Reference ranges of glycated hemoglobin (HbA1c) in capillary blood in the Spanish population

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HIGHLIGHTS

1. HbA1c increased gradually with age in Mediterranean population without diabetes.
2. Almost half of participants older than 65 years had prediabetes levels of HbA1c.
3. HbA1c reference values in Mediterranean population was similar to other cohorts.

Summary

Cross-sectional analysis describing HbA1c reference values by sex and age in a randomly selected Mediterranean general population sample. Using two methods, Point-of-Care systems and centralized laboratory, results show that HbA1c values increase with age. Almost half of the sample aged 65 years or older had median values >5.7% (prediabetes cut-off point).

1. Introduction

HbA1c level, a diagnostic test for diabetes, provides an accurate and reliable biomarker of mean 90-day blood glucose values, yielding highly reproducible results not only for diagnosis but also for follow-up monitoring of patients with diabetes [1]. The level of HbA1c is usually estimated in a central laboratory from venous blood sample. However, new techniques allow its measurement in capillary blood, obtained by pricking the pulp of the finger, and quick analysis with a Point of Care (POC) system [2, 3].

Mean HbA1c values and their association with cardiovascular risk factors have been analysed in differing geographic areas [4-6]. However, reference values of this biomarker in capillary blood have not been previously described in a general Mediterranean population. The objective of this study was to determine HbA1c levels by age group and sex in a Mediterranean population sample, using two different techniques: venous blood tested in a central laboratory and a capillary sample tested by a POC system.

2. Methods and results

A randomized population-based cross-sectional study was conducted in adult residents of the city of Girona and surrounding areas (northeastern Spain), aged 35- 74 years with no history of diabetes or cardiovascular disease. Fasting biological samples (venous and capillary blood) were both collected on the same day. Methodology has been previously described [7].

Capillary blood analysis to determine HbA1c was performed instantaneously with the Cobas b101 POC device, using latex agglutination procedures (Roche Diagnostics, Basel, Switzerland). This device meets the generally accepted performance criteria for HbA1c [8].

Venous samples were withdrawn in <60 seconds after 10–14 h fasting and stored at -80°C for analysis within 6 months by a central laboratory. Glycaemia was determined with enzymatic methods (ABX-Horiba). Glycated hemoglobin was determined in EDTA plasma by colorimetry and latex agglutination procedures (ABX-Horiba). In a previously published analysis, the intraclass correlation coefficient for both methods was 0.72 (0.67-0.76) for women and 0.91 (0.89-0.93) for men [7].

Percentiles 5, 10, 25, 50, 75, 90 and 95 of the HbA1c distribution were estimated by 10-year age groups (i.e. 35-44, 55-54, 55-64, 65-74) and by sex for both the POC and the central laboratory results. Pearson correlations were performed between glycaemia and HbA1c determined with both methods. All statistical analyses were performed with the R Statistical Package (V.3.3.2).

The present study included 895 individuals (53.3% women; mean age 50 years [standard deviation=10]). Median POC values of HbA1c were slightly higher than the centralized laboratory values (5.5% [5.3-5.7] vs. 5.4% [5.2-5.7], respectively). Table 1 summarizes the main participant characteristics by sex. HbA1c levels obtained by each method increased

with age in both men and women (Figure 1). The 75th percentile of HbA1c in both men and women was 5.7%, the cut-off point for the diagnosis of prediabetes [1]. When stratified by age, almost half of our sample aged 65 or older had HbA1c values ≥5.7%. We observed greater variability in the results from the centralized laboratory, particularly at the low ranges. However, in both men and women the Pearson correlations between HbA1c and fasting glucose were similar with both methods (Figure 2).

3. Discussion and conclusion

The present study describes the HbA1c age distribution in a Mediterranean population without a history of diabetes or cardiovascular disease, estimated by central laboratory and by POC testing. The mean HbA1c observed was similar to previously described results in American and Chinese populations [4, 5]. In addition, Ma et al. described a gradual age-associated increase in HbA1c in the Chinese population aged 18 to 99 years [5]. In our population, a high percentage of the population older than 70 years had values indicative of prediabetes. Although this finding should not lead to the prescription of a drug treatment, non-pharmacological approaches including nutritional intervention and lifestyle changes can be applied. Other individual factors and the personal risk of developing diabetes should also be taken into account, especially in older adults [1].

The POC measurement of HbA1c is a relatively recent approach that is gaining users, given its convenience of use. The intraclass correlation coefficients for the comparison of POC with the central laboratory method was fair to good in women and excellent in men [9]. On the one hand, it benefits the patient who obtains integrated care in less time, without requiring a second visit to obtain the results. On the other hand, it offers healthcare providers

the possibility of timely decisions that improve effectiveness and strengthen the preventive message transmitted to patients [3, 10, 11].

HbA1c was increased across all age groups, with similar interquartile range in both men and women. The central laboratory and POC techniques yielded similar HbA1c concentrations. The capillary blood results can be used as reference values in a Mediterranean population with no history of diabetes or cardiovascular disease.

Conflict of interest

The authors state that they have no conflicts of interest.

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Ethical approval

Written informed consent was obtained from all participants. The present study was approved by the Clinical Research Ethics Committee of Parc de Salut Mar (CEIC-PSMAR, #2014/5815/I).

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Author contributions

All authors made substantial contributions to study conception and design and to data acquisition or analysis and interpretation, took part in drafting the article or revising it critically for important intellectual content, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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FIGURE LEGENDS

Figure 1. HbA1c percentiles (5, 10, 25, 50, 75, 90, 95) for point-of-care and central laboratory, by age and sex. The black line marks prediabetes cut-off point (HbA1c = 5.7%).

Figure 2. Correlation between Hba1c measured with central laboratory and point-of-care methodologies and fasting plasma glucose by sex.

Table 1. Characteristics of the participants, by sex

	Women N=479	**Men N=416**	**p-value**
Age, years, mean (SD)	50 (10)	49 (10)	0.036
Education, n (%)			0.135
Less than primary school	3 (0.6)	0 (0.0)	
Primary school	106 (39.7)	84 (20.4)	
Secondary school	188 (39.7)	188 (45.7)	
University	177 (37.3)	139 (33.8)	
Smoking status, n (%)			<0.001
Non smoker	251 (52.6)	155 (37.3)	
Former smoker	136 (28.5)	143 (34.5)	
Current smoker	90 (18.9)	117 (28.2)	
Body mass index, kg/m^2, mean (SD)	25.8 (4.7)	26.9 (3.9)	<0.001
Waist circumference, cm, mean (SD)	85.6 (12.5)	94.8 (11.0)	<0.001
Obesity, n (%)	238 (49.7)	270 (64.9)	<0.001
Systolic blood pressure, mmHg, mean (SD)	106 (16)	118 (15)	<0.001
Diastolic blood pressure, mmHg, mean (SD)	71 (11)	78 (10)	<0.001
Hypertension, arterial, n (%)	85 (17.9)	138 (33.6)	<0.001
Total cholesterol, mmol/l, mean (SD)	5.38 (0.96)	5.46 (0.98)	0.229
HDL cholesterol, mmol/l, mean (SD)	1.55 (0.34)	1.32 (0.28)	<0.001
LDL cholesterol, mmol/l, mean (SD)	3.39 (0.82)	3.52 (1.01)	0.041
Triglycerides, mmol/l, median [IQR]	1.84 [1.42-2.51]	2.33 [1.71-3.18]	<0.001
Glucose, mmol/l, mean (SD)	2.28 [2.15-2.46]	2.41 [2.28-2.56]	<0.001
Central laboratory HbA1c mmol/mol (%), median [IQR]	5.4 [5.3-5.7]	5.4 [5.2-5.7]	0.206
POC HbA1c mmol/mol (%), median [IQR]	5.5 [5.3-5.7]	5.5 [5.3-5.7]	0.538

SD: Standard deviation. HDL: High-density lipoprotein. LDL: Low-density lipoprotein. IQR: Interquartile range. POC: Point of care

Figure 1.

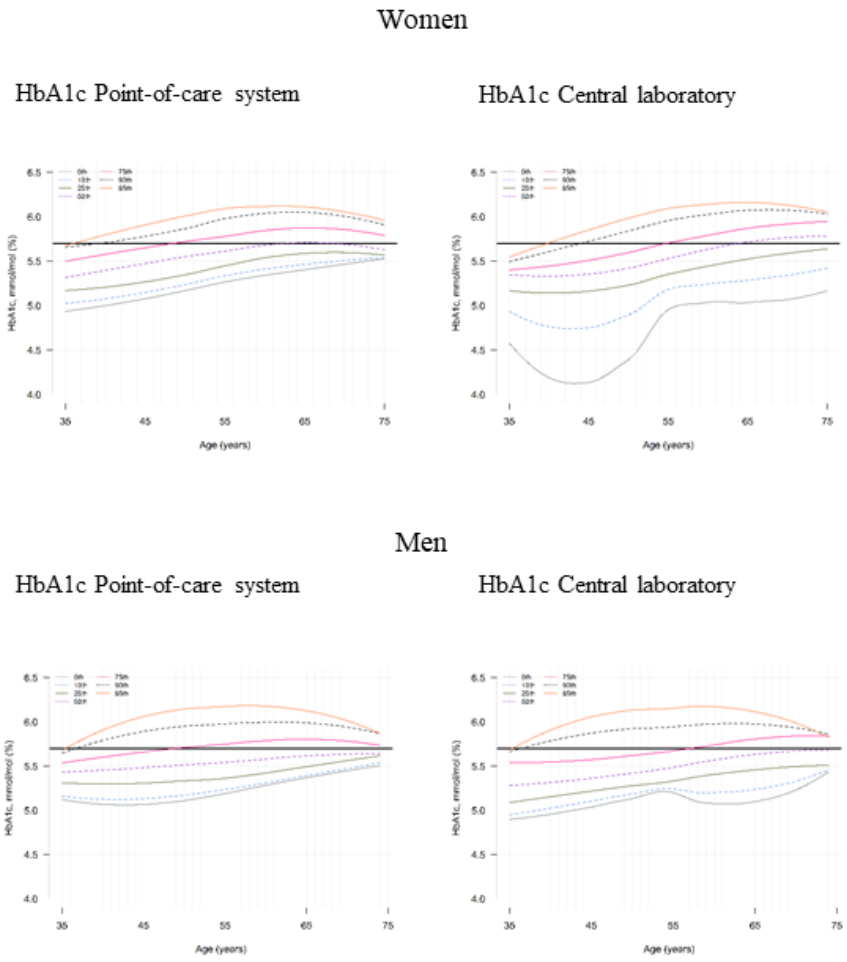
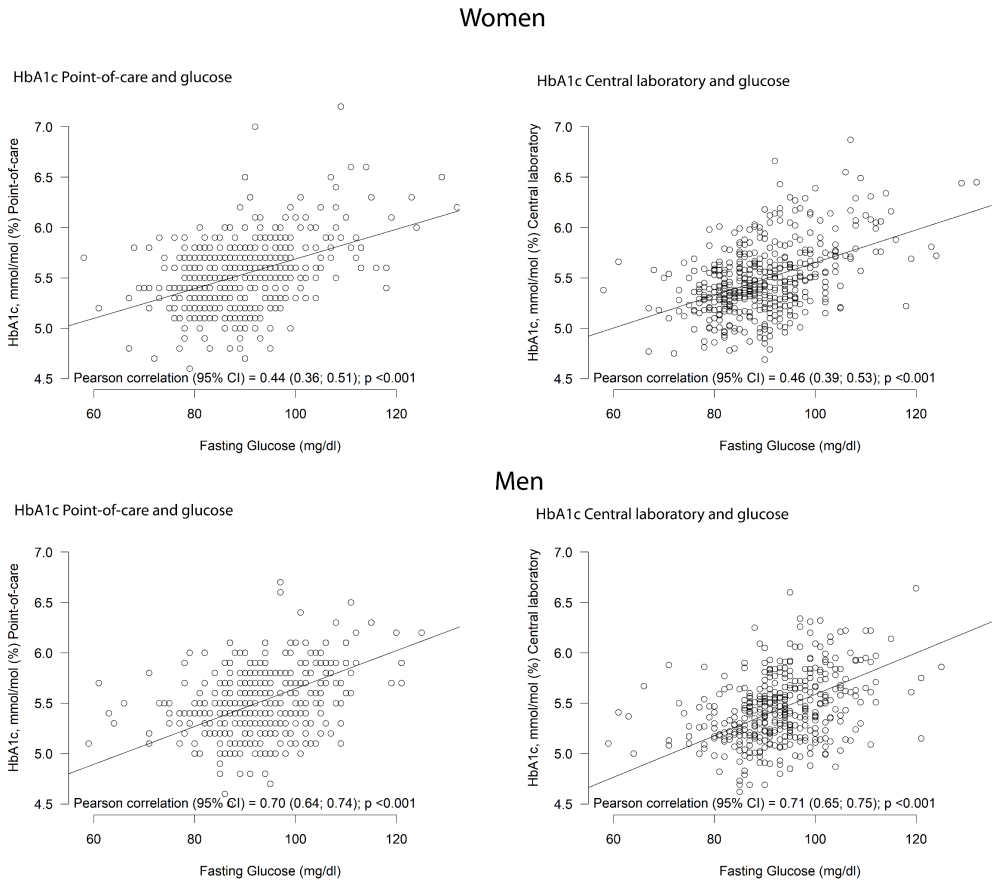

Women
HbA1c Point-of-care system
HbA1c Central laboratory
Men
HbA1c Point-of-care system
HbA1c Central laboratory
Age (years)

Figure 2.


Women
HbA1c Point-of-care and glucose
HbA1c, mmol/mol (%) Point-of-care
Pearson correlation (95% CI) = 0.44 (0.36; 0.51); p <0.001
Fasting Glucose (mg/dl)
HbA1c Central laboratory and glucose
HbA1c, mmol/mol (%) Central laboratory
Pearson correlation (95% CI) = 0.46 (0.39; 0.53); p <0.001
Fasting Glucose (mg/dl)
Men
HbA1c Point-of-care and glucose
HbA1c, mmol/mol (%) Point-of-care
Pearson correlation (95% CI) = 0.70 (0.64; 0.74); p <0.001
Fasting Glucose (mg/dl)
HbA1c Central laboratory and glucose
HbA1c, mmol/mol (%) Central laboratory
Pearson correlation (95% CI) = 0.71 (0.65; 0.75); p <0.001
Fasting Glucose (mg/dl)