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Research Article

Estimated HbA1c as an Index for Diabetes and Prediabetes Screening

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Abstract

Purpose: Different questionnaires have been suggested for the screening of diabetes mellitus. Values of these questionnaires for prediabetes screening is not clear. The aim of this study was to develop a new indicator-estimated value for screening HbA1c (ScrHbA1c), for diabetes mellitus and prediabetes screening.

Methods: 182 persons (46 men and 136 women) aged 20 - 79 years were examined by using questionnaires for diabetes, anthropometry, and blood pressure determination. A 2-hour glucose tolerance test (75g of glucose) was performed. The HbA1C examined by the SDA1c Care (SD biosensor, Korea). Fasting and post load venous plasma glucose was determined by Precision PCx Medi Sense (Abbot, USA). Anamnesis score, age, waist circumference, systolic and diastolic blood pressure was used in the calculation of the ScrHbA1c index by multiple linear regression method. Chi-square tests were applied to compare categorical variables. Qualitative characteristics of the diagnostic test as Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, Overall Diagnostic Accuracy and Youden Index were used for the evaluation of cut-off point for ScrHbA1c index.

Results: There was statistically significant correlation ($p < 0.001$ in all cases) between the real HbA1c and ScrHbA1 in training group ($n = 91$; $r = 0.5462$), as in control group ($n = 91$; $r = 0.5140$) and in total study group ($n = 182$; $r = 0.5245$). The ScrHbA1c values in the training group and in the control group were significantly higher ($p < 0.001$ in both cases) in individuals with impaired glucose metabolism (Diabetes + Prediabetes) than in individuals without normal glucose metabolism. The values of the ScrHbA1c index did not significantly differ when comparing individuals with normal glucose metabolism (or impaired glucose metabolism) in training group and in control group ($p < 0.05$).

Conclusion: The new indicator - Estimated value for screening HbA1c named ScrHbA1c has been developed to select individuals who need to be screened for diabetes and prediabetes. The use of the cut-off point 44 mmol/mol allows to identify 100% of patients with diabetes mellitus, 69.6% of prediabetes cases and requires examination of 20% persons without carbohydrate metabolism disorders.

Keywords: *Estimated Value for Screening HbA1c Index; Prediabetes; Diabetes Mellitus; Questionnaires; Screening*

Abbreviations

AAEDTE: Azerbaijan Association of Endocrinology, Diabetology and Therapeutic Education; ADA: American Diabetes Association; Ag: Age in Years; AS: Anamnesis Score; BMI: Body Mass Index; CG: Control Group; DBP: Diastolic Blood Pressure; DM: Diabetes Mellitus; IGM: Impaired Glucose Metabolism; NGM: Normal Glucose Metabolism; OGTT: Oral Glucose Tolerance Test; PD: Prediabetes; SBP: Systolic Blood

Pressure; ScrHbA1c: Estimated Value for Screening HbA1c; TG: Training Group; TSG: Total Study Group; WC: Waist Circumference

Introduction

The dramatic increase in diabetes mellitus (DM) and its complications prevalence leads to an exorbitant increase in the burden of this disease [1-3].

Prediabetes (PD) is a mandatory stage in the development of DM. One in three people in the USA has PD [4,5].

Development of the macrovascular [6], microvascular [7-9] and neurological [10] diabetes complications can begin already at the stage of PD. The encouraging factor is that during PD it is possible to reverse to normal glucose metabolism (NGM), and it may be the result of lifestyle modification [11] and/or pharmacological intervention [12], or spontaneous changes [13].

Early detection of DM is possible by screening of this disease [14]. A number of questionnaires have been proposed to identify people with an increased risk of DM [15-20]. Some of these questionnaires are also suggested for the screening of PD [16,17], but at the present time it is not entirely clear whether these questionnaires are applicable for prediabetes screening or not.

Aim of the Study

The aim of the study was to develop a new indicator for DM and PD screening, based on age, blood pressure, anthropometric and anamnestic data.

Materials and Methods

Subjects and clinical examination

A selection from Azerbaijan Association of Endocrinology, Diabetology and Therapeutic Education (AAEDTE) database was created to conduct this research. The total group consisted of 182 cases (46 men and 136 women) who had previously passed the required examination, which included:

- Age from 20 to 79 years;
- The responses to the questionnaires for screening of diabetes American Diabetes Association Risk Calculator (ADA) [16], The Australian type 2 diabetes risk assessment tool (AUSDRISK) [20], The Canadian diabetes risk questionnaire (CANRISK) [18], Finnish Diabetes Risk score (FINDRISC) [19];
- Registration of anthropometric data: height, weight, waist circumference (WC). Body Mass Index (*BMI)* was calculated dividing the weight (kg) by the height in meters squared (m^2) and evaluated by the classification of World Health Organization [21];
- Office blood pressure measurement;
- Laboratory examination.

Laboratory examination included the study of glycohemoglobin (HbA1c) by the SDA1c Care (SD biosensor, Korea) and venous plasma glucose by Precision PCx Medi Sense (Abbot, USA). Fasting glucose and 2-hour oral glucose tolerance test (OGTT) (75 g glucose) samples (at 30, 60, 90,120 minutes) were measured.

Diagnosis of prediabetes and diabetes was carried out in accordance with the proposed for discussion AAEDTE Standards [22], presented in table 1.

Parameter	Norma	Prediabetes	Diabetes mellitus
HbA1c	≤ 5,6% (≤ 38 mmol/mol)	5,7-6,4% (39 - 47 mmol/mol)	≥ 6,5% (≥ 48 mmol/mol)
Fasting glucose	< 110 mg/dl (< 6.1 mmol/l)	110 - 125 mg/dl (6.1 - 7.0 mmol/l)	≥126 mg/dl (≥7.0 mmol/l)
OGTT 120 min glucose	≤ 139 mg/dl (≤ 7.7 mmol/l)	140 - 199 mg/dl (7.8 - 11.0 mmol/l)	≥ 200 mg/dl (11.1 mmol/l)

Table 1: *Diagnostic criteria for diabetes mellitus and prediabetes according to AAEDTE [22].*

DM was detected in 36 persons, PD - in 46 cases and NGM - in 100 persons.

We focused on the variables that are needed for the screening of DM and PD. Both simple indicators and their combinations were analyzed. The total number of analyzed indicators was 288. As a result, the following indicators were selected to calculate the Estimated value for screening HbA1c (ScrHbA1c) index: anamnesis score (AS), age in years (Ag), waist circumference (WC) in cm, systolic blood pressure (SBP) and diastolic blood pressure (DBP) in mmHg.

The procedure for using of these indicators and calculation of ScrHbA1c index was published earlier [23].

Subsequently, the patients of the total group (n = 182) were randomly assigned to 2 groups: The Training Group (TG) (n = 91) and the Control Group (CG) (n = 91).

Based on the TG data, the ScrHbA1c index was to be created and applied. The CG was necessary for the objective control over the developed methodology, and for this reason CG in composition was as close as possible to TG.

As it is seen from table 1, TG and CG did not differ significantly in age, sex, height, weight, WC, BMI, SBP, DBP, HbA1c, fasting glucose, OGTT 2-hour glucose. Differences between two groups in frequency of normal body weight, overweight, and obesity, including obesity I, obesity II, and obesity III, were not statistically significant (in all cases, $p > 0.05$).

The average values ± Standard Deviation are presented in this article. The statistical significance of the differences between the average values was determined by the Student's T-test. Chi-square tests were applied to compare categorical variables [24]. A correlation analysis of the relationship between HbA1c and various anamnestic, anthropometric indicators, SBD, and DBP was performed [25]. ScrHbA1c index was developed using the multiple linear regression method [26].

To determine the qualitative characteristics of the diagnostic test, the following indicators were used: Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, Overall Diagnostic accuracy and Youden Index [27,28].

Results

There were equal numbers of men (n = 23; 25.3%) and women (n = 68; 74.7%) in TG and CG. Numbers of DM cases (n = 17; 18.7%), PD (n = 24; 26.4%), and NGM (n = 50; 54.9%) in TG and CG also were equal.

The main characteristics of TG and CG are presented in table 2.

Parameter	Training group (n = 91)	Control group (n = 91)	P value
Age in years (M ± SD)	50.1 ± 14.86	51.5 ± 14.69	> 0.05
Height in cm (M ± SD)	163.2 ± 8.84	162.9 ± 9.07	> 0.05
Weight in kg (M ± SD)	81.1 ± 19.06	78.2 ± 17.88	> 0.05
WC in cm (M ± SD)	97.2 ± 14.10	94.7 ± 14.30	> 0.05
BMI in kg/m^2 (M ± SD)	30.6 ± 7.11	29.5 ± 6.04	> 0.05
Normal weight (n; %)	18 (19.8)	17 (18.7)	> 0.05
Overweight (n; %)	30 (33.3)	38 (41.8)	> 0.05
Obesity (n; %)	43 (47.3)	36 (39.6)	> 0.05
Obesity I (n; %)	23 (25.3)	18 (19.8)	> 0.05
Obesity II (n; %)	14 (15.4)	13 (14.3)	> 0.05
Obesity III (n; %)	6 (6.6)	5 (5.5)	> 0.05
SBP in mmHg (M ± SD)	130.5 ± 18.97	82.5 ± 10.60	> 0.05
DBP in mmHg (M ± SD)	129.8 ± 17.99	82.3 ± 10.70	> 0.05
HbA1c (mmol/mol)	41.0 ± 15.60	41.0 ± 15.42	> 0.05
Fasting glucose (mg/dl)	115.4 ± 49.90	114.5 ± 41.14	> 0.05
OGTT 2-hour glucose	134.3 ± 52.19	134.5 ± 53.60	> 0.05

Table 2: *Training group and control group characteristics.*

Calculation of the ScrHbA1c index

ScrHbA1c index (mmol/mol) was calculated by the using the following equation:

$ScrHba1c = 6.3573 - X_1 \times 0.0032 + X_2 \times 0.1176$

where:

$X_1 = Y_1 + Y_2 + Y_3 + Y_4 + Y_5$;

$X_2 = Y_6 + Y_7 + Y_8 + Y_9 + Y_{10}$;

"+" - addition sign; $Y_1 = 10LN(a * b)$; $Y_2 = 10LN(a * c)$; $Y_3 = 10LN(a * d)$;

$Y_4 = 10LN(b * c)$; $Y_5 = 10LN(b * d)$; $Y_6 = 10LN(a * e)$; $Y_7 = 10LN(b * e)$;

$Y_8 = 10LN(f * e)$; $Y_9 = 10LN(c * e)$; $Y_{10} = 10LN(d * e)$; "*" - multiplication sign;

a - age in years; b - WC in cm; c -SBP in mmHg; d - DBP in mmHg;

e - Anamnesis Score (AS); f - BMI in kg/m^2;

$e = 2.61 - G_1 * 1{,}61 + G_2 * 7.43 + G_3 * 1.89 + G_4 * 14.10$

The features (and their scores) presented in table 3 were used for Anamnesis Score (AS) calculation.

Anamnestic feature	Explanation	Score in points	
		Yes	No
Physical activity (G_1)	At least 30 minutes of physical activity every day at work and/or during leisure time [19]	1	0
History of arterial hypertension (G_2)	Use of blood pressure medication and/or history of high blood pressure [19]	1	0
Family history of DM (G_3)	Was restricted to first relatives only [16]	1	0
History of gestational DM (G_4)	Diagnosed with gestational diabetes in women during pregnancy or the birth of a large baby weighing 4.1 kg or more [16,18]	1	0

Table 3: *Features (and their scores) using for Anamnesis Score (AS) calculation [16,18,19].*

Data on the correlation between real and HbA1c are shown at figure 1.

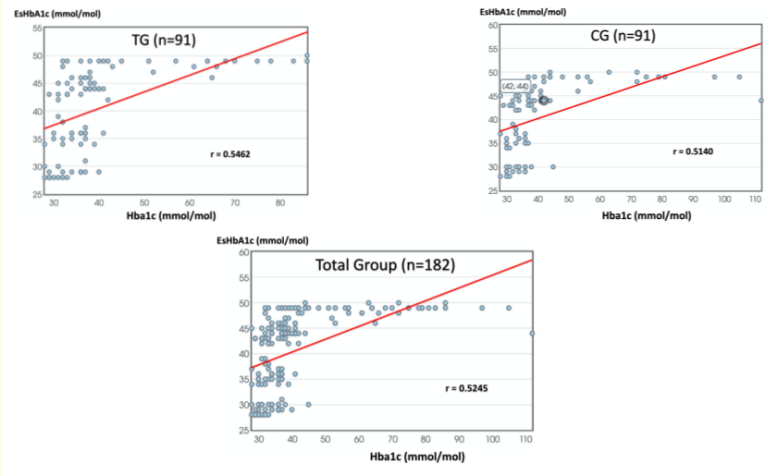

Figure 1: *Correlation between real HbA1c and ScrHbA1c.*

As it is seen from figure 1, there was statistically significant correlation ($p < 0.001$ in all cases) between the real HbA1c and ScrHbA1 in TG ($r = 0.5462$), as in CG ($r = 0.5140$) and in total group ($r = 0.5245$).

The average values of the real HbA1c and ScrHbA1 did not differ in TG (40.6 ± 13.68 mmol/mol and 40.6 ± 13.24 mmol/mol, respectively). These values differed slightly in CG (41.4 ± 1.77 mmol/mol and 40.5 ± 0.76 mmol/mol respectively; $p > 0.05$).

The differences between each real HbA1c and ScrHbA1 were 19.6 ± 13.97% in TG and 19.4 ± 13.24% in CG.

Figure 2 shows data on the average levels of ScrHbA1c in individuals with NGM and IGM in two analyzed groups.

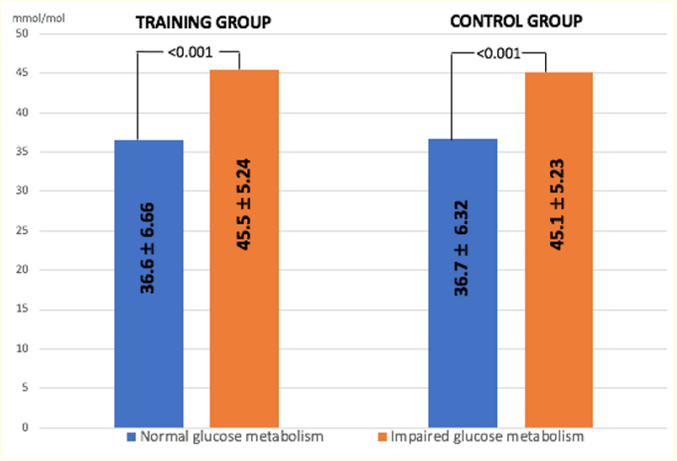

Figure 2: *The average levels of ScrHbA1c in individuals with NGM and IGM in two analyzed groups.*

As can be seen from figure 2, the ScrHbA1c values in the TG and in the CG were significantly higher from the statistical point of view ($p < 0.001$ in both cases) in individuals with IGM (45.5 ± 5.24 mmol/mol and 45.1 ± 5.23 mmol/mol, respectively) than in individuals without glucose metabolism disorders (36.6 ± 6.66 mmol/mol and 36.7 ± 6.32 mmol/mol, respectively). At the same time, the values of the calculated A1c did not significantly differ when comparing individuals with NGM and IGM in these two groups ($p < 0.05$).

The cut-off point was found after the TG and CG were combined into a TSG (n = 182).

Figure 3 shows data on the detectability of glucose metabolism disorders (DM + PD), and the percentage of healthy people who should not be examined when using various ScrHbA1c cut-off points.

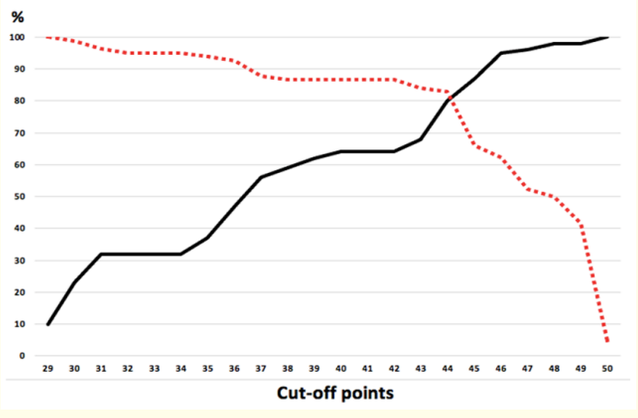

Figure 3: *Detectability of glucose metabolism disorders (DM + PD), and the percentage of healthy people who should not be examined when using various ScrHbA1c cut-off points. Total group data.*

People with normal glucose metabolism who should not be examined when using various ScrHbA1c cut-off points.

People with impaired glucose metabolism (DM + PD) who should be diagnosed after examination

As can be seen from figure 3, at the cut-off point of 29 mmol/mol, all 100% of cases of DM and PD will be detected during the subsequent examination. At the same time, it will be necessary to examine 90% of people with normal glucose metabolism. At the cut-off point of 50 mmol/mol, no person with normal glucose metabolism will have to be examined, but no cases of DM and PD will be detected. Thus, it is necessary to find a point between the cut-off points of 29 mmol/mol and 50 mmol/mol, which will identify all patients with DM and the maximum number of people with PD without exceeding the reasonable limits of people with normal glucose metabolism to be examined. The number of DM patients who will be detected becomes less than 100% at the cut-off point of 44 mmol/mol and higher. The number of PD people who will be detected becomes less than 100% at the cut-off point of 29 mmol/mol and comes to 0% at cut-off point 50 mmol/mol.

Table 4 shows the data on the qualitative characteristics of the ScrHbA1 test when various cut-off points are used.

Cut-off point	Characteristics of the test when proposed cut- off point applying to form a group of people to be examined for DM and PD					
	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Overall Diagnostic accuracy	Index Jouden
39	86.6	62.0	65.1	84.9	73.1	48.6
40	86.6	64.0	66.4	85.3	74.2	50.6
41	86.6	64.0	66.4	85.3	74.2	50.6
42	86.6	64.0	66.4	85.3	74.2	50.6
43	84.1	68.0	68.3	84.0	75.3	52.1
44	82.9	80.0	77.3	85.1	81.3	62.9
45	65.9	87.0	80.6	75.7	77.5	52.9
46	62.2	95.0	91.1	75.4	80.2	57.2
47	52.4	96.0	91.5	71.1	76.4	48.4

Table 4: *Characteristics of the ScrHbA1 test when using different cut-off points.*

Table 4 shows cut-off points from 39 to 47. It is well known that for diagnostics it is advisable to use those tests which have the Youden Index below 50.0% [27,28]. In this regard, the use of cut-off points 39 and 47 should not be considered. The others presented in the cut-off points table should be discussed to select the optimal one.

Discussion

A new indicator for the screening of DM and PD named ScrHbA1c and based on age, blood pressure, anthropometric and anamnestic data has been developed.

Values of this indicator correlates with the values of the real HbA1c.

The value of ScrHbA1 cut-off point 44 mmol/mol means that those who have not reached it are considered healthy and are not subject to examination. Others should be examined. This point is characterized by maximum Youden Index (62.9%), by the highest (81.3%) Overall Diagnostic Accuracy. Such characteristics as Sensitivity (82.9%), Specificity (80.0%), Positive Predictive Value (77.3%), Negative Predictive Value (85.1%), although not the maximum, are at the same time quite high. Cut-off point "44 mmol/mol" is characterized by both a minimal spread in the values of qualitative indicators (SD = 8.0) and an average value of the six analyzed qualitative indicators (78.3%). ScrHbA1c cut-off point 44 mmol/mol provides 100% diagnosis of DM during subsequent examination.

At this cut-off point it is necessary to conduct a survey of a small amount (20%) of people who do not have disorders of glucose metabolism. Only 69.5% of cases of PD are detected.

Perhaps even more promising points can be considered 38 mmol/mol - 43 mmol/mol. However, a speculative discussion of which point is optimal is hardly appropriate at a time when there are powerful mathematical possibilities for objectifying the assessment of the qualitative characteristics of diagnostic tests [28]. The results of the application of this mathematical apparatus with the determination of sensitivity, specificity, Positive Predictive Value, Negative Predictive Value, Overall Diagnostic Accuracy and others will be the subject of further publications.

Conclusion

The new indicator - Estimated value for screening HbA1c named ScrHbA1c has been developed to select individuals who need to be screened for diabetes and prediabetes. The use of the cut-off point 44 mmol/mol allows to identify 100% of patients with diabetes mellitus, 69.6% of prediabetes cases and requires examination of 20% persons without carbohydrate metabolism disorders.

Conflict of Interest

There is no any financial interest and conflict of interest to declare.

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