diabetesresearchandclinicalpractice188(2022)109929

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.journals.elsevier.com/diabetes-research-and-clinical-practice

Aging of glucose profiles in an adult population without diabetes

Marcos Pazos-Couselo [a,b,c,*], Cristina Portos-Regueiro [a], María González-Rodríguez [a], Jose Manuel García-Lopez [b,d], Manuela Alonso-Sampredro [c,f], Raquel Rodríguez-González [a,b,e], Carmen Fernández-Merino [c,g], Francisco Gude [b,c,f]

[a] Faculty of Nursing, University of Santiago de Compostela, Santiago de Compostela, Spain
[b] Department of Psychiatry, Radiology, Public Health, Nursing and Medicine, University of Santiago de Compostela, Santiago de Compostela, Spain
[c] Research Methods (RESMET), Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain
[d] Santiago de Compostela University Hospital Endocrinology Service, Spain
[e] Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain
[f] University Hospital of Santiago de Compostela, Department of Clinical Epidemiology, Spain
[g] Primary Care Center of A Estrada, A Estrada, Spain

ARTICLE INFO

Keywords:
Continuous glucose monitoring
Aging
Prediabetes
Glucose profiles
Time in range

ABSTRACT

Aims: This study aimed to determine the effect of aging on glucose profiles in a population without diabetes. **Methods:** We investigated the evolution of glucose profiles in an adult population without diabetes using continuous glucose monitoring (CGM) in two periods separated by 5 years. Anthropometrics, laboratory tests (HbA1c, fasting blood glucose) and CGM data (mean glycemia level, coefficient of variation, time in range) were measured in both periods to study the change in values over time. **Results:** 125 participants (68% women) mean age 43.1 ± 12.4 years and classified as normoglycemic at baseline were included. Of the total population 15.2% had worsened glycemic status after 5 years, age and baseline glucose values (HbA1c and percentage of values above 175 mg/dL) were the variables related with this change. Related to CGM, we found that after 5 years there was a decrease in the percentage of values between 70 and 99 mg/dl (45.0% to 38.7%, $p = 0.002$) and an increase in the 100–139 mg/dL range (52.9% to 57.5% $p = 0.016$). **Conclusions:** Our results indicate that in an adult population without diabetes there are changes in glucose profiles with aging highlighting the reduction of blood glucose values below 100 mg/dL.

1. Introduction

Aging can be defined as the irreversible, time-related, proliferative deterioration of an organism's physiological processes that maintain the organism's functional balance [1]. These processes result in a progressive loss of the constantly operating compensatory and homeostatic mechanisms that preserve the biochemical balance and prevent phenotypic derangements. Aging also results in a functional decline in physiological integrity and tissue and organ function. These mechanisms are highly effective and provide a robust homeostasis; however, they deteriorate over time [2]. Glucose homeostasis is a complex process in which glucose levels are maintained within a narrow range. The ability to maintain normal blood glucose homeostasis is an important determinant of an individual's capacity to regulate fasting glucose values and the glycemic response to food intake. In fact, blood glucose regulation has important implications for health. Despite this, there is still a lack of knowledge regarding glycemic behavior and its deterioration with age.

Technological advances related to glucose measurement have provided a greater view of glucose profiles in individuals with diabetes and, more recently, in healthy individuals. Continuous glucose monitoring (CGM) systems are minimally invasive devices that help ascertain glycemic behavior and the degree of metabolic control more accurately than classical measurement systems (e.g., capillary blood glucose, fasting plasma glucose [FPG], oral glucose overload, and glycated hemoglobin [HbA1c]). CGM systems provide information on the magnitude and duration of glycemic oscillations, providing major utility for the control and follow-up of patients with diabetes.

Although its use is mainly focused on patients with diabetes, CGM has in recent years been increasingly employed in epidemiological studies in healthy volunteers. The main advantage of CGM for research, in addition to the information provided, is the device's portability, ease of use, cost-effectiveness, and ability to be used during normal daily

* Corresponding author at: Avda. Xoan XXIII, 15782 Santiago de Compostela, Spain.
E-mail address: marcos.pazos@usc.es (M. Pazos-Couselo).

https://doi.org/10.1016/j.diabres.2022.109929
Received 25 March 2022; Received in revised form 6 May 2022; Accepted 10 May 2022
Available online 14 May 2022

activities [3].

A few studies with CGM have involved healthy volunteers [4–11], however, there have been no studies analyzing the effect of aging on these profiles in a normoglycemic population. The information on the progression of glucose profiles over time in individuals without diabetes is therefore limited. Glycemic behavior and its progression over time in healthy participants without diabetes need to be understood to identify the changes that occur with aging, define where the age-related deterioration in the glycemic status begins, and to develop strategies that help identify and prevent dysglycemia conditions and its effects on health.

This study was conducted to determine the effect of aging on glucose profiles in a population without diabetes.

2. Material and methods

2.1. Study design

The study is based on a previous project funded by the Carlos III Health Institute entitled "Inflammation and Glycation in a General Adult Population, A-Estrada Glycation and Inflammation Study (AEGIS)". A summary of the project can be found at https://www.clinicaltrials.gov (code NCT01796184). In the first published work of this study [9], there is a detailed description of the study.

AEGIS was a cross-sectional study conducted in the municipality of A-Estrada, in the northwest of Spain. An age-stratified random sample of the population aged 18 years and older was drawn from Spain's National Health System Registry. From November 2012 through March 2015, all participants successively attended a 1-day meeting at the primary care center of A-Estrada for evaluation, which comprised an interviewer-administered structured questionnaire that included demographic and anthropometric data; a lifestyle description that included physical exercise, alcohol consumption, and smoking habits; and fasting venous blood sampling. Study participants were also invited to participate in a sub-study of the glycation project (AEGIS1-CGM), which included CGM procedures.

The present study (AEGIS2-CGM) consisted of a new cross-sectional examination 5 years after the start of the previous project's recruitment phase and a repetition of the CGM in those individuals classified as normoglycemic 5 years ago.

2.2. Study participants and procedures

2.2.1. Inclusion criteria

The study included participants with a completed CGM in the AEGIS1-CGM study and who were classified as normoglycemic when the first monitoring was performed.

2.2.2. Exclusion criteria

Participants who did not provide written informed consent were deemed ineligible for participation in the study. This group included patients with dementia, mental retardation, cerebrovascular disease, terminal cancer, or the inability to communicate. Subjects who had diabetes diagnosis at baseline were excluded.

2.2.3. Classification of participants according to their glycemic status

The classification of the participants according to their glycemic status (normoglycemia, prediabetes, and diabetes) was performed according to the American Diabetes Association criteria [12]. Normoglycemia, prediabetes, and diabetes were defined using the following cut-off points:

- FPG $<$ 100 mg/dL and HbA1c $<$ 5.7% for normoglycemia.
- FPG 100 to125 mg/dL or HbA1c 5.7 to 6.4% for prediabetes.
- FPG $\geq$ 126 mg/dL or HbA1c $\geq$ 6.5% for diabetes.

Fasting was defined as no caloric intake for at least 8 h. In the absence of unequivocal hyperglycemia, the diagnosis of diabetes was determined with two abnormal test results in two separate test samples (see Fig. 1).

2.2.4. CGM procedures

Each participant was assigned an iPro®2 MiniMed® continuous glucose monitoring system (Medtronic MiniMed Inc., Northridge, CA, USA). A research nurse inserted a sensor (Enlite™, Medtronic Inc.) subcutaneously into the abdomen, docked the iPro2 to the sensor, and instructed the participant in the use of the CGM device (iPro, Medtronic Inc.). After insertion, the sensor was visually checked for correct attachment.

The iPro2 continuously measures glucose levels in the interstitial fluid and digitally stores the mean sensor current every 5 min, within a range of 40–400 mg/dL (2.2–22.2 mmol/L).

Participants were provided with a conventional glucometer (One-Touch® Verio® Pro; LifeScan, Milpitas, CA, USA) and compatible lancets and test strips for calibrating the CGM. Participants were asked to perform at least 3 capillary blood glucose measurements (usually before the main meals). The capillary blood glucose readings were used to calibrate the iPro2 CGM system. On the seventh day, the sensor was removed, and the data were downloaded and stored for further analysis.

To avoid the high measurement noise present at the beginning of the glucose monitoring, the data were discarded for analysis on the first day of use. In the event the number of data-acquisition "skips" per day totaled more than 2 h, the entire day's data were discarded.

CGM systems (iPro®2 MiniMed® with sensor Enlite™), glucose strips for calibration (OneTouch® Verio® Pro), and the training that the participants received to use the device were the same for the two monitoring procedures (AEGIS1-CGM and AEGIS2-CGM).

2.2.5. Anthropometrics

At the study center, the participants' height, weight, and waist and hip circumference were measured. The body mass index was calculated dividing their weight (kg) by the height squared (m^2).

2.2.6. Laboratory tests

HbA1c levels were determined by high-performance liquid chromatography. All HbA1c values were converted to Diabetes Control and Complications Trial-aligned units [13]. Glucose levels were measured in the fasting serum samples using the glucose oxidase peroxidase method.

2.2.7. CGM (glycemia and glycemic variability measurements)

The mean glucose level, the coefficient of variation (%) and the time in range (%) were calculated using the data provided by the continuous glucose monitoring device. We performed a sub-analysis by age groups of the CGM data. The sample was stratified by age groups ($<$30, 30–39, 40–49, 50–59 and $\geq$ 60 years) based on age at baseline.

2.2.8. Statistical analysis

The data were reported as means $\pm$ standard deviation or with interquartile ranges, depending on the variable distribution. The percentage time spent within a threshold was calculated as the number of CGM glucose readings that fell within the threshold divided by the total number of CGM glucose readings, represented as a percentage.

For the estimation of normality, the bias and coefficients of kurtosis were used, except in those samples that had $<$25 data points, in which case the Shapiro–Wilk test was performed. For the correlation studies, Student's *t*-test or Spearman's test was used, depending on the normality of the distributions in the continuous analytical series. To observe the differences between groups the one-way analysis of variance (ANOVA) and the Kruskal–Wallis H test as a non-parametric test were used. The presence of differences between the means was verified by applying the Mann–Whitney or Wilcoxon *U* test of range of sums.

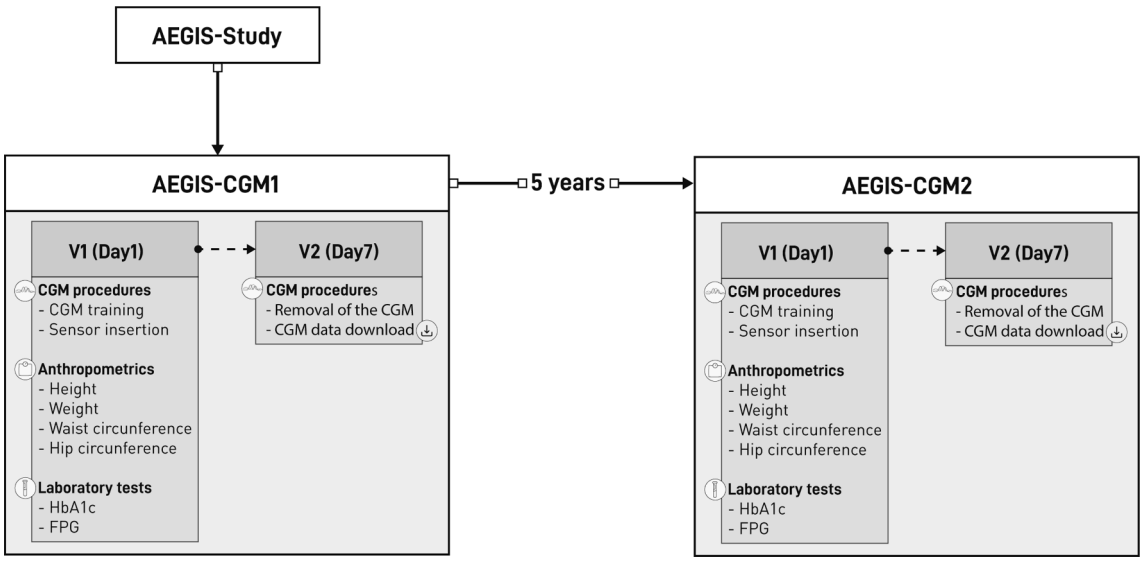

Fig. 1. Study procedures. CGM: continuous glucose monitoring. HbA1c: glycosylated hemoglobin. FPG: fasting plasma glucose.

3. Results

3.1. Characteristics of the study population

A total of 170 individuals were screened for the study, 45 of whom were excluded because they were not classified as normoglycemic in the AEGIS1-CGM study.

A total of 125 participants (68% women) classified as normoglycemic in the AEGIS1-CGM study were included. The AEGIS1-CGM population's mean age was 43.1 ± 12.4 years. Of the total population, 19 (15.2%) had worsened glycemic status after 5 years (18toprediabetesand1todiabetes). Table 1 shows the clinical characteristics of the study participants at baseline and after 5 years. There was a significant increase at 5 years in the study's anthropometric and biochemical variables except for fasting plasma glucose.

3.2. CGM data

CGM glucose values were obtained for a median and interquartile range of 129.0 (128.2, 130.1) hours per subject at baseline and 142.6 (113.0,152.8) hours per subject in the in the second monitoring process. In the AEGIS1-CGM, 6% of participants completed at least 6 days of CGM, 86% 5 days, 6% 4 days, 1% 3 days, and 1% 2 days. In the AEGIS2-CGM, 50% of individuals completed at least 6 days of CGM, 25% 5 days, 11% 4 days, 10% 3 days, and 4% 2 days. A total of 1.2% of CGM data (0.5% in AEGIS1-CGM and 0.5% in AEGIS2-CGM) were discarded because of more than 2 h without CGM data on a day.

Table 1
Anthropometric and biochemical variables.

	Baseline	5 years	Mean difference (95% CI)	P
HbA1c (%)	5.2 ± 0.2	5.3 ± 0.2	0.08 (0.04,0.12)	<0.001
FPG (mg/dL)	83.7 ± 7.8	84.5 ± 9.9	0.81(0.79,2.42)	n/s
BMI (kg/m^2)	26.9 ± 4.7	27.2 ± 5.5	0.36(−0.14,0.87)	0.004
Waist (cm)	86.7 ± 12.9	90.6 ± 13.8	3.88(2.53,5.22)	<0.001
Hip (cm)	99.7 ± 10.8	105.4 ± 10.3	5.67(4.38,6.96)	<0.001

HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; BMI, body mass index; Waist, waist circumference; Hip, hip circumference; n/s: not significant; CI: Confidence interval. Results are expressed as mean ± standard deviation.

Data collected from the CGM systems were compared between baseline and at 5 years. Overall, the individual mean 24-h glucose level in the AEGIS1-CGM study was 103.7 mg/dL, and the mean intra-individual coefficient of variation (a measure of glucose variability) was 14.6%; at 5 years, the mean glucose level and coefficient of variation were 106.77 mg/dL and 15.5%, respectively.

Table 2 and Fig. 2 show the progression in glucose values after 5 years and the cumulative frequency distributions measured by CGM.

The CGM-related parameters that changed significantly over time (Table 2) were glucose values between 70 and 140 mg/dL. We observed a decrease in the values between 70 and 99 mg/dL (45.0% to 38.7%, p = 0.002) and an increase in the 100–139 mg/dL range (52.9% to 57.5% p = 0.016). Percentage of values below 70 mg/dL also change significantly after 5 years (p = 0.042).

In Fig. 2 we can observe that, after 5 years, there is a shift in the curve to the right of the glucose values measured with the CGM. When we analyze the main differences of the general profiles at the first and second time point there is a significant decrease in the values between 60 and 99 mg/dl and a significant increase in the glucose ranges of 110–114 mg/dL, 120–124 mg/dL, 155–159 mg/dL and 160–164 mg/dL.

In the stratified analysis by age groups (Table 2) we can observe that, at baseline, as age increases the CGM mean glucose values increases. Regarding to the percentage of values in the different ranges analyzed, at the first time point, the percentage of values between 70 and 99 mg/dL decrease as age increases and the percentage of values between 100 and 139 mg/dL increases with age. Differences between age groups were significant for these glucose ranges (p = 0.029 and 0.003 respectively).

If we compare the baseline characteristics of the participants who experienced no deterioration in their glycemic status with those whose status worsened, we can see that the latter group presented significant differences in age and HbA1c levels at baseline. The CGM data shows statistically significant differences between the groups in the percentage of values in the 175–180 mg/dL range and in values greater than 180 mg/dL (Table 3).

4. Discussion

Our study provides data on the change in glucose profiles with aging in individuals without diabetes. Although there have been studies that have analyzed glucose profiles in populations without diabetes, there have been no studies on the progression of these profiles over time.

Knowledge of the impact of aging on glucose curves is essential for identifying those affected, determining the mechanisms behind the

Table 2
Continuous glucose monitoring variables.

		Baseline	5 years	Mean difference (95% CI)	P
CGM mean glucose (mg/dL)	All participants (n = 125)	103.7 ± 8.1	106.7 ± 10.6	2.96(1.17,4.74)	0.001
	<30 years (n = 21)	100.8 ± 7.1	102.3 ± 9.2	1.49 (−2.01,5.11)	n/s
	30–39 years (n = 29)	102.7 ± 7.8	105.4 ± 9.6	2.73 (−0.56,6.02)	n/s
	40–49 years (n = 36)	103.6 ± 8.7	108.3 ± 12.9	4.66 (0.64–8.67)	0.035
	50–59 years (n = 25)	105.4 ± 7.0	107.6 ± 9.1	2.18 (−2.09–6.46)	n/s
	≥60 years (n = 14)	107.6 ± 9.1	110.3 ± 9.3	2.64 (−3.84–9.14)	n/s
Percentage of glucose sensor values in range					
<70 (mg/dL)	All participants (n = 125)	1.3 ± 2.3	1.2 ± 3.2	−0.09 (−0.78, 0.60)	0.042
	<30 years (n = 21)	1.1 ± 1.7	0.5 ± 1.3	−0.61 (−1.68,0.44)	n/s
	30–39 years (n = 29)	1.8 ± 3.0	1.0 ± 2.5	−0.78 (−2.09–0.52)	n/s
	40–49 years (n = 36)	1.2 ± 1.9	1.7 ± 4.4	0.50 (−1.20,2.21)	n/s
	50–59 years (n = 25)	1.5 ± 2.9	1.8 ± 3.6	0.26 (−1.58,2.07)	n/s
	≥60 years (n = 14)	0.2 ± 0.4	0.2 ± 0.4	−0.02 (−0.44,0.39)	n/s
70–99 (mg/dL)	All participants (n = 125)	45.0 ± 21.3	38.7 ± 22.7	−6.25(−10.16, −2.33)	0.002
	<30 years (n = 21)	52.8 ± 20.6	46.3 ± 22.4	−6.52 (−15.22,2.17)	n/s
	30–39 years (n = 29)	49.1 ± 18.5	42.8 ± 22.8	−6.3 (−14.59,1.96)	n/s
	40–49 years (n = 36)	46.1 ± 21.8	37.4 ± 24.3	−8.62(−16.28, −0.96)	0.021
	50–59 years (n = 25)	39.3 ± 19.6	32.6 ± 20.8	−6.62 (−15.16,2.36)	n/s
	≥60 years (n = 14)	32.5 ± 24.2	33.6 ± 19.5	1.06 (−14,73,16.86)	n/s
100–139 (mg/dL)	All participants (n = 125)	52.9 ± 20.2	57.5 ± 20.1	4.55(0.87,8.24)	0.016
	<30 years (n = 21)	46.8 ± 20.1	54.2 ± 20.8	7.39 (−1.10,15.90)	n/s
	30–39 years (n = 29)	47.7 ± 16.9	54.1 ± 20.4	6.34 (−0.41,13.09)	n/s
	40–49 years (n = 36)	52.5 ± 20.4	56.6 ± 22.1	4.16 (−4.22,12.56)	n/s
	50–59 years (n = 25)	58.1 ± 19.5	63.4 ± 18.9	5.32 (−2.59,13.25)	n/s
	≥60 years (n = 14)	65.0 ± 22.2	61.2 ± 13.9	−3.78 (−16.49,8.92)	n/s
140–180 (mg/dL)	All participants (n = 125)	3.1 ± 4.1	4.6 ± 6.5	1.45(0.29,2.61)	n/s
	<30 years (n = 21)	2.0 ± 2.56	1.68 ± 3.68	−0.31 (−1.73,1.10)	n/s
	30–39 years (n = 29)	3.3 ± 4.4	3.9 ± 5.5	0.61 (−1.51,2.72)	n/s
	40–49 years (n = 36)	3.0 ± 4.8	6.2 ± 7.8	3.17(0.67,5.67)	0.002
	50–59 years (n = 25)	3.5 ± 3.4	4.4 ± 6.5	0.91 (−2.10,3.95)	n/s
	≥60 years (n = 14)	4.3 ± 4.1	6.7 ± 7.8	2.40 (−2.22,7.04)	n/s
TIR 70–180 (mg/dL)	All participants (n = 125)	95.3 ± 4.9	93.6 ± 8.6	−1.68 (−3.22,0.14)	n/s
	<30 years (n = 21)	96.8 ± 2.9	97.7 ± 3.9	0.87 (−1.01,2.75)	n/s
	30–39 years (n = 29)	94.4 ± 6.3	94.3 ± 7.9	−0.09 (−3.36,3.18)	n/s
	40–49 years (n = 36)	95.5 ± 5.5	91.6 ± 10.8	−3.95(−7.45, −0.45)	0.011
	50–59 years (n = 25)	94.9 ± 3.9	93.4 ± 8.1	−1.44 (−5.03,2.14)	n/s
	≥60 years (n = 14)	95.2 ± 4.5	91.8 ± 8.2	−3.37 (−8.33,1.58)	n/s

Continuous glucose monitoring data and percentage of values in different ranges at baseline and at 5 years. CGM, continuous glucose monitoring; TIR, time in range; CI, Confidence interval; n/s, not significant. Results Baseline and 5 years expressed as mean ± standard deviation.

changes, and identifying risk situations in which interventions and strategies can be applied that could reduce the risk of developing diabetes. These data can be used as a benchmark for studying glycemic aging in individuals without diabetes.

CGM is an accurate technology that provides more information than conventional measurement systems [14–15]. Although CGM is mainly used for individuals with diabetes, recent studies have shown that CGM is a useful, reliable, and accurate diagnostic tool for studying glycemic behavior in populations without diabetes [3,10]. Recent studies have shown the need for using other types of glycemic measurements, such as time in range, which is strongly associated with the risk of microvascular complications and should be an acceptable endpoint for clinical trials [16].

Current knowledge on normoglycemia is largely based on studies with populations without diabetes [17–18,4–11], in which the progression of glucose profiles has not been studied, resulting in a limited understanding of the real-life blood glucose patterns of healthy individuals. Determining how long normoglycemic individuals spend at different blood glucose levels in real-life conditions and the progression of those levels over time is a necessary step in establishing reference points for more detailed studies of altered glycemic states.

Fifteen percent of our population had a worsened glycemic status after 5 years (mainly from prediabetes to diabetes). Other authors [19] have had similar results (11%) with the same follow-up time. Approximately 5%–10% of individuals with prediabetes transition to diabetes annually, although the conversion rate varies by population characteristics and prediabetes definition [20–22]. Several trials have demonstrated reductions in the risk of developing diabetes among prediabetic individuals after lifestyle and drug-based interventions [20,23–28]. In the general population, prediabetes was associated with an increased risk of all-cause mortality, and blood glucose levels are a risk marker for cardiovascular disease among apparently healthy individuals without diabetes [29]. Identifying the changes in glucose profiles that occur in aging is therefore essential for preventing complications derived from hyperglycemia.

The participants without diabetes in our study exceeded the threshold of 140 mg/dL at some point during the day and spent a median of 3.3% of the time (range 0.3%–4.3%) above this level, with these values increasing after 5 years. In addition, 14.4% of the study participants had values above 180 mg/dL in the CGM, a percentage that increased in the second measurement (24.8%). Previous smaller studies have suggested similar patterns [4–8], although they did not study the progression of the profiles. These findings suggest that glucose levels in individuals without diabetes frequently reach out-of-range concentrations and that these values increase over time. In fact, we found that the

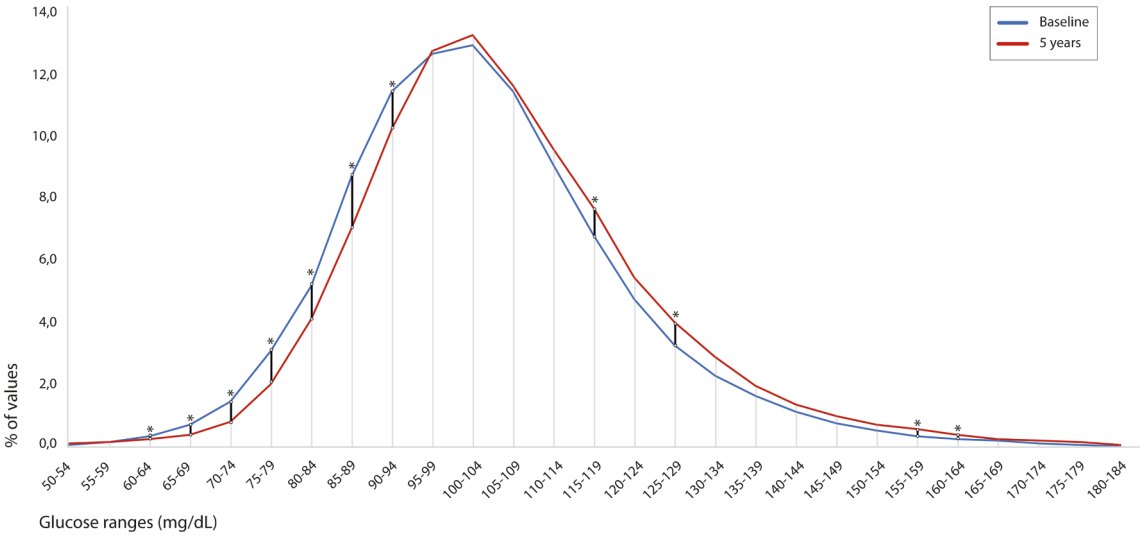

Fig. 2. Glucose values from the continuous glucose monitoring system by range. Distribution of glucose values from the continuous monitoring data by ranges.

Table 3
Characteristics of participants based on glycemic status after 5 years.

	Participants whose glycemic status did not worsen after 5 years (n = 106)	Participants whose glycemic status worsened after 5 years (n = 19)	P
Age (years)	41.9 ± 12.2	50.2 ± 11.6	0.005
HbA1c (%)	5.2 ± 0.2	5.4 ± 0.1	0.001
Differences at baseline of the sociodemographic parameters and between the participants whose glycemic status did not change and those whose glycemic status worsened after 5 years.			
HbA1c, glycosylated hemoglobin.			
Results expressed as mean ± standard deviation.			
(175–180) (%)	0.1 (0.0–0.0)	0.2 (0.0–0.3)	0.039
>180 (%)	0.1 (0.0–0.0)	0.6 (0.0–0.2)	0.005
Differences at baseline of the continuous glucose monitoring data between the participants whose glycemic status did not change and those whose glycemic status worsened after 5 years.			
HbA1c: glycosylated hemoglobin.			
Results expressed as mean ± standard deviation.			

values that represent the glycemic load (HbA1c and mean blood glucose level of the CGM) increase significantly after 5 years of follow-up. However, the fasting plasma glucose level does not change after 5 years, which might be because postprandial blood glucose exposure contributed more than preprandial exposure to the variation in glucose profiles in the individuals without diabetes [30].

Although there have been studies that have evaluated the methods for measuring glycemic variability in healthy individuals and its association with demographics and lifestyles [9,18,31], there is a need for analytical tools adapted to individuals without diabetes that can analyze and detect changes over time, an important aspect for future study.

In this analysis based on repeated CGM measurements under free-living conditions, we observed a significant reduction after 5 years in the recorded CGM values below 100 mg/dL and a significant increase in the 100–140 mg/dL interval. It therefore appears that, in an adult population without diabetes, aging in glucose profiles is manifested by a slight shift in the curve to the right, with a predominance in the reduction of values between 70 and 100 mg/dL.

If we analyze the data obtained according to age groups in the first time point, we observe that mean glucose increases with age, although we did no find significant differences between the groups. However, we found significant differences in the percentage of values in glucose range between 70 and 140 mg/dL with respect to age groups (a decrease in values below 100 mg/dL and an increase in values between 100 and 140 mg/dL). The Shah et al study [11], who also analyzed CGM profiles in healthy nondiabetic participants found statistically significant differences in mean glucose and median time spent in the glucose range of 70–140 mg/dL only in the group of participants ≥ 60 years with respect to the other age groups studied (6 to < 12, 12 to < 18, 18 to < 25 and 25 to < 60 years). The distribution of the groups, and the number of participants over 60 years in our study may explain why we did not find statistically significant differences in mean glucose. In the case of time in range, in our study we analyzed values below 100 mg/dL and values between 100 and 140 mg/dL separately.

This finding highlights the influence of age on glucose values in an adult population without diabetes not only in the existence of a higher percentage of values above a certain range and their increase over time, but also in the decrease of values below 100 mg/dL after 5 years.

After analyzing the clinical characteristics and monitoring data of the individuals whose glycemic status worsened after 5 years, we observed they were older and had higher HbA1c levels and a higher percentage of values above 175 mg/dL at baseline. Given that age is one of the factors included in diabetes risk models [20,32], it is to be expected that the individuals whose glycemic status worsened after 5 years were older than those whose status did not deteriorate. The presence of CGM values above 180 mg/dL in normoglycemic patients and the involvement of those values in the risk of developing prediabetes or diabetes is an aspect to be analyzed in future studies. The study of glucose profiles using CGM will enable the inclusion of new parameters in predicting dysglycemia.

4.1. *Strengths and limitations*

This is the first study to evaluate the progression of glucose profiles measured by CGM in general adult population without diabetes. Our study highlights the ability to obtain CGM data in real-life conditions at 2 different time points, with the same monitoring system and in the same population, allowing us to study the effect of aging on the deterioration of glucose metabolism. The follow-up time might have been too short to identify certain changes in variables related to glycemic variability; however, we found differences between the 2 glucose monitoring periods.

It is possible that, because of the regression to the mean effect, some individuals who just happened to have a lower glucose level during the first data collection period could have been classified as normoglycemic and, therefore, included in the analysis. Although the effect of regression to the mean can never be ruled out, we consider that the influence on the

results is low because we used 2 measurements (FPG and HbA1c) to classify the participants, the subjects who had clinical diabetes diagnosis at baseline were excluded and the variables studied are based on the multiple measurements provided by the CGM of each participant.

Our results have important public health implications and support the use of CGM for studying the progression of glucose profiles in healthy individuals. Knowledge of the progression of glucose profiles in an adult population without diabetes will help in understanding the changes that occur in aging. These findings could lead to speculation about the suitability of current diagnostic practice and whether CGM systems can identify changes in glycemic status with greater precision.

5. Conclusions

Based on our results, we can conclude that, in an adult population without diabetes, the main changes that are manifested in glucose profiles with aging are the reduction of blood glucose values below 100 mg/dL.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This study was supported by grants from the Carlos III Institute of Health (-ISCIII/PI20/01069/Co-funded by European Union), the Network for Research on Chronicity, Primary Care, and Health Promotion (Instituto de Salud Carlos III-ISCIII/RD21/0016/0022/Co-funded by European Union), and the Spanish Diabetes Society.

References

[1] Dodig S, Čepelak I, Pavić I. Hallmarks of senescence and aging. Biochem Med (Zagreb) 2019 Oct 15;29(3); 2019. 10.11613/BM.2019.030501.
[2] Ferrucci L, Gonzalez-Freire M, Fabbri E, Simonsick E, Tanaka T, Moore Z, et al. Measuring biological aging in humans: A quest. Aging Cell 2020;19(2). https://doi.org/10.1111/acel.v19.210.1111/acel.13080.
[3] Akintola AA, Noordam R, Jansen SW, et al. Accuracy of continuous glucose monitoring measurements in normo-glycemic individuals. PLoS One 2015 Oct 7;10 (10), 2015, 10.1371/journal.pone.0139973.
[4] Borg R, Kuenen JC, Carstensen B, Zheng H, Nathan DM, Heine RJ, et al. Real-life glycaemic profiles in non-diabetic individuals with low fasting glucose and normal HbA1c: the A1C-Derived Average Glucose (ADAG) study. Diabetologia 2010;53(8): 1608–11.
[5] Mazze RS, Strock E, Wesley D, Borgman S, Morgan B, Bergenstal R, et al. Characterizing glucose exposure for individuals with normal glucose tolerance using continuous glucose monitoring and ambulatory glucose profile analysis. Diabetes Technol Ther 2008;10(3):149–59.
[6] Derosa G, Salvadeo SAT, Mereu R, D'Angelo A, Ciccarelli L, Piccinni MN, et al. Continuous glucose monitoring system in free-living healthy subjects: results from a pilot study. Diabetes Technol Ther 2009;11(3):159–69. https://doi.org/10.1089/dia.2008.0101.
[7] Fox LA, Beck RW, Xing D. Juvenile diabetes research foundation continuous glucose monitoring study group. Variation of interstitial glucose measurements assessed by continuous glucose monitors in healthy, nondiabetic individuals. Diabetes Care 2010;33(6):1297–9. https://doi.org/10.2337/dc09-1971.
[8] Nomura K, Saitoh T, Kim GU, Yamanouchi T. Glycemic profiles of healthy individuals with low fasting plasma glucose and HbA1c. ISRN Endocrinol 2011; 2011:1–6. https://doi.org/10.5402/2011/435047.
[9] Gude F, Díaz-Vidal P, Rúa-Pérez C, Alonso-Sampedro M, Fernández-Merino C, Rey-García J, et al. Glycemic variability and its association with demographics and lifestyles in a general adult population. J Diabetes Sci Technol 2017;11(4):780–90. https://doi.org/10.1177/1932296816682031.
[10] Rodriguez-Segade S, Rodriguez J, Camiña F, Fernández-Arean M, García-Ciudad V, Pazos-Couselo M, et al. Continuous glucose monitoring is more sensitive than HbA1c and fasting glucose in detecting dysglycaemia in a Spanish population without diabetes. Diabetes Res Clin Pract 2018;142:100–9. https://doi.org/10.1016/j.diabres.2018.05.026.
[11] Shah VN, DuBose SN, Li Z, et al. Continuous glucose monitoring profiles in healthy nondiabetic participants: A multicenter prospective study. J Clin Endocrinol Metab 2019 1;104(10):4356-4364. 10.1210/jc.2018-02763.
[12] American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020.Diabetes Care 2020, 43(Suppl 1): S14-S31. 10.2337/dc20-S002.
[13] Hoelzel W, Weykamp C, Jeppsson JO, et al. IFCC Working Group on HbA1c Standardization: IFCC reference system for measurement of hemoglobin A1c in human blood and the national standardization schemes in the United States, Japan, and Sweden: a method-comparison study. Clin Chem 2004 50: 166-174. 10.1373/clinchem.2003.024802.
[14] Beck RW, Connor CG, Mullen DM, Wesley DM, Bergenstal RM. The fallacy of average: how using HbA1c alone to assess glycemic control can be misleading. Diabetes Care 2017;40(8):994–9. https://doi.org/10.2337/dc17-0636.
[15] Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care 2019;42:1593–603. https://doi.org/10.2337/dci19-0028.
[16] Beck RW, Bergenstal RM, Riddlesworth TD, Kollman C, Li Z, Brown AS, et al. Validation of time in range as an outcome measure for diabetes clinical trials. Dibates Care 2019;42(3):400–5. https://doi.org/10.2337/dc18-1444.
[17] Zhou J, Li H, Ran X, Yang W, Li Q, Peng Y, et al. Reference values for continuous glucose monitoring in Chinese subjects. Diabetes Care 2009;32(7):1188–93. https://doi.org/10.2337/dc09-0076.
[18] Zhou J, Li H, Ran X, Yang W, Li Q, Peng Y, et al. Establishment of normal reference ranges for glycemic variability in Chinese subjects using continuous glucose monitoring. Med Sci Monit 2011;17(1):CR9–13.
[19] Engberg S, Vistisen D, Lau C, Glümer C, Jørgensen T, Pedersen O, et al. Progression to impaired glucose regulation and diabetes in the population-based Inter99 study. Diabetes Care 2009;32(4):606–11. https://doi.org/10.2337/dc08-1869.
[20] Tabák AG, Herder C, Rathmann W, Brunner EJ, et al. Prediabetes: A high-risk state for developing diabetes. Lancet 2012 Jun 16; 379(9833): 2279–2290. 10.1016/S0140-6736(12)60283-9.
[21] Forouhi NG, Luan J, Hennings S, Wareham NJ. Incidence of Type 2 diabetes in England and its association with baseline impaired fasting glucose: the Ely study 1990–2000. Diabet Med 2007;24(2):200–7. https://doi.org/10.1111/j.1464-5491.2007.02068.x.
[22] Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, Pratley R, et al. Impaired fasting glucose and impaired glucose tolerance: implications for care. Diabetes Care 2007;30(3):753–9. https://doi.org/10.2337/dc07-9920.
[23] Knowler WC, Fowler SE, Hamman RF, et al. 10-year follow-up of diabetes incidence and weight loss in the diabetes prevention program outcomes study. Lancet 2009 Nov 14;374(9702):1677–86. https://doi.org/10.1016/S0140-6736(09)61457-4.
[24] Gerstein HC, Yusuf S, Bosch J, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet 2006 Sep 23;368(9541):1096–105. https://doi.org/10.1016/S0140-6736(06)69420-8.
[25] Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346: 393–403. https://doi.org/10.1056/NEJMoa012512.
[26] Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia 2006;49(2):289–97. https://doi.org/10.1007/s00125-005-0097-z.
[27] Torgerson JS, Hauptman J, Boldrin MN, et al. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care 2004 Jan;27(1):155–61. https://doi.org/10.2337/diacare.27.1.155.
[28] Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344(18):1343–50.
[29] Levitan EB, Song Y, Ford ES, Liu S. Is nondiabetic hyperglycemia a risk factor for cardiovascular disease?: A meta-analysis of prospective studies. Arch Intern Med 2004;164(19):2147. https://doi.org/10.1001/archinte.164.19.2147.
[30] Færch K, Alssema M, Mela DJ, Borg R, Vistisen D. Relative contributions of preprandial and postprandial glucose exposures, glycemic variability, and non-glycemic factors to HbA1c in individuals with and without diabetes. Nutr Diabetes 2018;8(1). https://doi.org/10.1038/s41387-018-0047-8.
[31] Hill NR, Oliver NS, Choudhary P, Levy JC, Hindmarsh P, Matthews DR. Normal reference range for mean tissue glucose and glycemic variability derived from continuous glucose monitoring for subjects without diabetes in different ethnic groups. Diabetes Technol Ther 2011;13(9):921–8. https://doi.org/10.1089/dia.2010.0247.
[32] Rodriguez-Segade S, Rodriguez J, Camiña F, Sanmartín-Portas L, Gerpe-Jamardo J, Pazos-Couselo M, et al. Prediabetes defined by HbA 1c and by fasting glucose: differences in risk factors and prevalence. Acta Diabetol 2019;56(9):1023–30. https://doi.org/10.1007/s00592-019-01342-5.