Evaluation of Glycated Hemoglobin (HbA1c) for Diagnosing Type 2 Diabetes and Prediabetes among Palestinian Arab Population

Akram T. Kharroubi1*, Hisham M. Darwish2, Ahmad I. Abu Al-Halawe3, Umaiyeh M. Khammash4

1 Department of Medical Laboratory Sciences, Faculty of Health Professions, Al-Quds University, Jerusalem, Palestine, 2 Faculty of Medicine, Molecular Genetics Laboratory, Al Quds University, Jerusalem, Palestine, 3 Augusta Victoria Hospital, Jerusalem, Palestine, 4 United Nation Relief and Working Agency (UNRWA), Jerusalem, Palestine

Abstract

The purpose of the study is to compare the potential of HbA1c to diagnose diabetes among Palestinian Arabs compared to fasting plasma glucose (FPG). A cross-sectional sample of 1370 Palestinian men (468) and women (902) without known diabetes and above the age of 30 years were recruited. Whole blood was used to estimate HbA1c and plasma for FPG and total lipid profile. Fasting plasma glucose was used as a reference to diagnose diabetes (≥ 126 mg/dL) and prediabetes (100–125 mg/dL). The area under the receiver operating characteristic curve (AUC) for HbA1c was 81.9% to diagnose diabetes and 63.9% for prediabetes. The agreement between HbA1c and diabetes as diagnosed by FPG was moderate (κ = 0.498) and low with prediabetes (κ = 0.142). The optimal cut-off value for HbA1c to diagnose diabetes was ≥ 6.3% (45 mmol/mol). The sensitivity, specificity and the discriminant ability were 65.6% (53.1–76.3%), 94.5% (93.1–95.6%), 80.0% (72.8–87.3%), respectively. However, using cut-off value of ≤ 6.5% (48 mmol/mol) improved specificity. At this cut-off value, the sensitivity, specificity and the discriminant ability were 67.2% (57.1–67.9%), 56.3% (53.1–59.4%) and 59.5% (56.3–62.5%), respectively. HbA1c at cut-off value of ≤ 6.5% (48 mmol/mol) by itself diagnosed 5.3% and 48.3% as having diabetes and prediabetes compared to 4.5% and 24.2% using FPG, respectively. Mean HbA1c and FPG increase significantly with increasing body mass index. In conclusion, the ROC curves showed HbA1c could be used for diagnosing diabetes when compared to FPG but not for prediabetes in Palestinians Arabs even though only about 50% of the diabetic subjects were identified by the both HbA1c and FPG.

Introduction

The Center for Disease Control (CDC) reported a world-wide prevalence of diabetes in its national diabetes fact sheet to be 11.57% [1]. According to Hare et al. [2], diabetes mellitus is the greatest public threat of the 21st Century with currently 285 million people world-side having diabetes and is expected to double to 439 million by 2030 with an additional half billion people are expected to be at high risk. These are conservative figures since, on one hand, type 2 diabetes mellitus is spreading among the young generation due to changes in their life style all over the world and, on the other hand, new diagnostic criteria of diabetes mellitus using HbA1c is emphasizing specificity over sensitivity as recommended by the International Expert Committee [3] which may underestimate the prevalence of diabetes [4].

Since the recommendation of the International Expert Committee in 2009 to use HbA1c test to diagnose diabetes [3], the American Diabetes Association (ADA), the Endocrine Society [5], the Word Health Organization [6] and most scientists in different countries all over the world have endorsed using HbA1c to diagnose diabetes. The advantages of using HbA1c over fasting plasma glucose (FPG) to diagnose diabetes include greater convenience and preanalytical stability, lower CV (3.6%) compared to FPG (5.7%) and 2h – Oral Glucose Tolerance Test (OGTT) (16.6%). Stronger correlation with microvascular complications especially retinopathy, a marker for glycemic control and glycation of proteins is the direct link between diagnosis of diabetes and its complications [7–12].

Most studies with different ethnic groups have endorsed a cut-off value for an HbA1c of ≥ 6.5% (48 mmol/mol) to diagnose diabetes as has been recommended by the International Expert Committee [3]. The ADA considers people to be at high risk (prediabetes) if HbA1c is 5.7–6.4% (39–46 mmol/mol) [4]. Different cut-off values have been reported for diagnosing diabetes in different ethnic groups and ethnicity seems to have a strong influence on cut-off values to diagnose diabetes [13,14]. Cut-off values of 5.5% (37 mmol/mol) [15]; 6.5% (48 mmol/mol) [16] have been reported in a Japanese studies, 6.0% (42 mmol/mol) in National Health and Nutrition Examination Survey (NHANES III), 6.2% (44 mmol/mol) in a Pima Indian study, 6.3%
Diagnosing Type 2 Diabetes Using HbA1c

Materials and Methods

Ethics Statement

Ethical approval for the study protocol was obtained from the Research Ethics Committee of Al-Quds University in the West Bank region in Palestine. Written informed consent was obtained from all participants involved in the study.

Participants

A convenient cross-sectional sample of 1370 adult Palestinian men (468) and women (902) without known diabetes and above the age of 30 years were recruited (based on their volunteer attendance to clinics) from central and southern refugee camps in Ramallah, Bethlehem and Hebron districts administered by UNRWA. All subjects were instructed to fast for 10–12 hours before coming to the clinic at 8:00 am. A special questionnaire concerning family history and health-related information was filled for all participants by direct interviews with the researchers. People previously diagnosed with diabetes or hemoglobinopathies were ruled out from the study. Blood samples were collected from all subjects using EDTA tubes and centrally analyzed for HbA1c. Plasma was also used to analyze FPG and total lipid profile, total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL). Blood pressure (BP) and BMI were also measured by the medical staff in the clinics. Body mass index (BMI) in kg/m² was categorized as normal (BMI < 25), overweight (BMI ≥ 25 to < 30) and obese (BMI ≥ 30). The cut-off values for diabetes using FPG was ≥ 126 mg/dL, prediabetes 100–125 mg/dL and normal subjects having FPG < 100 mg/dL. Specificity, sensitivity, and the area under the ROC curve (AUC) for HbA1c using different cut-off values were calculated using FPG as the “gold standard”.

Analytical procedures

Blood samples were tested for FPG, HbA1c, total lipid profile including TC, TG, LDL, and HDL. Fasting plasma glucose and total lipid profile (TC, TG, HDL) were measured enzymatically using Chemwell chemistry analyzer (Awareness Tech, USA). LDL cholesterol (C) was calculated from the equation of Friedewald equation (LDL-C = TC – [HDL-C + (TG/5)]). HbA1c was measured using 3 μL EDTA blood by ion-exchange HPLC using TOOSOH G8. Hemoglobin levels and CBC were measured for anemia evaluation as well hemoglobin variants were analyzed because of their interference with HbA1c levels. HbA1c assay was standardized to the Diabetes Control and Complications Trial (DCCT) assay method.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). Pearson’s correlation coefficient was used to test for co-linearity between the continuous variables, statistical comparisons between different groups for these continuous variables were carried out using Student’s t test and ANOVA. Pearson’s Chi-Square statistic was used to assess for relationships between categorical variables. Receiver operating characteristic (ROC) curves were constructed to calculate sensitivity, specificity, predictive value positive (PVP) and predictive value negative (PVN) at different cut-off values for HbA1c. Kappa (κ) coefficients were used to test for agreement between HbA1c and diabetes status based on FPG levels (diabetes and prediabetes). The ROC curve plots the sensitivity against 1 minus the specificity at all possible HbA1c cut-off values. The higher the AUC the better the predictive value of HbA1c based on the logistic regression model. An AUC value of 0.5 would indicate no predictive value, whereas a value of 1.0 would indicate perfect predictive value with no false positives or false negatives. Sensitivity at each possible HbA1c cut-off value was calculated as [TP/(TP + FN)] X 100, where TP = true positive (diabetic FPG and HbA1c cut-off value) and FN = false negative (diabetic FPG, ≤ cut-off value for HbA1c). The specificity represents the percentage of those with fasting plasma glucose < 126 mg/dL (7.0 mmol/L) who are classified as positive according to HbA1c. Specificity was calculated as [TN/(TN + FP)] X 100, where TN = true negative (non-diabetic FPG and ≤ cut-off value for HbA1c) and FP = fake positive (nondiabetic FPG, > cut-off value for HbA1c). The specificity represents and percentage of those with FPG < 126 mg/dL (7.0 mmol/L) who are classified as negative according to the HbA1c. Youdin index and the discriminant ability at each cut-off value for HbA1c were used to determine the optimal cut-off value for HbA1c to diagnose diabetes. The discriminant ability is the average of sensitivity and specificity at each cut-off value. Venn diagrams were used for visual display or concordance/ discordance between FPG and HbA1c-based classification of participants. Statistical significance was accepted at p<0.05. Because of missing values the number of each group in different comparisons is different.

Results

Fifty percent of the subjects that participated in this study were between the age of 40–49 years. They had no previous diagnosis of diabetes, but 56% of them had a family history of diabetes. The percentage of subjects with hypertension defined as systolic BP ≥ 120 mmHg or diastolic BP ≥ 90 mmHg was about 5.1 and 6.1, respectively. The percentage of subjects with high TC (≥ 5.5 mmol/L), TG (≥ 2.0 mmol/L) and LDL (≥ 3.5 mmol/L) was 16.2%, 15.4% and 27.1% respectively; whereas the percentage of subjects with high HDL (≥ 2.0 mmol/L) were 36.8%. The mean values of age, FPG, HbA1c, TC, LDL were not significantly different between males and females whereas mean values of systolic BP, diastolic BP, and TG were significantly higher (p<0.001) in males compared to females and mean HDL and BMI were significantly higher (p<0.001) in females compared to males using t test to compare means.

Figure 1 shows the ROC curves for HbA1c using FPG as a reference. The area under the ROC curve is 0.819 (0.75–0.89) for diagnosing diabetes (Figure 1 A) and 0.639 (0.60–0.68) for prediabetes (Figure 1 B). The agreement between HbA1c and diabetes was moderate (k = 0.498) and low with prediabetes (k = 0.142). The cut-off value of equal sensitivity and specificity or the closest point to 100% sensitivity for diagnosing diabetes was about 5.9% (41 mmol/mol).

Different cut-off values were tested for their ability to diagnose diabetes using FPG as the gold standard. Table 1 shows that
HbA1c with cut-off value of \( \geq 6.3\% \) (45 mmol/mol) has the highest discriminant ability (80.0%) with sensitivity of 65.6% and specificity of 94.5%. Youden index also gave an optimum cut-off value of \( \geq 6.3\% \). A cut-off value of \( \geq 6.5\% \) (48 mmol/mol) gave a specificity of 97.1% and a reasonable sensitivity (57.4%). However, a cut-off value of \( \geq 5.9\% \) (41 mmol/mol) gave a specificity of 71.1% and a sensitivity of 75.4%. Lower cut-off values less than 5.9% (41 mmol/mol) gave poor specificity. The percentage of subjects diagnosed as having diabetes using FPG (\( \geq 126\, \text{mg/dL} \)) and HbA1c at cut-off values of 6.5% (48 mmol/mol), 6.3% (45 mmol/mol), and 5.9% (41 mmol/mol) were 4.5%, 5.3%, 8.2%, and 30.4%, respectively.

From a total of 1370 subjects, 61 (4.5%) were diagnosed with diabetes using the criteria of FPG (\( \geq 126\, \text{mg/dL} \)) and 73 (5.3%) were diagnosed having diabetes using the criteria of HbA1c \( \geq 6.5\% \) (48 mmol/mol). Thirty five subject were diagnosed with diabetes (2.6%) having both criteria. Thirty eight subjects (2.8%) were diagnosed to have diabetes by HbA1c but not by FPG criteria whereas 26 subjects (1.9%) were diagnosed to have diabetes by FPG but not HbA1c criteria. At a cut-off value of \( \geq 6.5\% \) (48 mmol/mol) HbA1c diagnosed 57.4% of subjects to have diabetes from those diagnosed by FPG (\( \geq 126\, \text{mg/dL} \)), whereas HbA1c diagnosed 55.8% of subjects to be normal (\( < 5.7\% \), 39 mmol/mol) from those diagnosed by FPG (\( < 100 \, \text{mg/dL} \)). On the other hand, HbA1c diagnosed 628 (45.8%) as having prediabetes (5.7–6.4%, 39–46 mmol/mol) compared to 337 (24.6%) by FPG (100–125 mg/dL), 193 (14.1%) met both criteria.

The Venn diagrams for diabetes using ADA classification criteria are shown in Figure 2. Only 35.4% of subjects with diabetes meet both FPG and HbA1c criteria whereas 38.4% are diagnosed by HbA1c only and 26.3% by FPG only. In prediabetes Figure 2 shows that only 26.5% have prediabetes with both FPG and HbA1c criteria whereas HbA1c diagnosed 57.8% and FPG diagnosed 15.8%. Approximately 50% of normal subjects are diagnosed by both HbA1c and FPG, however, only 11.6% are diagnosed normal by HbA1c and not by FPG and 39.1% are diagnosed normal by FPG and not by HbA1c.

### Table 1.

The effect of different cut-off values of HbA1c on sensitivity, specificity, PVP, PVN, percent of diabetes and area under ROC curves using FPG to diagnose diabetes (cut-off value \( \geq 126\, \text{mg/dL} \)).

| Cut-off value | Sensitivity | Specificity | PVP | PVN | Diabetes | Discriminant Ability (%)† |
|---------------|-------------|-------------|-----|-----|---------|----------------------------|
| \( \geq 5.5 \) (37) | 91.8 | 30.1 | 5.8 | 98.7 | 70.9 | 60.9 |
| \( \geq 5.6 \) (38) | 83.6 | 40.3 | 6.1 | 98.1 | 60.8 | 61.9 |
| \( \geq 5.7 \) (39) | 80.3 | 50.2 | 7.0 | 98.2 | 51.2 | 65.3 |
| \( \geq 5.8 \) (40) | 78.7 | 61.3 | 8.6 | 98.4 | 40.5 | 70.0 |
| \( \geq 5.9 \) (41) | 75.4 | 71.1 | 11.1 | 98.4 | 30.4 | 73.3 |
| \( \geq 6.0 \) (42) | 72.1 | 81.6 | 15.4 | 98.4 | 20.8 | 76.8 |
| \( \geq 6.1 \) (43) | 70.5 | 87.9 | 21.3 | 98.5 | 14.7 | 79.2 |
| \( \geq 6.2 \) (44) | 67.2 | 91.7 | 27.5 | 98.4 | 10.9 | 79.5 |
| \( \geq 6.3 \) (45)‡ | 65.6 | 94.5 | 35.7 | 98.3 | 8.2 | 80.0 |
| \( \geq 6.4 \) (46) | 62.3 | 96.0 | 42.2 | 98.2 | 6.6 | 79.1 |
| \( \geq 6.5 \) (48) | 57.4 | 97.1 | 47.9 | 98.0 | 5.3 | 77.3 |
| \( \geq 7.0 \) (53) | 42.6 | 99.2 | 72.1 | 97.4 | 2.6 | 70.9 |
| \( \geq 8.0 \) (64) | 27.9 | 99.6 | 77.3 | 96.7 | 1.6 | 63.7 |

HbA1c values are % (mmol/mol); PVP: Predictive value positive; PVN: predictive value negative; ROC: Receiver operating characteristics; AUC: Area under ROC curve.

†Discriminant ability = (sensitivity + specificity)/2. ‡Highest discriminant ability seen for HbA1c of 6.3%.

doi:10.1371/journal.pone.0088123.t001

Figure 1. HbA1c receiver operating characteristic (ROC) curves for diabetes (A) and prediabetes (B) using FPG as a reference. AUC: area under the receiver operating characteristic curve. doi:10.1371/journal.pone.0088123.g001
Table 2 shows that all of the parameters measured (age, systolic BP, diastolic BP, FPG, HbA1c, TC, TG, LDL and BMI) were significantly higher in subjects with diabetes compared to controls using the criteria of FPG ($\geq 126 \text{ mg/dL}$) or HbA1c ($\geq 6.5\%$ or $48 \text{ mmol/mol}$) to diagnose diabetes except for HDL where the difference between the means was not significant. Other HbA1c cut-off values tested such as 5.5% (37 mmol/mol), 6.0% (42 mmol/mol) and 7.0% (53 mmol/mol) also gave similar differences using t-test to compare means (data not shown).

Pearson correlation coefficients assessed between parameters measured in all recruited subjects were significant ($p < 0.01$) between age and both FPG ($r = 0.146$) and HbA1c ($r = 0.259$), FPG and HbA1c, TC, TG, LDL and BMI ($r = 0.584, 0.242, 0.294, 0.135$ and $0.133$, respectively). HbA1c correlations with the above parameters were also similar ($r = 0.129, 0.124, 0.111$ and $0.166$ for TC, TG, LDL and BMI, respectively).

Approximately 47% of the subjects were obese (BMI $\geq 30$). Mean comparisons by ANOVA of both HbA1c and FPG in obese subjects increase slightly (5 and 8%, respectively) but significantly ($p < 0.05$) compared to normal subjects (BMI $< 25$). On the other hand, mean BMI values are significantly higher in diabetes compared to normal subjects based on FPG cut-off value of $126 \text{ mg/dL}$ (32.5 vs. 29.7 respectively, $p < 0.001$). There is also a similar increase in mean values of HbA1c and FPG in overweight subjects (BMI 25 to $< 30$) compared to normal subjects (5.7%, 39 mmol/mol vs. 5.5%, 37 mmol/mol, respectively, for HbA1c, and 5.29 vs. 5.07 mmol/L, respectively, for FPG). Table 3 shows that diabetic and cardiovascular risk factors were nearly the same whether subjects were diagnosed by HbA1c or FPG or both. The only difference among tested parameters was the TC where the number of diabetic subjects diagnosed by HbA1c or both FPG and HbA1c was statistically higher than those diagnosed by FPG.

**Discussion**

This study demonstrated the feasibility of using HbA1c in Palestinian Arabs to diagnose diabetes with area under the ROC curve of 0.819. The ideal cut-off value from the ROC curve was approximately 5.9% (equal sensitivity and specificity), however, the optimal cut-off value with the highest discriminant ability was 6.3%.
This cut-off value is in agreement with the study on Abu Dhabi Arab population of the United Arab Emirates, UAE, [25–31] which reported a cut-off value of 6.4%. At cut-off value of ≥ 6.5%, the sensitivity, specificity, and the discriminability were comparable between this study and that of Abu Dhabi (65.6%, 94.5%, 80% compared to 72.0%, 84.3%, 78%, respectively). The lower percentage of subjects diagnosed with diabetes by HbA1c cut-off value compared to that of Abu Dhabi study (9.2% vs. 21.0%, respectively) was not surprising since the prevalence of diabetes in the UAE (25% in UEA citizens, and 20% in UAE) is the second highest in the world [26] and subjects at high risk (HbA1c ≥ 6.1%, 43 mmol/mol, and obese with mean BMI 30.4 kg/m²) were second highest in the world [26] and subjects at high risk (HbA1c ≥ 6.5%, FPG $\geq 126$ mg/dL) to diagnose diabetes HbA1c diagnosed 73.4% of subjects compared to 61 subjects by FPG from a total of 1370 subjects 35 subjects where identified by both methods. This indicated a bad agreement between the two methods to recognize the same diabetic subjects. This was also the case in prediabetes where HbA1c diagnosed 62.6% and FPG 337 subjects from a total of 1370 subjects, only 193 were diagnosed by both methods which indicated that the two methods recognize different populations. Most previous studies reported HbA1c to diagnose less subjects with diabetes compared to OGTT [4,27,28]. This could be due to the delay in analysis that affected FPG due to glycolysis more than HbA1c since samples were transported to a central laboratory [18]. Other studies still reported higher percentages of detecting undiagnosed diabetes by HbA1c ≥ 6.5% (48 mmol/mol) compared to FPG ≥ 126 mg/dL [29–31]. Diagnosing higher percentages of pre-diabetes using HbA1c compared to FPG from this study is consistent with most previously published reports [18,30,32].

Correlation between HbA1c ≥ 6.5% and diabetes as diagnosed by FPG was moderate ($r = 0.498$). This is consistent with recent studies on Korean subjects ($r = 0.490$) by Seo and Lee [33] and Peru subjects ($r = 0.41$) reported by Miranda et al. [31].

### Table 3. Characteristics of individuals participating in the study according to HbA1c, FPG or both.  

| Parameter                  | HbA1c (Nondiabetic and Diabetic) | FPG (Nondiabetic and Diabetic) | HbA1c and FPG (Nondiabetic and Diabetic) |
|----------------------------|---------------------------------|--------------------------------|------------------------------------------|
| Sex                        | Male                            | 450 (34.0%)                     | 443 (33.8%)                              | 432 (34.0%)                              |
|                            | Female                          | 873 (66.0%)                     | 869 (66.2%)                              | 839 (66.0%)                              |
| Diastolic BP (mm Hg)       | ≤ 80 mm Hg                      | 120 (94.2%)                     | 1226 (94.0%)                             | 1192 (94.3%)                             |
|                            | > 80 mm Hg                      | 76 (5.8%)                       | 78 (6.0%)                                | 72 (5.7%)                                |
| Systolic BP (mm Hg)        | ≤ 120 mm Hg                     | 1252 (95.1%)                    | 1240 (95.1%)                             | 1206 (95.4%)                             |
|                            | > 120 mm Hg                     | 64 (4.9%)                       | 64 (4.9%)                                | 58 (4.6%)                                |
| Family History for Diabetes| Yes                             | 730 (56.2%)                     | 727 (55.5%)                              | 69 (55.3%)                               |
|                            | No                              | 568 (43.8%)                     | 583 (44.5%)                              | 562 (44.7%)                              |
| TC (mmol/L)                | < 5.5 mm Hg                     | 1101 (84.6%)                    | 1109 (84.6%)                             | 1081 (85.1%)                             |
|                            | ≥ 5.5 mm Hg                     | 202 (15.5%)                     | 202 (15.4%)                              | 189 (14.9%)                              |
| TG (mmol/L)$^1$            | < 2.0 mmol/L                    | 1112 (85.4%)                    | 1128 (86.1%)                             | 1096 (86.4%)                             |
|                            | ≥ 2.0 mmol/L                    | 190 (14.6%)                     | 182 (13.9%)                              | 173 (13.6%)                              |
| HDL (mmol/L)               | < 1.0 mmol/L                    | 829 (63.5%)                     | 839 (63.9%)                              | 811 (63.8%)                              |
|                            | ≥ 1.0 mmol/L                    | 475 (36.4%)                     | 473 (36.1%)                              | 460 (36.2%)                              |
| LDL (mmol/L)               | < 3.5 mmol/L                    | 954 (73.7%)                     | 956 (73.3%)                              | 934 (74.0%)                              |
|                            | ≥ 3.5 mmol/L                    | 341 (26.3%)                     | 348 (26.7%)                              | 329 (26.0%)                              |
| BMI                        | < 25                            | 216 (16.5%)                     | 214 (16.5%)                              | 211 (16.7%)                              |
|                            | 25 - < 30                       | 496 (37.9%)                     | 487 (37.5%)                              | 478 (37.9%)                              |
|                            | ≥ 30                            | 597 (45.6%)                     | 597 (46.0%)                              | 571 (45.3%)                              |

$^1p = 0.013$ between diabetic subjects diagnosed by HbA1c, FPG, and HbA1c+FPG.  
Diabetic [HbA1c ≥ 6.5%, FPG ≥ 126 mg/dL (≥ 7.0 mmol/L)]; Nondiabetic [HbA1c < 6.5%, FPG < 126 mg/dL (< 7.0 mmol/L)].  
doi:10.1371/journal.pone.0088123.t003
However, Cavagnolli et al. [27] and Pinelli at al. [24] reported poor correlation ($r = 0.217$ and $0.2035$, respectively). Not surprisingly, both studies reported low sensitivity for HbA1c $\geq 6.5\%$ (20.9% and 19%, respectively) compared to this study and most other studies that reported sensitivity close to 60% [15,25,30,34]. The above two studies with poor correlation and low sensitivity could be due to the study subjects with mixed ethnicity (Arabs in the United States and Southern Brazilians).

The lack of effect of age, sex and BMI on the diagnostic criteria of HbA1c as compared to FPG is consistent with previous studies [20,24,36]. Age-stratified analysis on the feasibility of using HbA1c to diagnose diabetes and prediabetes are consistent with the findings of Penelli et al. [24]. Identifying subjects with diabetes by HbA1c was not affected by age. However, the sensitivity for detecting prediabetes in individuals aged 40–49 years (33.2%) or 50–59 years (37.5%) was significantly higher than those aged 30–39 years (17.1%) (data not shown). There was no difference in the number of subjects with high risk for diabetes and cardiovascular disease diagnosed by HbA1c or FPG except for the parameter TG.

This indicates no serious disagreement between the two methods to identify high risk people for diabetes and cardiovascular disease.

The diversity within the Arab ethnic groups requires more studies on using HbA1c to accurately estimate the cut-off values for diagnosing diabetes in different populations. In the Palestinian Arab population raising the cut-off value to 6.5% (48 mmol/mol) increases the percentage of subjects that require preventive measures instead of treatment.

Acknowledgments

The authors thank Fida Zeidan from UNRWA for organizing the teams at different UNRWA clinics. Also, the authors thank the staff of UNRWA clinics for their cooperation in the study. Thanks to Dr. Khalidoun Bader from Al-Quds University for his assistance in statistical analysis. Guarantor: Akram T. Kharroubi.

Author Contributions

Conceived and designed the experiments: AK. Performed the experiments: UK AAA. Analyzed the data: AK. Contributed reagents/materials/analysis tools: UK AAA. Wrote the paper: AK HD.

References

1. Cavagnolli G, Gross JL, Camargo JL. (2012) HbA1c in the diagnosis of diabetes: which cut-off point? Diabetes Med 29: 286–287.
2. Hare MJ, Shaw JE, Zinman PB. (2012) Current controversies in the use of haemoglobin A1c. J Intern Med 271: 227–236.
3. (2009) International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 32: 1327–1334.
4. Association AD. (2010) Standards of medical care in diabetes—2010. Diabetes Care 33 Suppl 1: S11–61.
5. Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, et al. (2011) Guidelines and recommendations for laboratory analysis in the management of diabetes mellitus. Clin Chem 57: e1–e47.
6. WHO. (2011) Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus: Reported by a WHO Consultant. Shaw JE, d’Emden MC, Goodall J (2011) Is Australia ready to use glycated haemoglobin for the diagnosis of diabetes? Med J Aust 195: 7–8.
7. Davison MB (2011) Diagnosing diabetes with glucose criteria: worshiping a false God. Diabetes Care 34: 524–526.
8. Day A (2012) HbA1c and diagnosis of diabetes. The test has finally come of age. Ann Clin Biochem 49: 7–8.
9. Malkani S, Mordes JP (2011) Implications of using hemoglobin A1C for diagnosing diabetes mellitus. Am J Med 124: 395–401.
10. Sacks DB (2011) A1C versus glucose testing: A comparison. Diabetes Care 34: 518–523.
11. Cheng YJ, Gregg EW, Geiss LS, Imperatore G, Williams DE, et al. (2009) Association of A1C and fasting plasma glucose levels with diabetic retinopathy prevalence in the U.S. population: Implications for diabetes diagnostic thresholds. Diabetes Care 32: 2007–2032.
12. Dagege-Jack S (2010) Pitfalls in the use of HbA1c (e) as a diagnostic test: the ethnic conundrum. Nat Rev Endocrinol 6: 589–593.
13. Ma H, Gao X, Lan HD, Hu Y, Li XM, et al. (2015) Glycated Haemoglobin in Diagnosis of Diabetes Mellitus and Pre-diabetes among Middle-aged and Elderly Population: Shanghai Changfeng Study. Biomed Environ Sci 28: 155–162.
14. Mukai N, Doi Y, Ninomiya T, Hata J, Hirakawa Y, et al. (2012) Cut-off values for the diagnosis of type 2 diabetes in community-dwelling Japanese subjects: the Hisayama Study. Diabetes Med 29: 99–106.
15. Tsugawa Y, Takahashi O, Meigs JB, Davis RB, Imamura F, et al. (2012) New glycated hemoglobin (HbA1c) as a diagnostic criteria for diabetes in low- and middle-income settings: evidence from Peru. PLoS One 6: e18069.
16. Malik M, Bakir A, Saab BA, King H (2005) Glucose intolerance and associated factors in the multi-ethnic population of the United Arab Emirates: results of a national survey. Diabetes Res Clin Pract 69: 188–199.
17. Cavagnolli G, Comerlato J, Comerlato C, Renz PB, Gross JL, et al. (2011) HbA1c measurement for the diagnosis of diabetes: is it enough? Diabet Med 28: 31–35.
18. Hayes J, Hawthorne G, Unwin N (2012) Undiagnosed diabetes in the over-60s: performance of the Association of Public Health Observatories (APHO) Diabetes Prevalence Model in a general practice. Diabet Med 29: 115–120.
19. Costa B, Barrio F, Pinol JL, Cabrer J, Mundet X, et al. (2013) Shifting from glucose diagnosis to the new HbA1c diagnosis reduces the capability of the Finnish Diabetes Risk Score (FINDRISC) to screen for glucose abnormalities within a real-life primary healthcare preventive strategy. BMC Med 11: 45.
20. Ljpska KJ, De Rekeneire N, Van Ness PH, Johnson KC, Kanaya A, et al. (2010) Identifying dysglycemic states in older adults: implications of the emerging use of hemoglobin A1c. J Clin Endocrinol Metab 95: 5299–5305.
21. Miranda JJ, Bernabe-Orozco A, Stanoevska S, Malaga G, Gilman RH, et al. (2011) HbA1c as a diagnostic criteria for diabetes in low- and middle-income settings: evidence from Peru. PLoS One 6: e16069.
22. Bergous S, Cook CB, Wu Q, Burrett MF, Hernandez JS, et al. (2011) Hemoglobin A1c testing alone does not sufficiently identify patients with prediabetes. Am J Clin Pathol 135: 647–677.
23. Seo HA, Lee IK (2012) An emerging diabetes mellitus diagnosis modality: HbA1c. Korean J Intern Med 27: 39–40.
24. Rohlff CL, Little RR, Wiedmeyer HM, England JD, Madsen R, et al. (2000) Use of GHb (HbA1c) in screening for undiagnosed diabetes in the U.S. population. Diabetes Care 23: 167–191.
25. Yu Y, Ouyang XJ, Lou QL, Gu LB, Mo YZ, et al. (2012) Validity of glycated hemoglobin in screening and diagnosing type 2 diabetes mellitus in Chinese subjects. Korean J Intern Med 27: 41–46.
26. Tanich E, Bochi GV, Piva SJ, Reiter RS, Kober H, et al. (2012) HbA1c as a tool for the diagnosis of type 2 diabetes: comparison with fasting glucose. Clin Lab 58: 347–350.

PLOS ONE | www.plosone.org 6 February 2014 | Volume 9 | Issue 2 | e88123

Diagnosing Type 2 Diabetes Using HbA1c