Comparing the Diagnostic Accuracy of HbA1c for Pre-Diabetes and Diabetes Between Foreign-Born and Swedish-Born Primary Healthcare Patients

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Research article

Keywords: HbA1c, diagnostic accuracy, pre-diabetes, diabetes, OGTT, region of birth

DOI: https://doi.org/10.21203/rs.3.rs-228530/v1

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Abstract

Background

The aim of this study was to compare the diagnostic accuracy of HbA1c in detecting individuals with abnormally elevated blood glucose levels between foreign-born and Swedish-born primary healthcare patients. The secondary aim was to approximate appropriate HbA1c cut off values for the different populations to yield better sensitivity and specificity.

Methods

Data analysed in this study was collected in the Programme 4D (Four Diagnoses). Patients aged 18-74 years visiting Flemingsberg and Jakobsberg healthcare centres between years 2013-2015 were inquired about inclusion in the study. Exclusion criteria included having a diagnosis of diabetes. Screening included HbA1c, OGTT (including fasting plasma glucose) and questionnaires regarding country of birth as well as prediabetes/diabetes risk assessment questionnaires. In order to calculate diagnostic accuracy of HbA1c-testing, subjects with either both OGTT and HbA1c results and both fP-glucose and HbA1c results were included in the calculation. This totalled in 757 out of the 830 patients.

Results

Only 22 of 623 patients had elevated results on all three tests. For Swedish-born patients an HbA1c cut off of 42 mmol/mol yielded 12.7% sensitivity and the ROC (Receiver Operating Curve) analysis gave an AUC (Area Under Curve) of 0.756 (0.702-0.810 [95% CI]). For foreign-born patients, an HbA1c cut off value of 42 mmol/mol yielded 19.7% sensitivity and the ROC analysis gave an AUC of 0.6975 (0.646-0.749 [95% CI]).

Conclusions

The diagnostic accuracy for HbA1c in detecting prediabetes and diabetes might be better for the Swedish-born than the foreign-born group. For both groups, an HbA1c cut off value of 34 mmol/mol would yield a sensitivity of >70% which can be considered for further investigation. Comparing the AUC for the two groups might indicate greater diagnostic accuracy for the test in the Swedish-born population than the foreign-born population.

Significance Of This Study

What is already known about this subject?

- Drawbacks of HbA1c testing include differing levels of glycation in different ethnic groups leading to it poorly reflecting levels of hyperglycaemia in some groups.
- Higher levels of HbA1c in black Americans than white, even after adjusting for fasting plasma glucose.
- Lower sensitivity for HbA1c testing to detect prediabetes and diabetes in Asian populations compared to Caucasians

What are the new findings?
The ROC-analyses show that the diagnostic accuracy for HbA1c in detecting prediabetes and diabetes might be better for the Swedish-born than the foreign-born group.

For both Swedish-born and foreign-born patients an HbA1c cut off value of 34 mmol/mol would yield a sensitivity of >70%.

**How might these results change the focus of research or clinical practice?**

- We suggest that the usage of an HbA1c cut off value of 34 mmol/mol can be considered for further investigation.

**Background**

*Diabetes and pre-diabetes*

Type 2 diabetes (T2DM) is one of the world’s most common medical conditions. The prevalence of diabetes is estimated to rise globally, from 8% in 2019 to 10% in 2045 with T2DM accounting for about 90% of all cases of diabetes [1]. In Sweden it is estimated that 500 000 people, about 4% of the population, have diabetes and that one third of all individuals with T2DM are unidentified [2]. This indicates that reliable screening and testing needs to be further researched to identify individuals at risk of developing diabetes. If these individuals who are at risk of developing T2DM are detected in time the progression of the condition can be halted through lifestyle interventions [3-6].

Clinically used tests for diagnosing diabetes include fasting plasma glucose (fP-glucose), oral glucose tolerance test (OGTT) and Glycated haemoglobin (HbA1c). A fasting plasma glucose is a simple venous or capillary glucose test performed on a fasting patient. Alternatively, an OGTT can be performed. In an OGTT a fasting patient will drink a solution of glucose and water, plasma glucose is measured at minutes 0 and 120. HbA1c value is a way to estimate long-term blood glucose levels; it represents the average blood sugar levels over the past three months. A big advantage of HbA1c testing over the other two is that it is a quick and simple test that do not require the patient to be fasting. HbA1c values are, in contrast to OGTT and fasting glucose, not affected by stress or nicotine/caffeine intake. Drawbacks of HbA1c testing include differing levels of glycation in different ethnic groups leading to it poorly reflecting levels of hyperglycaemia in some groups. Studies conducted on US populations show higher levels of HbA1c in black Americans than white, even after adjusting for fasting plasma glucose [7]. A Canadian study shows lower sensitivity for HbA1c testing to detect pre-diabetes and diabetes in Asian populations compared to Caucasians [8]. OGTT is out of the three the most reliable way of diagnosing diabetes and is a good way of detecting abnormal glucose tolerance, especially in asymptomatic patients. Using only fasting plasma glucose up to 30% of undiagnosed diabetics will remain undetected. The obvious drawback of OGTT is the fact that it is a time-consuming test, both for the patient and the clinic. It can also cause discomfort and nausea, especially for undiagnosed diabetics where hyperglycaemia may occur.

Risk factors for developing T2DM include hypertension, hyperlipidaemia, obesity and being born in the Middle East, Asia or in Africa [9-11]. In particular, individuals originating from Middle Eastern countries, one of the largest immigrant groups in Sweden, are at elevated risk of developing T2DM [10, 12]. Pre-diabetes is another important risk factor. It is a term used to conveniently identify individuals with impaired glucose metabolism.
and it is estimated that 15-30% of individuals with pre-diabetes will develop diabetes within five years [12]. According to Stockholm's Diabetes Prevention Program (SDPP) the prevalence of pre-diabetes is four and seven percent for 35-55-year-old women and men respectively.

Following WHO (World Health Organisation) recommendations [13], pre-diabetes is defined by Swedish guidelines as either [14]: 1) IFG (impaired fasting glucose) - fP-glucose of 6.1-6.9 mmol/L and 2) IGT (impaired glucose tolerance) - 75g OGTT (oral glucose tolerance test) with a venous glucose of 7.8-11.0 mmol/L after 2 hours.

In accordance to WHO guidelines, HbA1c levels are not used in Sweden to define pre-diabetes. However, an HbA1c of 42-47 mmol/mol can be used to define an “at risk” population that need to be further tested with OGTT/FPG [13, 14]. In contrast to WHO guidelines which only include the usage of OGTT and FPG to define pre-diabetes, ADA (American Diabetes Association) additionally use HbA1c levels to define pre-diabetes [15]. The cut off values and criteria also vary considerably between the two organisations. ADA defines pre-diabetes as the following: OGTT result of 7.8-11.0 mmol/mol, FPG result of 5.6-6.9 mmol/mol, and HbA1c levels of 39-47 mmol/mol. While the thresholds for OGTT are the same for both WHO and ADA, the cut off for FPG levels is lower by ADA guidelines. The HbA1c cut off value is also lower for ADA than the “at risk” levels defined by WHO, 39-47 mmol/mol compared to 42-47 mmol/mol. It is unclear which criteria are best suited for identifying individuals with pre-diabetes, the varying diagnostic criteria are however important to regard when comparing incidence and prevalence rates between studies [14, 15].

Lifestyle changes in individuals with pre-diabetes have been shown to be successful in lowering the risk of developing T2DM [5, 6, 16-21]. Intervention during prediabetic stages can normalize the blood levels of glucose and significantly reduce the risk of T2DM in these patients. American studies show that the implementation of programs promoting lifestyle changes in populations at high risk for developing T2DM is a cost-effective way of preventing T2DM and thereby reducing future healthcare costs. If these results are transferable to a Swedish population is yet to be investigated [4, 22].

A Swedish study published in 2015 showed that screening for a HbA1c value of ≥42 mmol/mol only detected 16% of patients with IGT (diagnosed by OGTT). Meanwhile, the mean HbA1c levels for patients with IGT was 36.3 mmol/mol and for patients with IFG was 37.9 mmol/mol. However, for patients with an HbA1c value of >42 mmol/mol the specificity for IGT was 0.94. This study was conducted on a randomized population from the two smaller Swedish communities, Vara and Skövde. The final population consisted of 573 participants of which less than 10% were of non-European origin [23]. Another Swedish study using four cohorts including patients with Middle-Eastern ancestry and Swedish origin concluded that an HbA1c is insensitive screening tool: third of those with diabetes were detected by HbA1c≥48 mmol/mol, a third of those with pre-diabetes were detected by HbA1c≥39 mmol/mol and a HbA1c≥42 mmol/mol would detect only 15% of those with pre-diabetes [24]. Other studies have also shown a disparity between HbA1c testing and OGTT in the identification of individuals with pre-diabetes and diabetes [23, 25, 26]. The previously described study was conducted on a population mainly consisting of individuals born in Europe; disparities in HbA1c levels between ethnic groups have been found but are not well studied. A need for individualised HbA1c cut off and target values for different ethnicities therefore seems reasonable [8, 27].
HbA1c testing is not recommended as screening for pre-diabetes in Sweden as cut off values with adequate specificity and sensitivity are not yet determined, finding such would provide great benefits in the screening of pre-diabetes since HbA1c levels are easily tested compared to OGTT and fasting glucose levels. Because of the variability of HbA1c levels in different ethnicities specific cut off values for different groups need to be determined in order to achieve optimal sensitivity and specificity. In order for HbA1c testing to be used as a clinically relevant screening tool at least 70-80% of patients with diabetes/pre-diabetes should be found. While studies comparing HbA1c and OGTT previously have been conducted on Swedish populations, no studies have focused on the relation between HbA1c and OGTT/ in populations of predominantly foreign-born people in Sweden. Studies investigating differences in HbA1c accuracy between Swedish-born and foreign-born individuals are yet to be conducted. This study will attempt to fill this knowledge gap and possibly set the basis for future studies to find individualised cut off values for different groups.

The aim of this study was to compare the diagnostic accuracy of HbA1c in detecting individuals with abnormally elevated blood glucose levels between foreign-born and Swedish-born primary healthcare patients. The secondary aim was to approximate appropriate HbA1c cut off values for the different populations to yield better sensitivity and specificity.

**Methods**

*Data collection and population*

Data analysed in this cross-sectional study was collected in the Programme 4D (Four Diagnoses) study conducted between years 2013-2015. Included in Programme 4D was screening for T2DM and pre-diabetes in patients at two primary healthcare centres in Flemingsberg and Jakobsberg. Screening included HbA1c, OGTT (including fasting plasma glucose) and questionnaires regarding lifestyle factors and country of birth as well as pre-diabetes/diabetes risk assessment questionnaires. The questionnaires used in the 4D study included (a) validated risk-prediction tool for diabetes Finnish Diabetes Risk Score FINDRISC [28], (b) validated questions regarding for example self-rated health [29], lifestyle and demographic characteristics and (c) specifically developed for this study questions for example self-reported sensation of burning feet, developed for this study. The entire questionnaire is not published yet in any study protocol. At the healthcare centres chosen, a big proportion of patients were of foreign origin. Subjects with newly discovered diabetes during the study received proper medical examinations and treatment according to existing care programs. Subjects with newly discovered pre-diabetes were offered lifestyle interventions and yearly check-ups.

All patients aged 18-74 visiting Flemingsberg and Jakobsberg healthcare centres were inquired about inclusion in the study. Exclusion criteria included having a diagnosis of diabetes. 830 patients were included in the study.

In order to calculate diagnostic accuracy of HbA1c-testing, patients with either both OGTT and HbA1c results and both fP-glucose and HbA1c results were included in the calculation, the rest of the subjects were excluded. This totalled in 757 out of the 830 patients.

The study was approved by the by the Swedish Ethical Review Authority (Review number 2013/2303-31/3).
Variables

Variables analysed were the following: place of birth, healthcare centre, age, sex, OGTT-result, fP-glucose levels and HbA1c.

*Place of birth* was determined by a questionnaire which allowed the participants to choose from 245 different countries. For this study these answers were used to create two groups dividing the study population into Swedish-born (SB) and foreign-born (FB) participants. Participants were also divided into groups based on which healthcare centre they were recruited at. *OGTT*, *fP-glucose* and *HbA1c* was determined through blood samples.

The following categorical variables were created: *OGTT* (1) normal (2hr P-glucose: \(<7.8 \text{ mmol/L}\)) and (2) elevated (IGT) (2hr P-glucose: \(\geq 7.8 \text{ mmol/L}\)). *HbA1c* values were classified in accordance with the primary care guidelines for Stockholm: (1) normal test (HbA1c <42 mmol/mol) and (2) elevated test (HbA1c \(\geq 42 \text{ mmol/mol}\)). *Fasting plasma glucose*: (1) normal (fP-glucose <6.1 mmol/L) and (2) elevated fP-glucose (IFG) (fP-glucose \(\geq 6.1 \text{ mmol/L}\)).

The reference group was then created by combining those with either elevated fP-glucose or elevated OGTT.

Statistics

All data was analysed using STATA statistical software version 14.2 (StataCorp LLC 2015, College Station TX USA). The tables were created using both STATA and Microsoft Excel. Significance level was set to 5% for this study. The variables OGTT, HbA1c, fP-glucose, region of birth, sex, and healthcare centre were treated as categorical variables. Chi-squared test was used to determine the p-value for these variables in studied groups. The only continuous variable analysed was age, T-test was used to determine the p-value for this variable in foreign- and Swedish-born. The Venn diagram was created using the STATA module “pvenn” (downloaded through SCC). To calculate the diagnostic accuracy of HbA1c the function ROCTAB was used. This yielded the sensitivity and specificity for each different HbA1c cut off value as well as the ROC figure and AUC. This was done for both the Swedish-born and foreign-born groups.

Results

The characteristics of all 830 participants are shown in Table 1. They were divided into groups based on region of birth. Significant differences in OGTT results, HbA1c levels, age and healthcare centre were found between the two groups. No significant difference was found for FPG levels between the groups. Note that although all 830 participants are included in Table 1, not all 830 had conducted an OGTT (n=666) and FPG test (n=714). Figure 1 shows a Venn diagram of the participants who had conducted all three tests (n=623), the circles display the patients with an elevated result from the respective test. Only 22 participants had elevated results on all three tests. Figures 3 and 4 give a visual representation of the discrepancy between the number of participants with HbA1c values \(\geq 42 \text{ mmol/mol}\) and those with elevated OGTT and/or fP-glucose.

Table 1 Characteristics of the entire study population, p-values <0.05 are considered significant and marked with an asterisk. P-values were calculated using chi-squared test.
Total | Foreign-born | Swedish-born | P-value
---|---|---|---
N=830 | N=474 | N=356

Age, mean | 49.0 (14.7) | 46.6 (12.8) | 52.2 (16.4) | <0.0001*

Healthcare centre
- Jakobsberg | 436 (52.5%) | 195 (41.1%) | 241 (67.7%) | <0.0001*
- Flemingsberg | 394 (47.5%) | 279 (58.9%) | 115 (32.3%)

Sex
- Female | 475 (57.2%) | 272 (57.4%) | 203 (57.0%)
- Male | 355 (42.8%) | 202 (42.6%) | 153 (43.0%)

OGTT
- <7.8 mmol/L | 449 (67.4%) | 240 (63.5%) | 209 (72.6%)
- ≥7.8 mmol/L | 217 (32.6%) | 138 (36.5%) | 79 (27.4%)

HbA1c
- <42 mmol/mol | 759 (91.4%) | 426 (89.9%) | 333 (93.5%)
- ≥42 mmol/mol | 71 (8.6%) | 48 (10.1%) | 23 (6.5%)

fP-glucose
- <6.1 mmol/L | 546 (76.5%) | 319 (78.6%) | 227 (73.7%)
- ≥6.1 mmol/L | 168 (23.5%) | 87 (21.4%) | 81 (26.3%)

To find out if there was a significant difference in the relation of HbA1c and OGTT/fP-glucose levels between the FB and SB groups, HbA1c levels for those with elevated OGTT and/or fP-glucose was significance tested between the groups. This is displayed in Table 2, in total 309 had either an elevated OGTT and/or fP-glucose. In total 16.8% of subjects in the reference group had an HbA1c of ≥42 mmol/mol. In the foreign-born population 19.7% of the reference group had an HbA1c of ≥42 mmol/mol compared to the Swedish-born population of the reference group where 12.7% had an HbA1c of ≥42 mmol/mol, p-value 0.040. The mean HbA1c level for the reference group was 37.2 mmol/mol, with no significant difference in mean HbA1c levels between the foreign-born and Swedish-born groups.

Table 2 Patients with elevated fP-glucose (≥6.1 mmol/L) and/or elevated OGTT (≥7.8mmol/L), n=309, divided by place of birth foreign-born (FB) and Swedish-born (SB). P-value was calculated using chi-squared test.
|                        | Total     | FB patients with elevated fP-glucose and/or OGTT | SB patients with elevated fP-glucose and/or OGTT | P-value |
|------------------------|-----------|--------------------------------------------------|--------------------------------------------------|---------|
|                        | N=309     | N=183                                            | N=126                                            |         |
| HbA1c                  |           |                                                  |                                                  | <0.0001*|
| <42 mmol/mol           | 257 (83.2)| 147 (80.3)                                       | 110 (87.3%)                                      |         |
| ≥42 mmol/mol           | 52 (16.8%)| 36 (19.7%)                                       | 16 (12.7%)                                       |         |
| HbA1c, mean value      |           |                                                  |                                                  | 0.78    |
|                        | 37.2 (6.1)| 37.3 (6.3)                                       | 37.1 (5.8)                                       |         |

**Diagnostic accuracy**

Since there was found to be a significant difference between the Swedish-born and foreign-born reference groups regarding rate of positive HbA1c (values ≥ 42 mmol/mol) outcomes (see Table 2), ROC-AUC-analysis was performed for each group separately. Table 3 displays the sensitivity, specificity and percentage correctly classified for different HbA1c values in the Swedish-born group. From this we can see that a HbA1c cut off of 42 mmol/mol yields 12.7% sensitivity whilst the ADA cut off value of 39 yields 25.4% sensitivity. To diagnose at least 70% of those with elevated OGTT and/or FPG an HbA1c cut off of 34 would be required. The ROC analysis for the Swedish-born group is shown in figure 2, AUC = 0.756 (0.702-0.810 [95% CI]). Figure 3 displays the specificity and sensitivity for each HbA1c cut off value in the Swedish-born group.

**Table 3** Sensitivity, specificity and % correctly classified in the Swedish-born and Foreign-born populations for different cut off values. Marked in grey is the WHO guideline cut off value for pre-diabetes (42 mmol/mol), marked in blue is the ADA guideline cut off value for diagnosing pre-diabetes (39 mmol/mol).
The same analyses were performed on the foreign-born population. Table 4 shows the sensitivity, specificity and percentage correctly classified for different HbA1c values in the foreign-born group. An HbA1c cut off value of 42 mmol/mol in this group yields 19.7% sensitivity, the ADA cut off of 39 mmol/mol yields 33.8% sensitivity. To diagnose at least 70% of those with an elevated OGTT and/or FPG in the foreign-born group an HbA1c cut off of 34 mmol/mol would be required, same value as in the Swedish-born group. The ROC analysis for the foreign-born group is shown in figure 4, AUC=0.6975 (0.646-0.749 [95% CI]). Figure 5 displays the specificity and sensitivity for each HbA1c cut off value in the foreign-born group. Comparing the AUC for the two groups yielded an AUC of 0.756 for the Swedish-born group and 0.698 for the foreign-born group which might indicate greater diagnostic accuracy for the test in the Swedish-born population than the foreign-born population.

| HbA1c cut off value | Sensitivity | Specificity | Correctly classified | Sensitivity | Specificity | Correctly classified |
|---------------------|-------------|-------------|----------------------|-------------|-------------|----------------------|
| >= 29               | 100.00%     | 6.90%       | 42.55%               | 95.63%      | 5.71%       | 44.16%               |
| >= 30               | 97.62%      | 14.78%      | 46.50%               | 94.54%      | 10.61%      | 46.50%               |
| >= 31               | 95.24%      | 25.12%      | 51.98%               | 89.62%      | 20.00%      | 49.77%               |
| >= 32               | 88.10%      | 37.93%      | 57.14%               | 84.70%      | 28.98%      | 52.80%               |
| >= 33               | 80.95%      | 47.78%      | 60.49%               | 78.69%      | 41.63%      | 57.48%               |
| >= 34               | 73.81%      | 58.13%      | 64.13%               | 73.22%      | 54.29%      | 62.38%               |
| >= 35               | 65.87%      | 72.41%      | 69.91%               | 61.75%      | 67.35%      | 64.95%               |
| >= 36               | 58.73%      | 82.27%      | 73.25%               | 57.92%      | 75.51%      | 67.99%               |
| >= 37               | 45.24%      | 88.67%      | 72.04%               | 46.99%      | 83.27%      | 67.76%               |
| >= 38               | 36.51%      | 92.12%      | 70.82%               | 39.34%      | 88.98%      | 67.76%               |
| >= 39               | 25.40%      | 95.57%      | 68.69%               | 32.79%      | 91.84%      | 66.59%               |
| >= 40               | 22.22%      | 97.04%      | 68.39%               | 26.78%      | 95.10%      | 65.89%               |
| >= 41               | 15.08%      | 98.52%      | 66.57%               | 23.50%      | 97.14%      | 65.65%               |
| >= 42               | 12.70%      | 98.52%      | 65.65%               | 19.67%      | 97.96%      | 64.49%               |
| >= 43               | 9.52%       | 99.51%      | 65.05%               | 13.66%      | 99.18%      | 62.62%               |
| >= 44               | 6.35%       | 100.00%     | 64.13%               | 10.93%      | 99.59%      | 61.68%               |
Table 4. Sensitivity, specificity and percentage correctly classified subject for different HbA1c cut off values. Marked in grey is the WHO guideline cut off value for prediabetes (42 mmol/mol), marked in blue is the ADA guideline cut off value for diagnosing prediabetes (39 mmol/mol).

| HbA1c cut off value (mmol/mol) | Sensitivity  | Specificity  | Correctly classified |
|-------------------------------|--------------|--------------|---------------------|
| >=29                          | 95,63%       | 5,71%        | 44,16%              |
| >=30                          | 94,54%       | 10,61%       | 46,50%              |
| >=31                          | 89,62%       | 20,00%       | 49,77%              |
| >=32                          | 84,70%       | 28,98%       | 52,80%              |
| >=33                          | 78,69%       | 41,63%       | 57,48%              |
| >=34                          | 73,22%       | 54,29%       | 62,38%              |
| >=35                          | 61,75%       | 67,35%       | 64,95%              |
| >=36                          | 57,92%       | 75,51%       | 67,99%              |
| >=37                          | 46,99%       | 83,27%       | 67,76%              |
| >=38                          | 39,34%       | 88,98%       | 67,76%              |
| >=39                          | 32,79%       | 91,84%       | 66,59%              |
| >=40                          | 26,78%       | 95,10%       | 65,89%              |
| >=41                          | 23,50%       | 97,14%       | 65,65%              |
| >=42                          | 19,67%       | 97,96%       | 64,49%              |
| >=43                          | 13,66%       | 99,18%       | 62,62%              |
| >=44                          | 10,93%       | 99,59%       | 61,68%              |

Discussion

Findings

The primary aim of this study was to investigate and compare the diagnostic accuracy of HbA1c in detecting pre-diabetes/diabetes between foreign-born and Swedish-born primary healthcare patients. As shown in tables 3-4, the WHO guidelines (used in Sweden) on HbA1c cut off value yielded a sensitivity of 12.70%, specificity of 98.52% for the Swedish-born group of our study population and a sensitivity of 19.67%, specificity of 97.96% for the foreign-born group. While the ADA guidelines yielded better sensitivity for both groups in this study population, it was still very low. Interestingly, the ROC-analyses suggest that the diagnostic accuracy for HbA1c is better for the Swedish-born population compared to the foreign-born population, AUC = 0.756 and 0.698 respectively.
The secondary aim of this study was to approximate new HbA1c cut off values for the two different study populations to yield better diagnostic accuracy. The findings conclude that for both the Swedish-born and foreign-born group in our study population the lowest possible cut off value that yields at least 70% sensitivity is 34 mmol/mol. The specificity for this cut off value is however rather low, 58.13% and 54.29% for the Swedish- and foreign-born groups respectively. These findings suggest that a cut off value of 34 mmol/mol would improve the sensitivity of HbA1c testing in both the Swedish-born and foreign-born group in this population.

The project this study was based on, Programme 4D, concluded that for HbA1c testing to be used as an efficient and reliable screening tool for detecting pre-diabetes, at least 70% of these with pre-diabetes needed to be found. This explains why we used this number to approximate the new cut off value. While a cut off of 34 mmol/mol increases the number of these with pre-diabetes and diabetics found with the test, it also increases the number of healthy individuals falsely classified as sick or increases excessive testing using FPG/OGTT. Both cut off values, 42 and 34 mmol/mol, yield similar percentage correctly classified individuals, around 62-65%. If the cost and overall health benefits of a lower cut off value is greater than those using WHO guideline cut off values is yet to be studied.

Comparison with other studies

As shown the current HbA1c cut off values, both those stated by ADA and the WHO guideline values, result in very low sensitivity which may lead to many individuals with pre-diabetes and diabetics being undiagnosed if only HbA1c is used. The findings in this study agree with the findings of several other studies on HbA1c cut off values regarding sensitivity and diagnostic accuracy while contradicting other studies. As mentioned earlier a Swedish study [30] found that using an HbA1c cut off of 42 mmol/mol only detected 16% of patients diagnosed with OGTT, numbers that agree very well with our findings. Another Swedish study [31] comparing the usage of HbA1c as a screening tool between populations of Swedish and Middle East ancestry also found it to be an inefficient tool for detecting pre-diabetes. Their study found that using HbA1c ≥42 mmol/mol and ≥39 mmol/mol yielded a sensitivity of 17% and 36% respectively. A large meta study [32] conducted on 148 studies showed sensitivity ranging from 0.28-0.72 for studies using WHO guidelines and OGTT +/- FPG as reference test and sensitivity ranging from 0.14-0.76 for studies using ADA guidelines. Important to note is that the studies included in the meta study varied greatly from each other regarding study population, both in terms of ethnic composition and sampling strategy. In some of the studies participants self-selected to attend for screening rather than using a randomly selected population meaning selection bias might be a source of bias in these studies. Nevertheless, most studies examined show that using current HbA1c cut off values as a screening tool for pre-diabetes yield low diagnostic accuracy.

Strengths and limitations

This study is the first Swedish study to investigate and compare diagnostic accuracy of HbA1c between a Swedish-born and foreign-born population. One if the study's primary strengths is due to the manner in which the population was recruited, since anyone between the ages 18-74 visiting one of the two healthcare centres during the recruitment period was asked about participating, the population should be representative of the real world patient population in Swedish immigrant frequent areas. Another strength is the fact that the study information was translated to numerous different languages ensuring that no big group was left out of
participating. One of the weaknesses with this study, and many studies of this kind, is that while the use of OGTT is often used as reference test in defining the population with pre-diabetes and diabetes it is barely used in clinical praxis. The reason for this being that OGTT is a very time and personnel consuming test for both the clinic and the patient when compared to for example FPG, because of these differences the transferability of results might be limited between study and real world. Another downside is the difference in group sizes, the group of participants found with HbA1c levels above 42 mmol/mol is for example much smaller than the group with levels below 42 mmol/mol. When this group is further divided up by country of birth the groups become even smaller meaning that even adding or subtracting individual participants from these group significantly changes the statistical outcome. To combat differing group sizes based on country of birth it was decided to divide the population into Swedish- and non-Swedish-born participants instead of dividing it based on individual countries of birth. This however led to another problem, since anybody with foreign heritage was grouped together this group consisted of people of wildly varying ethnic backgrounds. Because of the heterogeneity of this group nothing can be said about the diagnostic accuracy of people born in individual countries and areas, for example the Middle East or East Asia. It can be theorised that the outcome of this study would differ if the population was to be divided into several groups based on area of birth.

One of the main limiting factors of this study design is that participants with abnormally elevated blood glucose, either by OGTT or FPG, are all grouped together as one group. The same was done with HbA1c results were anyone with an HbA1c above the cut off value was grouped together, regardless of actual HbA1c value. This causes varying degrees of sickness in these groups, ranging from some participants with milder pre-diabetes to others with uncontrolled diabetes. The study was designed this way to avoid excluding as many participants as possible. If the population was to be divided further, say by creating groups with “Normal”, “Pre-diabetes”, and “Diabetes” results on the OGTT/FPG and HbA1c tests then this would result in a very uneven distribution of participants across the groups. To avoid such uneven distribution, participants were only divided depending on whether their results were above or below the cut off for each test.

As mentioned earlier OGTT is a time consuming and somewhat tedious test to perform, this is reflected in the fact that out of the total 830 study participants only 667 have OGTT results. The possible reason for this being a lack of time and commitment from the participants to complete the OGTT, another reason is that the participants with FPG of >7.0 mmol/mol were excluded from OGTT testing. The mean HbA1c value for the participants with missing OGTT result is 36 mmol/mol (33-40 interquartile range) while the mean HbA1c value for the participants with both OGTT and HbA1c results is 34 mmol/mol (31.5-36.5 interquartile range). Whether or not the results would be different if all 830 participants had completed the OGTT is uncertain. The higher HbA1c median in the group with missing OGTT results however suggests that perhaps the prevalence of pre-diabetes and diabetes is higher in this group, which might be a source of bias.

Further research on the effectiveness of HbA1c as a screening tool for pre-diabetes is required. Whether or not a lower cut off value for HbA1c yields any benefits for society regarding health care costs and overall health needs to be determined. While lowering the cut off value vastly improves the sensitivity of HbA1c testing, the number of false positives increases as well. Since not all individuals with pre-diabetes go on to develop diabetes [33-35], the lowered cut off would result in many patients undergoing unnecessary testing and or treatment. Perhaps a combination of a lowered cut off and for example risk scoring would yield better accuracy in detecting pre-diabetes [36].
Conclusions

The ROC-analyses show that the diagnostic accuracy for HbA1c in detecting pre-diabetes and diabetes might be better for the Swedish-born than the foreign-born group. We also found that for both these groups, an HbA1c cut off value of 34 mmol/mol would yield a sensitivity of >70%. Based on our findings we suggest that the usage of an HbA1c cut off value of 34 mmol/mol can be considered for further investigation. Comparing the AUC for the two groups yielded an AUC of 0.756 for the Swedish-born group and 0.698 for the foreign-born group which might indicate greater diagnostic accuracy for the test in the Swedish-born population than the foreign-born population.

Abbreviations

ADA    American Diabetes Association
AUC    Area Under the Curve
HbA1c  Glycated haemoglobin
IFG    Impaired fasting glucose
IGT    Impaired glucose tolerance
fP-glucose  Fasting plasma glucose
OGGT   Oral glucose tolerance test
SDPP   Stockholm’s Diabetes Prevention Program
T2DM   Type 2 Diabetes
ROC    Receiver Operating Curve
WHO    World Health Organisation

Declarations

Ethical Approval and consent to participate

The study procedure was approved by the Swedish Ethical Review Authority (Review number 2013/2303-31/3. All participants got information and consented to participate both verbally and in written form.

Consent for publication

Not applicable

Availability of data and materials
Sharing of the data with other researchers was not included in written informed consent and therefore neither data nor materials are publically available. The datasets used and/or analyzed during the current study is available from the corresponding author on reasonable request.

Competing interests

We declare that we have no conflicts of interest.

Funding

The 4D Diabetes subproject was a part of the 4D programme, a strategic project shared by the Karolinska Institutet and Stockholm County Council. The group running the project was selected by both authorities from both organizations and consisted of senior advisors and researchers in Endocrinology and Psychology. This group of senior advisors and researchers independently designed the 4D Diabetes subproject, including the collection, analysis, and interpretation of the data used in this manuscript.

Authors’ contributions

MT and HS wrote the draft and were responsible for preparation of final version. KS and CGÖ participated in the collecting 4D data, interpreting the results and editing the manuscript. VM performed statistics and contributed to writing of the method and result sections in the draft and interpretation of the results. All authors read and approved the final version of manuscript.

Acknowledgements

We express a warm thanks to all participants enrolled in the 4D Diabetes Project and to the 4D Programme organization - Karolinska Institutet and Stockholm County Council (renamed Region Stockholm) - for the opportunity to conduct this study.

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