)**
Clinical			
Age (years, mean ±SD)	44.2 ±7.28	44.23 ±7.10	44.1 ±7.45
≤ 44 years	151	69	82
45 - 49 years	44	18	26
≥ 50 years	57	28	29
Regular check up (N,%)	220 (87.3%)	98 (85.2%)	122 (89.1%)
Underlying disease (N,%)	16 (6.3%)	7 (6.1%)	10 (7.3%)
Hypertension	11	5	6
Dyslipidemia	7	3	4
Family history DM (N,%)	101 (40.1%)	48 (41.7%)	53 (38.7%)
Dietary control (N,%)	157 (62.3%)	73 (63.5%)	84 (61.3%)
Regular exercise (N,%)	106 (42.1%)	47 (40.9%)	59 (43.1%)
Current smoker (N,%)	44 (17.5%)	7 (6.1%)	37 (27.0%)
Current alcoholic (N,%)	89 (35.3%)	23 (20%)	66 (48.2%)
Pregnancy (N,%)		47 (40.9%)	
Prior GDM		5 (10.6%)	
Child >4 kg		2 (4.3%)	
BMI (kg/m^2, mean ±SD)	24.7 ±5.91	23.9 ± 6.31	25.4 ± 5.48
SBP (mmHg, mean ±SD)	133.6± 20.43	129.9 ± 21.5	136.6 ± 19.02
DBP (mmHg, mean ± SD)	78.9 ± 14.10	77.2 ± 14.3	80.35 ± 13.81
Laboratory Investigation			
Glucose (mg/dL, median [IQR])	93.0 [84-108]	93.0 [85-108]	94.0 [82.5-107.5]
HbA1c (%, mean ±SD)	5.56 ± 0.73	5.40 ± 0.70	5.57 ± 0.75
Hb (g/L, median [IQR])	14.5 [13.5-15.5]	13.7 ± 1.61	15.2 [14.5-15.9]
Creatinine (mg/dL, median [IQR])	0.88 [0.73-1.01]	0.73 [0.65-0.81]	0.98 [0.89-1.07]
eGFR (mL/min, median [IQR])	95.2 [83.7-105.9]	99.7 [84.0-108.5]	92.1 ± 15.3
Diabetes Risk Score			
Thai (median [IQR])	7.0 [5-10]	6.0 [4.0-9.0]	9.0 [5-11]
ADA (median [IQR])	3.0 [2.3-4.0]	3.0 [2.0-4.0]	4.0 [3.0-5.0]

DM, diabetes; GDM, gestational diabetes; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin

Data normally distributed expressed as means ± standard deviation; non-normally distributed expressed as median [interquartile range]

Table 3. Correlation between POC HbA1c and diabetes risk scores

HbA1c vs	Correlation	*p*-value
All individuals		
Thai	0.226	<0.001*
ADA	0.279	<0.001*
Female individuals		
Thai	0.228	0.014*
ADA	0.249	0.007*
Male individuals		
Thai	0.233	0.006*
ADA	0.318	<0.001*

Correlation using two-tailed Pearson's test
* Statistically significance at $p<0.05$

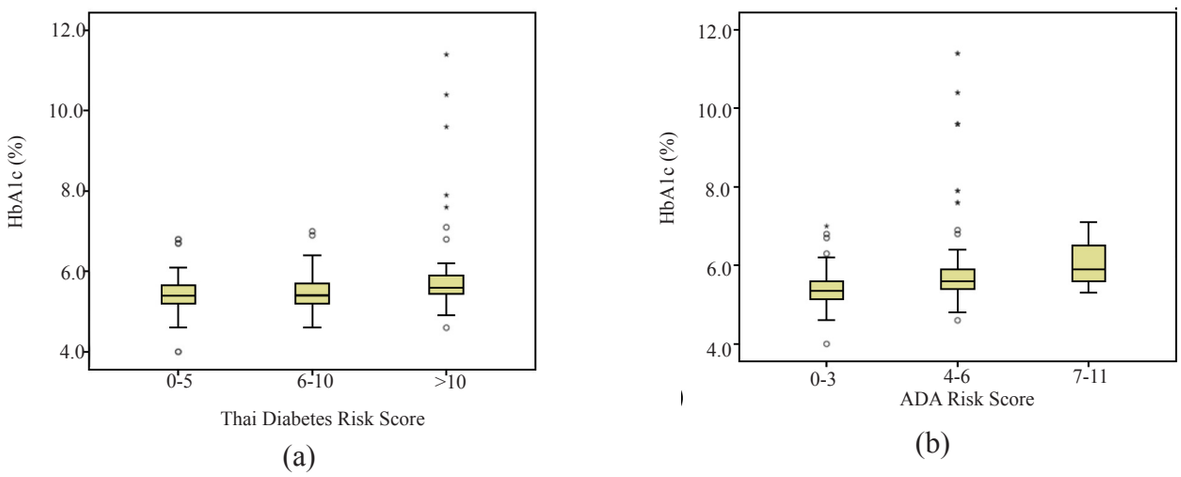

Figure 1. Changes in median, interquartile range, minimum and maximum HbA1c values of all participants in the associated risk categories of the (a) Thai diabetes risk score, and (b) ADA diabetes risk score

Correlation between POC HbA1c and diabetes risk scores

Weak positive correlations between POC HbA1c and both Thai and ADA diabetes risk scores were observed (**Table 3**). Subset analysis showed that POC HbA1c correlated with both male and female individuals. Higher correlation was observed when using the ADA risk score.

POC HbA1c values and risk prediction categories

Increasing diabetes risk scores were associated with higher POC HbA1c. Among all individuals, lower Thai risk scores were associated with lower HbA1c while higher scores were associated with higher HbA1c, many of which appeared outside the 1SD, identified as outliers (**Figure 1**). No significant differences were identified between lower and moderate scores using the Thai score. For the ADA risk score, however, individuals with moderate scores (4-6 points) showed the greatest variability in HbA1c with the highest HbA1c identified in this subgroup.

Male individuals showed similar findings concerning the analysis among all participants. The median HbA1c for high risk Thai and high risk ADA scores were 5.6% and 5.9%, respectively (**Figure 2**). High risk categories other than median HbA1c were highest for both Thai and ADA scores. For females, high risk category was associated with the highest HbA1c. However, no subjects were categorized as high risk. The median HbA1c for high-risk Thai and moderate-risk ADA scores were 5.75% and 5.7%, respectively (**Figure 3**).

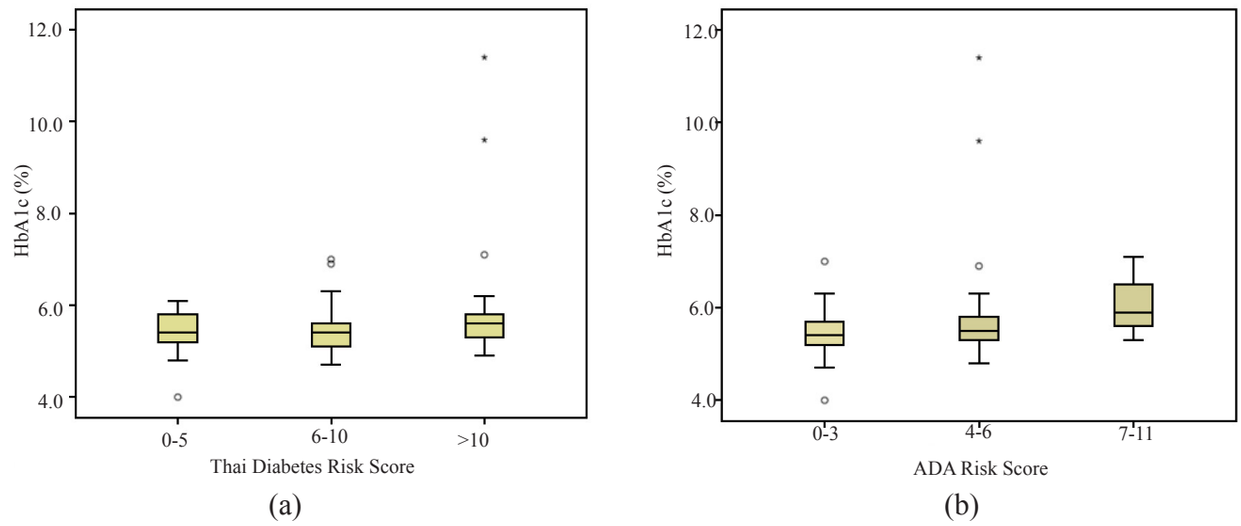

Figure 2. Changes in median, interquartile range, minimum and maximum HbA1c values of male participants in the associated risk categories of the (a) Thai diabetes risk score, (b) ADA diabetes risk score

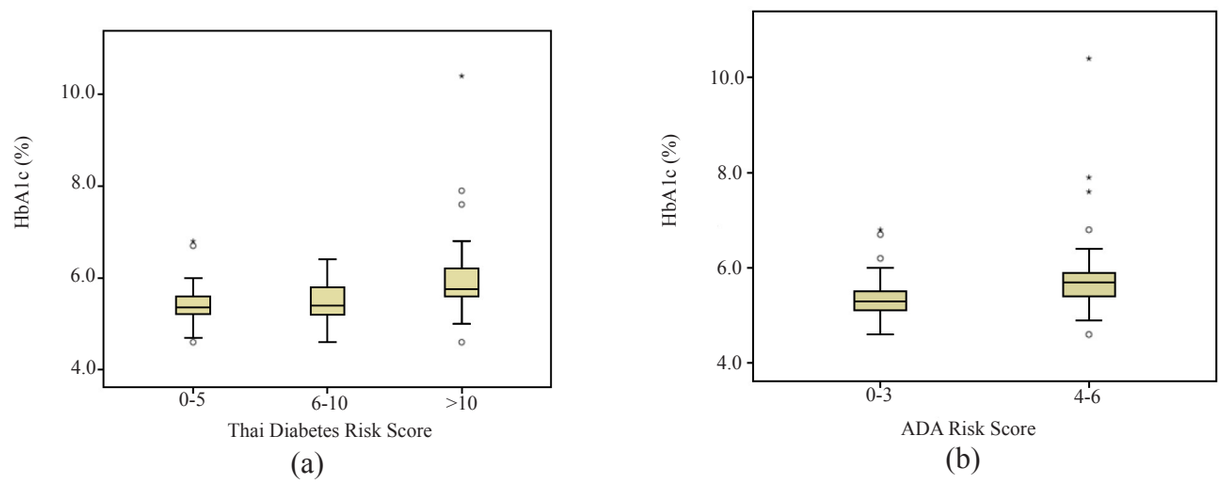

Figure 3. Changes in median, interquartile range, minimum and maximum HbA1c values of females in the associated risk categories of the (a) Thai diabetes risk score, (b) ADA diabetes risk score

Further analysis of the associations between HbA1c and other categorical factors were analyzed. Of all the anthropometric factors, waist circumference >90 cm among males ($p = 0.016$), BMI ≥27.5 ($p = 0.002$), and Thai diabetes risk score >10 ($p = 0.026$) were associated with the highest HbA1c. In multivariate analysis, waist circumference and BMI remained associated with high HbA1c.

Discussion

Early case detection of diabetes has been a key challenge in clinical practices. This study aimed to screen for diabetes in the out-of-clinic setting during blood donation, using diabetes risk scores, POC HbA1c and plasma glucose. The primary outcome showed a weak positive correlation between POC HbA1c and the Thai diabetes risk score. However, the association between HbA1c and diabetes risk has long-been established in related studies. [14, 15] This constituted the first time that POC HbA1c was used to study the correlation to Thai risk score.

POC HbA1c is a relatively recent development in testing glycated hemoglobin, using charge and structural differences of red blood cells to differentiate HbA1c values.[9] Although accuracy of POC systems is inferior to traditional blood samples[16-18], they offered greater access to immediate test results. POC HbA1c has been used

in a number of countries and has shown benefits in glycemic control. It facilitates treatment intensification by allowing immediate HbA1c results.[19] This has led to improved HbA1c by 0.5% over three months. However, paucity of data was found using POC HbA1c diabetes screening.[20] At the present time, the only US FDA-approved POC HbA1c is the Afinion HbA1c Dx Assay while many more are in development. Currently, the ADA and Thai guidelines do not recommend using POC HbA1c instead of HbA1c. Interestingly, a Thai study in testing POC HbA1c among individuals undergoing a dental procedure showed up to 33.8% of individuals presented POC HbA1c ≥5.7%.[21] In addition, a recent study in Indonesia revealed that the use of POC HbA1c showed potential in diagnosing diabetes with a sensitivity of 97% and specificity of 77%.[22]

One notable strength of this study was comparing Thai and ADA guidelines. The correlations demonstrated the validity of the two risk scores. However, the correlation appeared weak and may reflect on the POC system not being as accurate as the standard HbA1c. The other possibility would be the validity of risk scores themselves as demographics may change over the years, leading to a shift in risk score associations. For this study, comparison of the POC HbA1c and serum HbA1c was not available and thus might have reflected on the reliability of the POC HbA1c.

The other main difference in the study was using the out-of-clinic design. The majority of evidence in published literature is limited to in-clinic settings. However, the difference should not affect the HbA1c used as the main measure of this study.

Despite the weak correlation observed, one of the notable associations observed in this study were BMI and waist circumference. Obesity is a disease with rising prevalence and has close links with type 2 diabetes and metabolic syndrome. The Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD) and the National Health and Nutrition Examination Surveys (NHANES) showed that increased BMI was associated with increased prevalence of type 2 diabetes, hypertension, and dyslipidemia.[23] For this study, the association of higher HbA1c was likely to be driven by obesity.

Furthermore, the correlations were shown to be more significant in the higher risk group, while the lower risk group showed little difference. Individuals prone to develop diabetes often have multiple factors at play, as well as having IFG, IGT or both as risk enhancers. However, this study was unable to measure fasting glucose or OGTT and hence was unable to confirm this hypothesis. Interestingly, the ADA diabetes risk score showed significant heterogeneity in HbA1c results while Thai scores did not. This was likely due to fundamentals in the design of the scoring system itself to correlate with a specific population and would suggest that ADA may not be a validated tool for practical use in Thai populations.

Limitations in this study included firstly, the majority of participants did not have fasting glucose levels. General recommendations from the Blood Bank suggest having food before blood donation. Therefore, correlating HbA1c with FPG was not possible, and subsequently not possible to definitely diagnose diabetes according to the new recommendations from ADA. Secondly, the nature of this cross-sectional design was the lack of causality. Also, unlike related cohorts that could predict future risk of diabetes, this study was not designed to evaluate future risk. Thirdly, the use of POC HbA1c did not have a standard serum HbA1c to correlate the findings. Related studies have shown that POC HbA1c was comparable to standard HbA1c, albeit with slightly lower accuracy. Adding the standard HbA1c to the protocol would improve the credibility of the data in this study.

In summary, the weak correlations observed in this study may have suggested that the use of POC HbA1c as a screening tool for diabetes in the out-of-clinic setting is less likely to be of benefit.

Conclusion

Higher Thai diabetes risk score was associated with higher HbA1c. This association was valid for both HbA1c and POC HbA1c. Because of the more rapid test results, POC HbA1c may be more suitable for use in-clinic than out-of-clinic

situations especially among individuals with risk scores >10. Higher BMI and waist circumference are predictors of higher POC HbA1c and may warrant earlier and more comprehensive testing.

Disclosures

The authors declare they have no conflicts of interest.

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