


## Research Article

# Decade-Long Evolution of Diabetes Mellitus and the Impact of COVID-19 on Glycemic Control: A Retrospective Study (2012–2022)

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**Abstract:** The aims were to evaluate the evolution of diabetes mellitus (DM) in the 2012/22 decade and the influence of coronavirus disease 2019 (COVID-19). The study was carried out through retrospective analysis in an outpatient laboratory database. A total of 10,527 glycated hemoglobin (HbA1c) results corresponding to different users were analyzed retrospectively at three different times: 2012/13, 2017/18, and 2021/22. We determined the percentage of DM in these biennia and then the evolution of HbA1c levels of the diabetics themselves. By the World Health Organization (WHO) standards, in 2012/13, 2017/18, and 2021/22, 39.2%, 30.5% and 31.4% of the users of this laboratory had DM, respectively. The median (P25-P75) HbA1c decreased over the decade ( $p < 0.001$ ): 7.7% (7.0-8.8) in 2012/13, 7.4% (6.8-8.3) in 2017/18, and 7.3% (6.8-8.2) in 2021/22. However, there were no statistically significant differences between 2017/18 and 2021/22 ( $p = 1.00$ ). The same trend was observed for individuals older than 45 years ( $p < 0.001$ ), but not for individuals between 18 and 44 years old ( $p = 0.339$ ). There were no statistically significant differences ( $p = 0.374$ ) between female and male individuals. The overall decrease in HbA1c levels since 2012/13 seems to indicate better disease management of individuals with DM. It is possible that the COVID-19 pandemic and all its health and social consequences have negatively affected the downward trend in HbA1c levels. More studies are needed to assess the long-term public health impact of COVID-19, particularly regarding DM and other non-communicable chronic diseases.

**Keywords:** diabetes; HbA1c; COVID-19 pandemic

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## Introduction

Diabetes mellitus (DM) is characterized primarily by increased plasma glucose levels, resulting from either a complete or partial insufficiency of insulin secretion by the pancreas or impaired insulin function. This condition involves a multifactorial metabolic impairment, affecting not only carbohydrates but also lipids and proteins. Type 1 DM (DM1) is a genetic disease in which the immune system attacks and destroys insulin-producing cells, often manifesting early in life [1-3]. Type 2 diabetes mellitus (DM2) is characterized by decreased insulin production or increased resistance to its action. It typically appears in middle age and is closely related to lifestyle factors [4-6]. The significant increase in DM2 across all continents in recent decades has paralleled a more sedentary lifestyle, a high-calorie diet, and, consequently, increased obesity rates [5,7,8]. The complications of DM include both macrovascular and microvascular conditions, such as renal disease, retinopathy, coronary heart disease, stroke, neuropathy, and necrosis of distal tissues, including diabetic foot wounds. Vascular disease in DM is multifactorial, involving an impaired vasodilatory response due to nitric oxide inhibition, decreased fibrinolytic capacity,

thrombocytosis, and platelet aggregation. It also includes dysfunction of smooth muscle cells with overproduction of growth factors, hemodynamic changes, and the accumulation of toxic products resulting from non-enzymatic glycation reactions due to hyperglycemia, as well as the stimulation of oxidative stress [5]. According to the World Health Organization (WHO) global report (published on April 21, 2016), in 2012, DM alone caused 1.5 million deaths [9]. In its global statistics, the WHO reported a prevalence, in Europe, of 6% of diabetics in 2012, rising to 7.5% in 2014. A total of 310 million new cases of diabetes were diagnosed between 1980 and 2014 and the global prevalence was 8.5%. In 2021, the International Diabetes Federation (IDF) estimated that 536.6 million adults between the ages of 20 and 79 were living with DM, representing a global prevalence of 10.5%. According to this organization's predictions, this number is projected to increase to 12.2% by 2045 (783.2 million people with DM) [10–12]. The different laboratory methods for diagnosing DM include fasting glycosuria, fasting glycemia (FG), oral glucose tolerance test (OGTT), random glycemia, glycated hemoglobin (HbA1c), and the concentration of insulin and/or C-peptide or antibodies against pancreatic B cells. The OGTT measures the body's ability to metabolize glucose and eliminate it from the bloodstream, while HbA1c measures the percentage of hemoglobin bound to glucose, thus providing an integrative measure of long-term glycemic levels, reflecting the average blood glucose level over the past 120 days, the normal lifespan of a red blood cell, and is not subject to daily fluctuations in plasma glucose levels [3,13]. The diagnostic criteria for diabetes have been constantly evolving. The latest consensus by the WHO, IDF, and the American Diabetes Association (ADA) defines the diagnosis of DM as follows: fasting blood glucose  $\geq 126$  mg/dL on multiple occasions; HbA1c  $\geq 6.5\%$ ; random blood glucose  $\geq 200$  mg/dL; and a glycemia  $\geq 200$  mg/dl two hours after ingesting 75 g of glucose [3,9]. On March 11, 2020, the WHO declared COVID-19 a pandemic [14] and it was not long before researchers and clinicians observed a mutually exacerbating relationship between DM and this new virus [15,16]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is accompanied by a strong inflammatory reaction, leading to an increased production of cytokines, which attack vital organs, particularly the pancreas, resulting in  $\beta$ -cell dysfunction [16,17]. Likewise, DM is associated with a chronic inflammatory state, which promotes the development of the inflammatory response, increasing the risk of or worsening acute respiratory problems typical of this infection [18,19]. Recent research suggests that acute SARS-CoV-2 infection can worsen hyperglycemia and even induce the onset of diabetes in previously non-diabetic individuals [16,20]. Some studies involving both humans and non-human primates with COVID-19 have observed increased insulin resistance and loss of pancreatic  $\beta$ -cells, particularly among older individuals [21]. The SARS-CoV-2 virus uses the angiotensin-converting enzyme 2, an enzyme present in various pancreatic cells, including islet cells, to cross the cell membrane and disrupt cellular functions, potentially explaining the cases of acute pancreatitis and glucose metabolism dysfunction observed in some COVID-19 patients [22]. For all these reasons, the rapid rise of DM, particularly DM2, is currently among the largest public health crises worldwide and is likely to become the most pressing public health challenge in the near future. There is an urgent need to raise public awareness and take concrete measures to address this global problem to achieve concrete lifestyle changes, reduce the time between disease onset and diagnosis, and improve treatment [11,14,23,24].

At the same time, the scientific community must, more than ever, consider DM as a multifactorial metabolic disorder that interacts with other conditions, such as COVID-19 [15,16].

## Materials and Methods

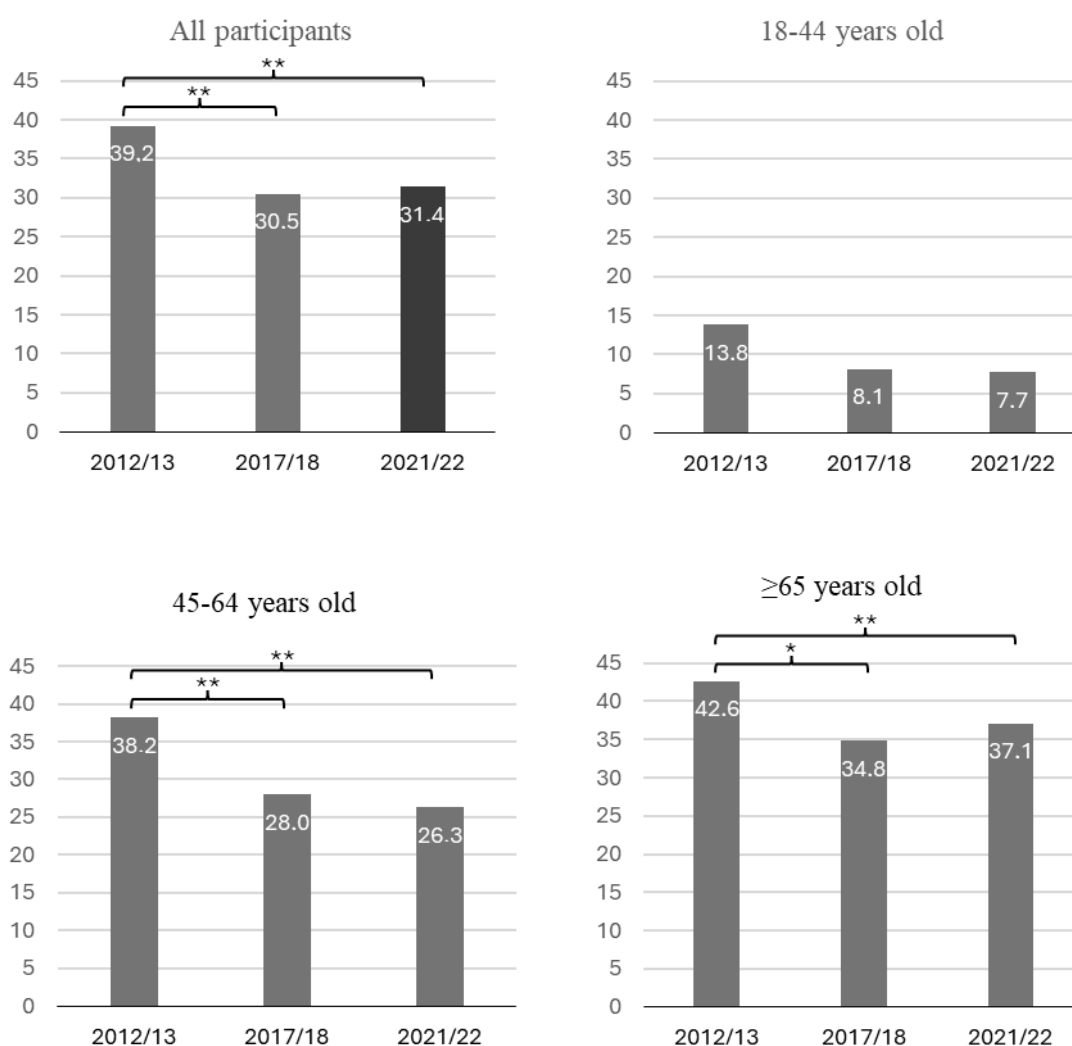
The objectives were to analyze, in a laboratory setting, the evolution of DM through the study of HbA1c levels during the 2012–2022 decade, in a Northeastern Portuguese population, and also to examine the influence of the COVID-19 pandemic, comparing with the years immediately before (2018) and after (2022) it. This study was approved by the University Fernando Pessoa Ethics Commission (ESS/PI – 583/24-3 Addendum, 10<sup>th</sup> of December 2024).

All HbA1c values in the laboratory database from the beginning of the decade (2012/13), before the pandemic (2017/18), and after the declaration of its end (2021/22) were retrospectively analyzed. First, we estimated the percentage of diabetics in the years 2012/13, 2017/18, and 2021/22. Diabetes was defined as a HbA1c value  $\geq 6.5\%$ , under the WHO guidelines. Since the same participant may have undergone multiple tests in the same year, the average of the results was considered so that each value corresponded to a different person. In total, 10,527 participants were included. Then, we looked at the disease progression of these participants over the years by comparing the changes in HbA1c data distribution over the decade. The participants' identities and all personal data were hidden by barcodes issued in the laboratory management program.

Statistical analysis was performed with IBM® SPSS® Statistics (version 29.0). The Kolmogorov-Smirnov test was used to assess the normality of the data distribution. Non-parametric Mann-Whitney and Kruskal-Wallis (with post-hoc Bonferroni correction) tests were used to assess differences between different study periods. Pearson's Chi-squared test was used to test the homogeneity of DM prevalence between the different study periods. Statistical significance was set at  $p < 0.050$ .

## Results

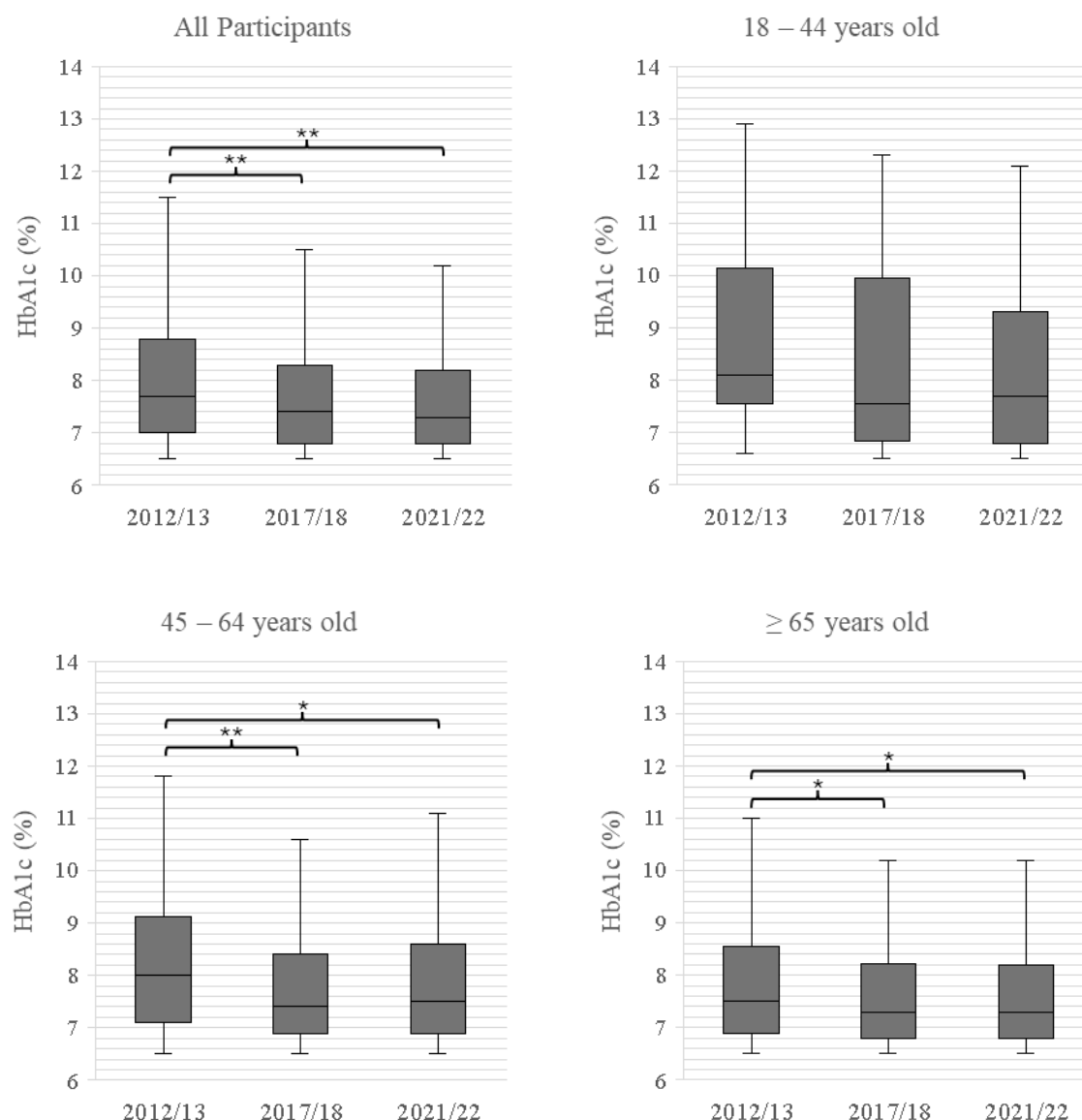
A total of 10,527 HbA1c values, corresponding to 10,527 different individuals, were included in this study. The mean age of the participants was 67 years (SD = 15). Eight hundred and one (7.6%) of the participants were 18-44 years old, 3,223 (30.6%) were 45-64 years old, and 6,503 (61.8%) were  $\geq 65$  years old. Fifty-one percent of the participants were female and 49% were male. According to the WHO standards, in 2012/13, 2017/18, and 2021/22, 39.2%, 30.5%, and 31.4% of the participants, respectively, were diabetic (Fig. 1). There were statistically significant differences between the DM prevalence in the studied periods ( $p < 0.001$ ). The percentage of individuals with DM aged between 18 and 44 was 13.8%, 8.1%, and 7.7% in 2012/13, 2017/18, and 2021/22, respectively. There were no statistically significant differences in DM prevalence within this age group across the studied periods ( $p = 0.112$ ). Among participants aged 45-64 years, the prevalence was higher but exhibited the same decreasing trend over the years of observation: 38.2%, 28.0%, and 26.3% for 2012/13, 2017/18, and 2021/22, respectively. There were statistically significant differences in DM prevalence within this age group across the studied periods ( $p < 0.001$ ). In individuals aged  $\geq 65$  years old (with the highest rates of diabetes), the prevalence of DM also decreased between 2012/13 and 2017/18 (42.6% to 34.8%;  $p < 0.001$ ), but, unlike the other groups, there was a small non-significant increase in the prevalence of DM after the pandemic (2021/22), to 37.1% ( $p > 0.050$ ; SPSS does not provide the exact value).



**Figure 1.** Percentage of diabetics (%), global and by age groups, in the Laboratory, in the three study periods. \* $p < 0.05$ ; \*\* $p < 0.001$ .

By checking the evolution of the disease in those with DM (HbA1c  $\geq 6.5\%$ ), we analyzed the evolution of their HbA1c values, over the years, by age group. The median (P25-P75) HbA1c decreased over the decade: 7.7% (7.0-8.8) in 2012/13, 7.4% (6.8-8.3) in 2017/18, and 7.3% (6.8-8.2) in 2021/22 (Fig. 2). There were statistically significant differences between 2012/13 and 2017/18 ( $p < 0.001$ ) and between 2012/13 and 2021/22 ( $p < 0.001$ ), but not between 2017/18 and 2021/22 ( $p = 1.00$ ). There were no statistically significant differences between the HbA1c levels of the 18-44-year-old participants across the three study periods ( $p = 0.339$ ). In 2012/13, the median (P25-P75) HbA1c levels in 45-64 years

individuals [8.0% (7.1–9.1)] were higher than in 2017/18 [7.4% (6.9–8.4);  $p < 0.001$ ] and in 2022/23 [7.5% (6.8–8.2);  $p = 0.003$ ], but there were no statistically significant differences between the years 2017/18 and 2021/22 ( $p = 1.00$ ). A similar trend was observed for individuals  $\geq 65$  years old. At the beginning of the decade, in 2012/13, the median (P25–P75) HbA1c levels were higher [7.5% (6.9–8.6)] than in 2017/18 [7.3% (6.8–8.2);  $p = 0.001$ ] and in 2022/23 [7.3% (6.8–8.2);  $p = 0.005$ ], but there were no changes between 2017/18 and 2021/22 [7.3% (6.8–8.2) and 7.3% (6.8–8.2), respectively;  $p = 1.00$ ]. There were no statistically significant differences ( $p = 0.374$ ) between the HbA1c levels in female [median (P25–P75) = 7.4% (6.8–8.3)] and male [median (P25–P75) = 7.4% (6.9–8.5)] individuals.



**Figure 2.** HbA1c (%) evolution, global and by age groups, in diabetics across the three study periods. \* $p < 0.05$ ; \*\* $p < 0.001$ .

## Discussion

The analysis of HbA1c values over a decade in this large sample of users seems to show a significant drop in the prevalence of DM, according to the WHO criteria, between 2012 and 2022. This finding appears to contradict the values reported by the WHO and the IDF at a global level. However, this study does not allow us to accurately estimate the prevalence of DM in Portugal, as it was conducted in an analysis laboratory where the users tend to be sick, thus not representing the general population. Additionally, the overall decreasing estimated prevalence of DM over the period retrospectively analyzed in this study may be explained by a more widespread prescription of HbA1c analysis by medical practitioners to the general public during routine checkups.

Better and more regular access to healthcare, new therapeutic options, and increased awareness of the harmful effects of this chronic disease are factors that have likely led to positive changes in diet and lifestyle [25]. The overall decrease in HbA1c levels since 2012/13 seems to indicate better disease

management of individuals with DM. However, despite the slight decrease in HbA1c levels in younger individuals with DM (18–44 years old), there were no statistically significant differences ( $p = 0.339$ ) between the three separate periods analyzed retrospectively in this study. The number of individuals included in this group was small, which limited statistical power. Of the 10,527 individuals included in the present study, only 801 (7.6%) were 18–44 years old and the DM prevalence ranged from 7.7% to 13.8% in this age group.

Regarding the effect of COVID-19, it was not possible to assess the participants' infection history, which constitutes a limitation in interpreting the results of this work. The WHO COVID-19 database reports a cumulative number of 5.7 million cases of COVID-19 in Portugal [26], but the real number is likely higher due to the underreporting of COVID-19 cases [27], a phenomenon usually observed with infectious diseases [28]. The influence of acute SARS-CoV-2 infection on DM is still poorly understood, but some evidence suggests that COVID-19 increases the risk of developing DM [29,30]. The most widely accepted explanation involves the development of inflammatory cytokines and chemokines, which cause systemic inflammation that can affect the pancreatic  $\beta$ -cells and insulin sensitivity [29]. The usage of glucocorticoids in hospitalized COVID-19 patients [31] might also influence their glycemic control [32]. There is also evidence that individuals with pre-existing DM have more severe symptoms and a higher mortality risk [33]. The COVID-19 pandemic and multiple lockdowns led to negative changes in dietary and physical activity habits [34], which, among other factors, may have contributed to worse glycemic control [5,7,8]. The non-statistically significant increase in DM prevalence observed from 2017/18 to 2021/22 in individuals  $\geq 65$  years old ( $p > 0.050$ , SPSS does not provide the exact value) may be explained by all the adverse health and social effects of the COVID-19 pandemic.

Other studies have observed a significant reduction in HbA1c levels in people with DM2 during the COVID-19 pandemic [35,36], particularly in individuals with higher initial HbA1c levels and among women. The authors examined the dietary habits and routine medication usage during the study period, concluding that the groups with reduced HbA1c levels had also reduced their consumption of ultra-processed foods [35,36].

The present study shows a clear decrease in HbA1c levels in individuals with DM from 2012/13 to 2017/18, which remained stable until 2021/22. It is possible that the COVID-19 pandemic and all its health and social consequences negatively impacted the downward trend in HbA1c levels, but the available data in this study does not allow for such analysis. More studies with additional data on participants' health, lifestyle habits, and SARS-CoV-2 infection history are needed to assess the long-term public health impact of COVID-19, particularly concerning DM and other non-communicable chronic diseases.

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## Author Contributions

RA was responsible for the study's methodology, formal analysis, and investigation, wrote the original draft, and reviewed and edited the manuscript. ID performed formal analysis and investigation, and reviewed and edited the manuscript. PA contributed to formal analysis and investigation. MD participated in the study's conceptualization, methodology, and supervision, wrote the original draft, and reviewed and edited the manuscript. All authors contributed to the study's conception and design and read and approved the final manuscript.

## Conflicts of interest

The authors declare no competing interests.

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