Original article

https://doi.org/10.6065/apem.2346180.090
Ann Pediatr Endocrinol Metab 2024;29:242-249

Annals of Pediatric Endocrinology & Metabolism
apem

Long-term tracking of glycosylated hemoglobin levels across the lifespan in type 1 diabetes: from infants to young adults

Sujin Kim[1],
Seo Jung Kim[1],
Kyoung Won Cho[1],
Kyungchul Song[1],
Myeongseob Lee[1],
Junghwan Suh[1],
Hyun Wook Chae[1],
Ho-Seong Kim[1],
Ahreum Kwon[2]

[1]Department of Pediatrics, Severance Children's Hospital, Endocrine Research Institute, Yonsei University College of Medicine, Seoul, Korea
[2]Dr Kwon's Growth Clinic, Seoul, Korea

Purpose: Glycosylated hemoglobin (HbA1c) is commonly used as a monitoring tool in diabetes. Due to the potential influence of insulin resistance (IR), HbA1c level may fluctuate over a person's lifetime. This study explores the long-term tracking of HbA1c level in individuals diagnosed with type 1 diabetes mellitus (T1DM) from infancy to early adulthood.
Methods: The HbA1c levels in 275 individuals (121 males, 43.8%) diagnosed with T1DM were tracked for an average of 9.4 years. The distribution of HbA1c levels was evaluated according to age with subgroups divided by gender, use of continuous glucose monitoring (CGM), and the presence of complications.
Results: HbA1c levels were highest at the age of 1 year and then declined until age 4, followed by a significant increase, reaching a maximum at ages 15–16 years. The levels subsequently gradually decreased until early adulthood. This pattern was observed in both sexes, but it was more pronounced in females. Additionally, HbA1c levels were higher in CGM nonusers compared with CGM users; however, regardless of CGM usage, an age-dependent pattern was observed. Furthermore, diabetic complications occurred in 26.8% of individuals, and the age-dependent pattern was observed irrespective of diabetic complications, although HbA1c levels were higher in individuals with diabetic complications.
Conclusion: HbA1c levels vary throughout the lifespan, with higher levels during adolescence. This trend is observed regardless of sex and CGM usage, potentially due to physiological IR observed during adolescence. Hence, physiological IR should be considered when interpretating HbA1c levels during adolescence.

Keywords: Type 1 diabetes mellitus, Adolescents, HbA1c, Age, Sex, Insulin resistance

Highlights

- In individuals with type 1 diabetes mellitus, glycosylated hemoglobin levels often peak during puberty and then decline, regardless of sex, continuous glucose monitoring (CGM) use, or complications.
- The physiological insulin resistance during adolescence makes glucose management challenging.
- Proactive strategies, including the use of CGM, are essential for achieving glycemic targets and preventing complications during this critical period.

Introduction

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease characterized by destruction of insulin-producing beta cells in the pancreas, resulting in a lifelong dependence

Received: 11 August, 2023
Revised: 2 November, 2023
Accepted: 12 December, 2023

Address for correspondence:
Ahreum Kwon
Dr Kwon's Growth Clinic, Banpo-daero, Seocho-gu, Seoul 06506, Korea
Email: armea@naver.com
http://orcid.org/0000-0002-9692-2135

ISSN: 2287-1012(Print)
ISSN: 2287-1292(Online)

on insulin therapy.[1] Strict glycemic control is essential for reducing the risk of complications, mortality, and morbidity related to diabetes.[2-4] This control is predominantly monitored through glycosylated hemoglobin (HbA1c) levels. Despite limitations in assessing glycemic variability due to fluctuations in blood sugar levels, measuring HbA1c is currently considered the gold standard for assessing long-term glycemic control in diabetic patients, as it provides an average glycemic level.[5] Numerous studies have demonstrated that HbA1c levels less than 7% significantly reduce both microvascular and macrovascular complications associated with diabetes.[6] However, in young children (aged <6 years), individualized glycemic targets are necessary to balance the risks of hypoglycemia and the developmental burdens of intensive treatment plans. The American Diabetes Association (ADA) recommends special consideration to the risk of hypoglycemia in children younger than 6 years, as they are often unable to recognize, articulate, and manage hypoglycemia.[7]

Meanwhile, variations in insulin sensitivity based on age and gender in children and adolescents have been documented.[8] During adolescence, it is presumed that fluctuations in sex hormone secretion[9] and growth hormone (GH)/insulin-like growth factor I (IGF-I) levels[10,11] occur due to growth, leading to insulin resistance (IR).[12] In other words, significant changes in GH/IGF-I and sex steroid levels during adolescence can result in physiological IR, regardless of obesity, leading to a decrease in insulin sensitivity by approximately 25%–30%.[13] Additionally, females show higher IR and homeostasis model assessment of IR values compared with males from prepubertal to pubertal stages.[14-16] Insulin sensitivity and resistance are critical factors influencing glycemic control in individuals with T1DM. Consequently, in such pediatric patients, the presence of physiological IR at different ages may contribute to variations in HbA1c based on age, puberty, and sex, even among those who have been effectively managing their diabetes.[17]

In this study, we investigated the longitudinal trajectory of HbA1c levels in individuals diagnosed with T1DM from infancy to early adulthood, specifically between the ages of 6 months and 30 years, to analyze the pattern of HbA1c levels across age groups. The pattern was analyzed using continuous glucose monitoring (CGM). Additionally, we investigated whether there were differences in HbA1c patterns between participants with and without diabetic complications.

Materials and methods

1. Design and study population

From November 2005 to November 2022, 279 participants with T1DM were recruited from the Pediatric Endocrinology Department at Severance Children's Hospital in South Korea. Two participants with syndromic diseases and 2 participants who had malignant tumors were excluded (Fig. 1). Therefore, the final study population comprised 275 participants, ranging in age from 6 months to 30 years, who were diagnosed with T1DM. The study focused on individuals with a minimum follow-up period of 6 months after diagnosis. HbA1c levels were measured at regular intervals, ranging from 3 to 6 months, between November 2005 and November 2022. HbA1c levels obtained at the time of initial diagnosis and within 3 months after diagnosis were excluded from the datasets. The distribution of HbA1c values was analyzed based on age. To evaluate the mean HbA1c levels across the lifespan, individuals were classified based on age at the time of HbA1c measurement regardless of body mass index (BMI) to include longitudinal datasets.

Moreover, this study investigated the average HbA1c values across age groups, considering sex and utilization of CGM as contributing factors. Additionally, longitudinal trajectories of HbA1c levels were monitored in subgroups categorized based on the presence of complications, including diabetic retinopathy, nephropathy, and neuropathy.

2. Measurements

HbA1c levels were measured at the outpatient clinic using the third-generation Roche Diagnostics immunoturbidimetric inhibition method (TINIA) and the Cobas c 513 instrument (Roche Diagnostics, Mannheim, Germany) following the manufacturer's guidelines.

Diabetic complications encompass ophthalmological, nephrological, and neurological complications. Diabetic retinopathy is diagnosed by an ophthalmologist based on the examination of 2 fundus photographs per eye, with one centered on the optic disc and the other on the macula. Diabetic nephropathy is defined as an estimated glomerular filtration rate less than 60 mL per minute per 1.73 m^2 and/or the presence of proteinuria and/or albuminuria. Albuminuria, which includes both microalbuminuria and macroalbuminuria, is defined as the presence of any of the following criteria: (1) urine albumin/creatinine ratio greater than 3 mg/mmol, (2) 24-hour total urine albumin exceeding 30 mg/24 hours, or (3) spot urine albumin exceeding 30 mg/L. Proteinuria is determined by either a 24-hour total urine protein greater than 3.5 g/day or an albumin/

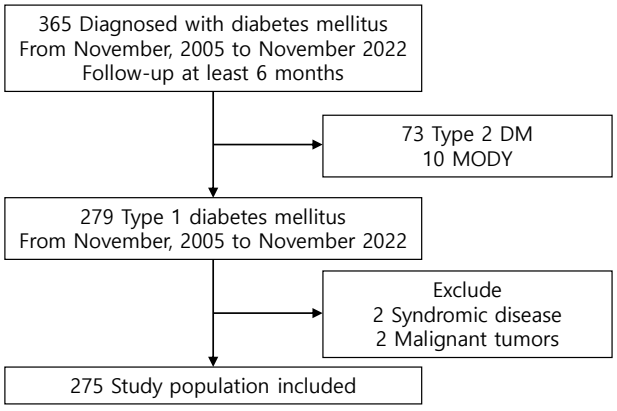

Fig. 1. Study selection and baseline population. DM, diabetes mellitus; MODY, Maturity-Onset Diabetes of the Young.

creatinine ratio greater than 30 mg/mmol. Neurological complications are assessed through autonomic nerve function tests and sensory and motor nerve conduction velocity tests using appropriate reference standards.[18]

3. Statistical methods

The results are presented as mean (percentage) with standard deviation using IBM SPSS Statistics ver. 26.0 (IBM Co., Armonk, NY, USA). An independent 2-sample *t*-test was used for continuous variables, and the Rao-Scott chi-square test was used for categorical variables. All *P*-values were calculated using the 2-tailed *t*-test, and *P*-values lower than 0.05 indicated significant differences. The figures in this study were generated using R ver. 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria), and the longitudinal trajectory curves for HbA1c were smoothed using the locally weighted scatterplot smoothing (LOESS) method.

4. Ethical statement

This study was approved by the Institutional Review Board of Yonsei University College of Medicine (approval number: 2023-1548-001) and was conducted according to the tenets of the Declaration of Helsinki.

Results

1. Baseline characteristics

A total of 275 participants (121 males, 43.8%) was enrolled. Table 1 presents the baseline characteristics of the participants. The mean age at diagnosis was 7.5±4.0 years (males, 7.7±4.1 years; females, 7.4±3.9 years). The total follow-up duration was 9.4±7.5 years (males, 9.0±7.7 years; females, 9.8±7.4 years). The average number of HbA1c measurements per individual was 22.3±14.3, totaling 6,135 HbA1c measurements in the study

Table 1. Baseline characteristics of the participants

Characteristic	Total (n=275)	Male (n=121, 43.8%)	Female (n=154, 56.2%)	*P*-value
Age at diagnosis (yr)	7.5±4.0	7.7±4.1	7.4±3.9	0.12
Follow-up period (yr)	9.4±7.5	9.0±7.7	9.8±7.4	0.31
HbA1c (%)	8.4±1.9	8.2±1.9	8.6±1.9	<0.01*
HbA1c measurement (n)	22.3±14.3	22.0±14.4	22.6±14.1	0.24
CGM	100 (36.2)	46 (38.0)	54 (35.1)	0.61
Diabetic complication	74 (26.8)	27 (22.3)	47 (30.5)	0.15
Retinopathy	31 (11.2)	9 (7.4)	22 (14.3)	0.20
Age at diagnosis (yr)	23.0±4.4	22.7±4.3	23.2±4.5	0.37
Duration until diagnosis (yr)	15.2±6.0	12.4±6.1	16.0±6.0	0.22
Nephropathy	30 (10.9)	10 (8.3)	20 (13.0)	0.17
Age at diagnosis (yr)	19.2±17.8	19.1±5.4	19.3±5.1	0.98
Duration until diagnosis (yr)	9.2±6.0	10.3±5.6	8.6±6.2	0.48
Neuropathy	35 (12.7)	15 (12.4)	20 (13.0)	0.09
Age at diagnosis (yr)	18.5±5.2	19.7±5.4	17.6±5.0	0.27
Duration until diagnosis (yr)	9.6±6.7	11.4±7.2	8.3±6.2	0.01*

Values are presented as mean±standard deviation or number (%).
HbA1c, glycosylated hemoglobin; CGM, continuous glucose monitoring.

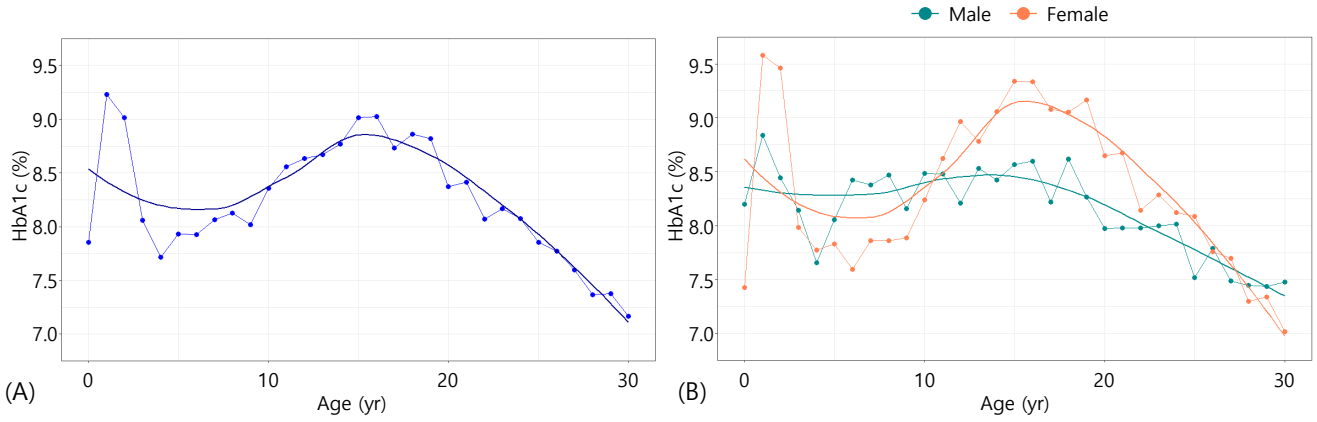

Fig. 2. Trajectory of HbA1c levels across age groups. (A) Total participants. (B) Groups divided by sex. HbA1c, glycosylated hemoglobin.

population. Among the study participants, 36.2% (n=100; males, 46.0%) utilized CGM, and 74 (26.8%) experienced complications related to diabetes. These complications included retinopathy, nephropathy, and neuropathy with respective incidences of 11.2%, 10.9%, and 12.7%. The duration from diabetes onset until complication occurrence was 15.2±6.0 years for retinopathy, 9.2±6.0 years for nephropathy, and 9.6±6.7 years for neuropathy (Table 1).

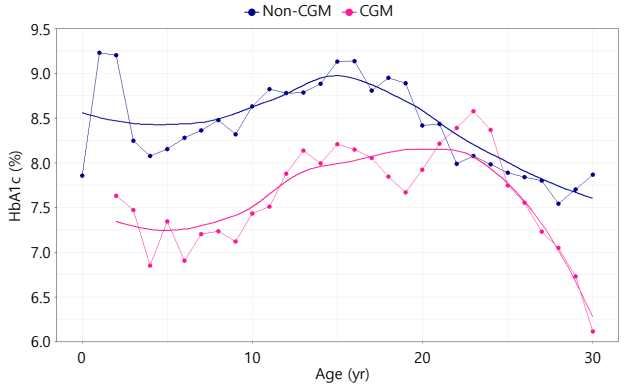

Fig. 3. Trajectory of HbA1c levels across age groups according to CGM use. HbA1c, glycosylated hemoglobin; CGM, Continuous glucose monitoring.

2. HbA1c levels across age groups

Mean HbA1c level was measured at various ages, ranging from 0–30 years, and is depicted in Fig. 2A and the Supplementary Table 1. The highest average HbA1c value observed was 9.2% (n=17) at the age of 1 year. Subsequently, HbA1c levels declined until the age of 4 years, reaching 7.7%. Thereafter, there was a significant increase in HbA1c levels, peaking at greater than 9% at ages of 15–16 years. Following this peak, HbA1c levels gradually decreased until age 30, with values near ~7% between 25–30 years. These data suggest that HbA1c levels are low during childhood, gradually increase during adolescence to a peak at ages 15–16, and gradually decrease thereafter.

3. HbA1c levels by sex

Fig. 2B depicts the trajectory of HbA1c levels stratified by sex. The patterns of changes in HbA1c levels across ages were similar to those shown in Fig. 2A, where HbA1c levels were low during childhood, gradually increased and peaked during adolescence, and exhibited a gradual decrease thereafter. However, the changes were more pronounced in females. Particularly, among females, there was a significant increase in HbA1c levels

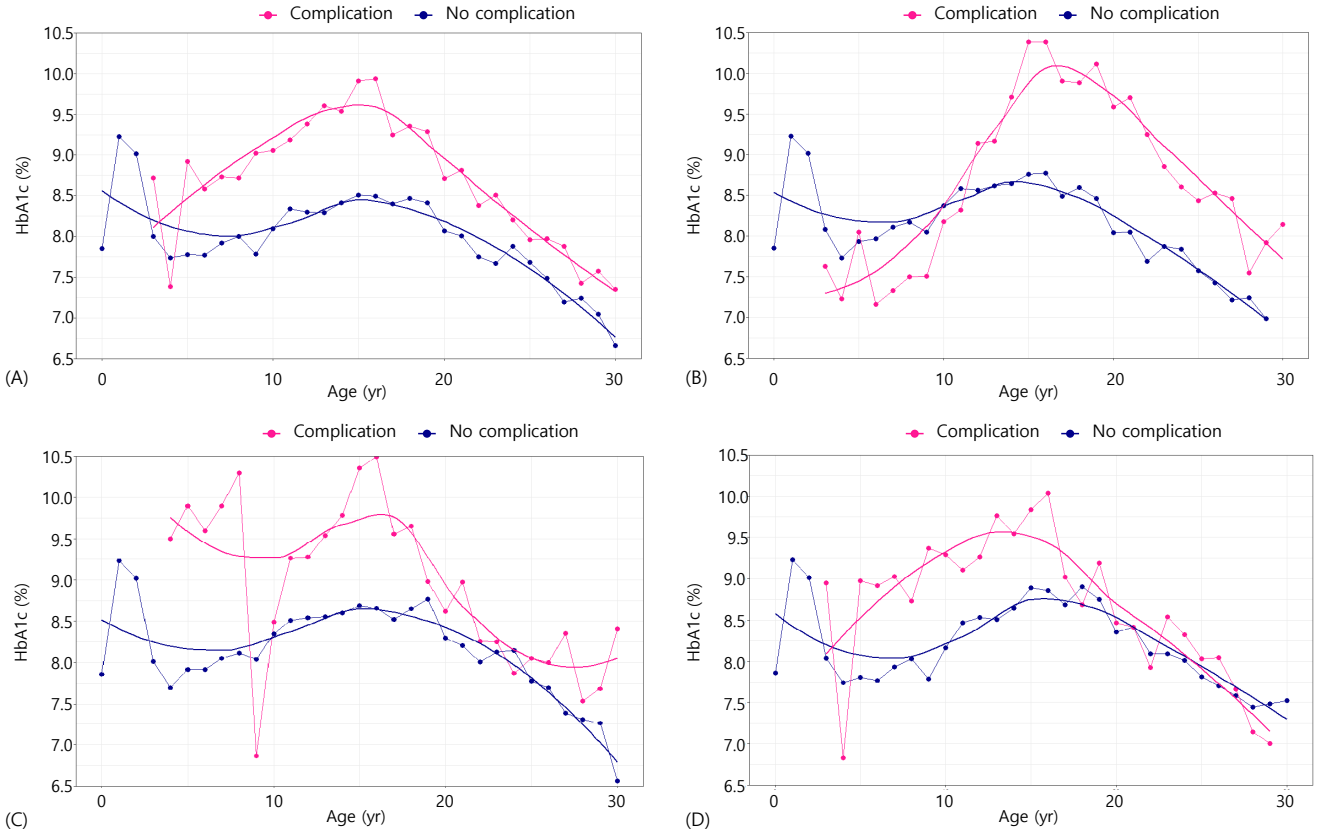

Fig. 4. Trajectory of HbA1c levels across age groups according to diabetic complications. (A) Diabetic complications. (B) Diabetic retinopathy. (C) Diabetic nephropathy. (D) Diabetic neuropathy. HbA1c, glycosylated hemoglobin.

between the ages of 9 and 12 years. At the peak point, which occurred at the age of 15, HbA1c levels in females reached 9.3%, which was higher than in males (8.6%). After the age of 15 to 16 years, both males and females exhibited a decrease in HbA1c levels. Overall, these observations indicate that HbA1c levels increase in both adolescent males and females and decrease afterward, but this pattern is more pronounced in females.

4. HbA1c levels according to CGM use

The study divided participants into 2 groups based on use of CGM and compared HbA1c levels different age groups, as shown in Fig. 3. In the group using CGM, HbA1c values were consistently lower across all age groups. Notably, the difference in HbA1c levels between the 2 groups was most pronounced in infants and prepubertal individuals. However, a similar pattern was observed in the 2 groups, as depicted in Fig. 2A, where the highest value was reached at the age of 15, followed by a gradual decrease. In summary, HbA1c levels increased during adolescence and subsequently decreased in early adults, regardless of CGM use, which can significantly reduce HbA1c levels.

5. HbA1c levels based on diabetic complications

Fig. 4 illustrates the trajectory of HbA1c levels in participants with and without diabetic complications. Individuals with any diabetic complications consistently exhibited elevated levels of HbA1c compared with those without complications, regardless of age (Fig. 4A). However, the overall trend in HbA1c levels in relation to age was similar to that observed in Fig. 2. We conducted further analysis to assess the progression of complications by categorizing them into retinopathy, nephropathy, and neuropathy. Among participants with retinopathy (Fig. 4B), HbA1c levels were initially lower or comparable before the age of 10, but there was a tendency toward higher HbA1c levels after puberty onset. In participants with diabetic nephropathy, the overall HbA1c levels were higher compared with participants without complications (Fig. 4C). Furthermore, in participants with diabetic neuropathy, HbA1c levels were elevated between the ages of 5 and 16 years, followed by a convergence of levels thereafter (Fig. 4D). Taken together, these findings suggest that HbA1c levels rise during adolescence regardless of diabetic complications.

Discussion

We generated a longitudinal trajectory of HbA1c levels across distinct age groups and stratified the data into subgroups based on sex, CGM use, and the presence of diabetic complications. Longitudinal tracking of HbA1c levels over time illuminates the dynamic nature of glycemic control in individuals with T1DM, with a notable increase in HbA1c levels during adolescence. This study demonstrates that the pattern of HbA1c levels remains consistent across subgroups of sex and CGM use. Furthermore, the increase in HbA1c levels during adolescence was consistent regardless of future occurrence of complications. Nevertheless, it is crucial to carefully regulate HbA1c levels during adolescence to minimize fluctuations, as this measure plays a significant role in preventing potential diabetic complications.

IR tends to increase during puberty, typically between the ages of 10 and 13 years.[19] It is presumed that variations in the secretion of sex hormones[9] and GH/IGF-I[10,11] occur in adolescence as the body grows, leading to IR.[12] In other words, pubertal children experience reduced insulin-stimulated glucose metabolism, leading to physiological IR.[14,15,20] The insulin response in pubertal children has been reported to be 30% lower than those in prepubertal children and adults.[12] Likewise, adolescents with T1DM also experience IR during puberty.[14,15,20] Physiological IR during puberty may exert an influence on high HbA1c levels. In a study examining factors influencing HbA1c in healthy children without diabetes, HbA1c levels increased with age, and the most significant difference was observed during pubertal development in both males and females. In females, HbA1c levels particularly increased during the transition from Tanner stage II to III.[21]

It is hypothesized that HbA1c levels increase during adolescence not only due to physiological IR, but also due to the influence of various social factors. This critical period, particularly between the ages of 14 to 18 years, usually entails greater individual responsibility for diabetes management. Parents often reduce their oversight of glucose monitoring, insulin adjustments, and injections during this period, leading to diminished compliance and self-care practices.[22] These sociological aspects, along with IR observed during puberty, likely contribute to elevated HbA1c levels. Pinhas-Hamiel et al.[23] similarly found that 75% of patients in the pubertal age group had higher HbA1c levels compared with the recommendations provided by the ADA. The elevated HbA1c levels during adolescence, which were also observed in the present study, may be attributed to physiological IR during puberty and various social factors influencing diabetes management in adolescence. Hovestadt et al.[21] also found that HbA1c levels were significantly lower even in healthy adolescents in high socioeconomic status groups. These findings indicate that many external factors can be responsible for fluctuations in HbA1c levels throughout life.

The pattern of HbA1c increase during adolescence exhibited a consistent trend even when analyzed by sex. Nonetheless, this trend was more pronounced in females. In males, HbA1c levels were generally higher than in females younger than 10 years, with a slight increase during puberty. In contrast, in females, a substantial increase in HbA1c levels from ages 10 to 12 years was observed, reaching a peak at 14 and 15 years, and this increase was more pronounced in females than males. These findings are consistent with previous studies[8,23] that also found elevated HbA1c levels in females compared with males. The observed differences in HbA1c levels between sexes may be attributed to the increased degree of IR in females during puberty compared with males.[24-26] The observed sex disparity in IR is often attributed to variations in adiposity or the timing

of pubertal development. However, even after accounting for these factors,[25,27] a significant unexplained difference in IR between sexes remained. Consequently, higher IR in females relative to males leads to elevated HbA1c levels. The findings of this study further support the consistent presence of this trend in T1DM. In other words, among adolescents with T1DM, HbA1c increases in both males and females due to physiological IR. However, because IR is higher in females than in males, this tendency is believed to be more pronounced in females. We also analyzed HbA1c pattern based on age at the time of diagnosis, but there was no significant difference.

Recently, CGM use in individuals with T1DM has increased from 7% in 2010–2012 to 30% in 2016–2018.[28] CGM implementation has been shown to significantly decrease HbA1c levels compared with blood-glucose self-monitoring,[29] and it has also been associated with a reduction in severe hypoglycemic events among individuals with T1DM.[30-32] Mean HbA1c level among CGM users was significantly lower compared with nonusers. However, both CGM users and nonusers exhibited the observed HbA1c increase pattern from early childhood to adolescence. In other words, while CGM use can decrease the magnitude of HbA1c and aid in glucose control management in T1DM, it may not mitigate physiologic IR during adolescence.

Fig. 4A demonstrates that HbA1c levels are consistently higher in patients with diabetic complications across all measured ages. However, there is a pattern of increase from 5 years to 15 years, followed by a decline and a subsequent stable trend after 25 years of age. This pattern is similar in patients without complications, indicating that the characteristic age-related pattern observed in HbA1c levels is maintained regardless of diabetic complications. High HbA1c levels have consistently been associated with an increased risk of chronic diabetic complications.[33-35] Furthermore, when analyzing each subgroup of complications, distinct characteristics can be observed. In patients with diabetic retinopathy, HbA1c levels showed a significant increase from ages 10–15 years during puberty, even though lower HbA1c levels were observed in individuals younger than 10 years (Fig. 4B). Puberty is considered one of the risk factors contributing to diabetic retinopathy,[36,37] suggesting that the combination of challenges in glycemic control in this age group, along with concurrent hormonal changes, accelerates the risk of diabetic retinopathy during puberty.[37-39] In patients with diabetic nephropathy and neuropathy, higher HbA1c levels were observed across all age groups, especially for individuals 5–15 years old (Fig. 4C and D), compared with those without these complications, underscoring the importance of blood-glucose management. Patients who have both diabetic nephropathy and neuropathy account for 10.8% of individuals with diabetic complications. At the time of HbA1c measurement, average HbA1c was higher than that of the total complications group (9.5%±2.8% vs. 8.8%±2.2%, $P<0.01$). Elevated HbA1c may contribute to higher values in younger individuals. However, because complications studies typically begin after the 5-year post-diagnosis point or when the patient is 10 years old or older, the dataset for HbA1c values for individuals 8 years old or younger who also have complications may be relatively limited, which would result in insufficient statistical adjustments, potentially leading to an overestimation of HbA1c values. In diabetic retinopathy, puberty has also been implicated in development of diabetic nephropathy and neuropathy.[40] From this perspective, despite the potential increase in HbA1c levels during puberty due to IR, it is crucial to strictly adhere to guidelines for effectively preventing diabetic complications.

The strength of this study lies in its ability to provide clinicians with a longitudinal HbA1c track in T1DM across age groups. This allows clinicians to assess glycemic control in comparison to guidelines and to observe similar patterns across ages, regardless of sex and CGM use. Additionally, by analyzing HbA1c patterns in patients with diabetic complications, it becomes possible to identify specific time points when greater attention should be given to glycemic control.

However, some limitations should be considered. First, we measured HbA1c levels in patients of different ages without considering height, weight, and BMI to include extensive longitudinal datasets. In future research, incorporating BMI values into the analysis of the longitudinal HbA1c trajectory would likely enable a more comprehensive investigation. Second, we analyzed HbA1c levels across ages without considering specific individual Tanner stages and socio-economic background. We included longitudinal data to the fullest extent possible to mitigate these factors. Third, regarding diabetic complications, particularly retinopathy, there were some patients who did not undergo regular examinations. As a result, there is a possibility of delayed diagnosis; however, it is presumed that the majority of cases was detected early, and significant bias is not expected.

In conclusion, in individuals with T1DM, HbA1c levels peak during puberty and then decline regardless of sex, CGM use, or presence of diabetic complications. This suggests that maintaining proper sugar levels may be challenging due to physiological IR during adolescence. Nevertheless, it is crucial to acknowledge that inadequate blood-glucose control during this phase can increase the risk of diabetic complications. Therefore, proactive interventions are essential for achieving glycemic targets during puberty, with CGM potentially playing a pivotal role in facilitating glycemic control and preventing complications.

Notes

Supplementary material: Supplementary Table 1 can be found via https://doi.org/10.6065/apem.2346180.090.

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

Funding: This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Data availability: The data that support the findings of this study can be provided by the corresponding author upon

reasonable request.

Author contribution: Conceptualization: AK, SK; Data curation: SK, SJK, KS; Formal analysis: ML, HWC; Methodology: JS, HSK; Project administration: ML, HSK; Visualization: SK, KWC; Writing - original draft: SK, AK; Writing - review & editing: SK, AK, HSK.

ORCID
Sujin Kim: 0000-0003-0907-9213
Seo Jung Kim: 0000-0002-9799-0148
Kyoung Won Cho: 0000-0002-9881-0903
Kyungchul Song: 0000-0002-8497-5934
Myeongseob Lee: 0000-0001-7055-3100
Junghwan Suh: 0000-0002-2092-2585
Hyun Wook Chae: 0000-0001-5016-8539
Ho-Seong Kim: 0000-0003-1135-099X
Ahreum Kwon: 0000-0002-9692-2135

References

1. Mayer-Davis EJ, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, et al. Incidence trends of type 1 and type 2 diabetes among youths, 2002-2012. N Engl J Med 2017;376:1419-29.
2. Silverstein J, Klingensmith G, Copeland K, Plotnick L, Kaufman F, Laffel L, et al. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. Diabetes Care 2005;28:186-212.
3. Secrest AM, Becker DJ, Kelsey SF, Laporte RE, Orchard TJ. Characterizing sudden death and dead-in-bed syndrome in Type 1 diabetes: analysis from two childhood-onset type 1 diabetes registries. Diabet Med 2011;28:293-300.
4. Stettler C, Allemann S, Jüni P, Cull CA, Holman RR, Egger M, et al. Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: meta-analysis of randomized trials. Am Heart J 2006;152:27-38.
5. American Diabetes Association. (2) Classification and diagnosis of diabetes. Diabetes Care 2015;38 Suppl:S8-16.
6. Brown A, Reynolds LR, Bruemmer D. Intensive glycemic control and cardiovascular disease: an update. Nat Rev Cardiol 2010;7:369-75.
7. American Diabetes Association Professional Practice Committee. 6. Glycemic targets: standards of medical care in diabetes-2022. Diabetes Care 2022;45(Suppl 1):S83-96.
8. Gerstl EM, Rabl W, Rosenbauer J, Gröbe H, Hofer SE, Krause U, et al. Metabolic control as reflected by HbA1c in children, adolescents and young adults with type-1 diabetes mellitus: combined longitudinal analysis including 27,035 patients from 207 centers in Germany and Austria during the last decade. Eur J Pediatr 2008;167:447-53.
9. Guercio G, Rivarola MA, Chaler E, Maceiras M, Belgorosky A. Relationship between the growth hormone/insulin-like growth factor-I axis, insulin sensitivity, and adrenal androgens in normal prepubertal and pubertal girls. J Clin Endocrinol Metab 2003;88:1389-93.
10. Cook JS, Hoffman RP, Stene MA, Hansen JR. Effects of maturational stage on insulin sensitivity during puberty. J Clin Endocrinol Metab 1993;77:725-30.
11. Roemmich JN, Clark PA, Lusk M, Friel A, Weltman A, Epstein LH, et al. Pubertal alterations in growth and body composition. VI. Pubertal insulin resistance: relation to adiposity, body fat distribution and hormone release. Int J Obes Relat Metab Disord 2002;26:701-9.
12. Amiel SA, Sherwin RS, Simonson DC, Lauritano AA, Tamborlane WV. Impaired insulin action in puberty. A contributing factor to poor glycemic control in adolescents with diabetes. N Engl J Med 1986;315:215-9.
13. Ball GD, Huang TT, Gower BA, Cruz ML, Shaibi GQ, Weigensberg MJ, et al. Longitudinal changes in insulin sensitivity, insulin secretion, and beta-cell function during puberty. J Pediatr 2006;148:16-22.
14. Jeffery AN, Metcalf BS, Hosking J, Streeter AJ, Voss LD, Wilkin TJ. Age before stage: insulin resistance rises before the onset of puberty: a 9-year longitudinal study (EarlyBird 26). Diabetes Care 2012;35:536-41.
15. Lee JM, Okumura MJ, Davis MM, Herman WH, Gurney JG. Prevalence and determinants of insulin resistance among U.S. adolescents: a population-based study. Diabetes Care 2006;29:2427-32.
16. Peplies J, Jiménez-Pavón D, Savva SC, Buck C, Günther K, Fraterman A, et al. Percentiles of fasting serum insulin, glucose, HbA1c and HOMA-IR in pre-pubertal normal weight European children from the IDEFICS cohort. Int J Obes (Lond) 2014;38 Suppl 2:S39-47.
17. Greenbaum CJ. Insulin resistance in type 1 diabetes. Diabetes Metab Res Rev 2002;18:192-200.
18. Rahmati M, Keshvari M, Mirnasuri S, Yon DK, Lee SW, Il Shin J, et al. The global impact of COVID-19 pandemic on the incidence of pediatric new-onset type 1 diabetes and ketoacidosis: a systematic review and meta-analysis. J Med Virol 2022;94:5112-27.
19. Shashaj B, Luciano R, Contoli B, Morino GS, Spreghini MR, Rustico C, et al. Reference ranges of HOMA-IR in normal-weight and obese young Caucasians. Acta Diabetol 2016;53:251-60.
20. Almeida CA, Pinho AP, Ricco RG, Pepato MT, Brunetti IL. Determination of glycemia and insulinemia and the homeostasis model assessment (HOMA) in schoolchildren and adolescents with normal body mass index. J Pediatr (Rio J) 2008;84:136-40.
21. Hovestadt I, Kiess W, Lewien C, Willenberg A, Poulain T, Meigen C, et al. HbA1c percentiles and the association between BMI, age, gender, puberty, and HbA1c levels in healthy German children and adolescents. Pediatr Diabetes 2022;23:194-202.
22. Gordon CM, Mansfield MJ. Changing needs of the patient with diabetes mellitus during the teenage years. Curr Opin Pediatr 1996;8:319-27.
23. Pinhas-Hamiel O, Hamiel U, Boyko V, Graph-Barel C, Reichman B, Lerner-Geva L. Trajectories of HbA1c levels in children and youth with type 1 diabetes. PLoS One 2014;9:e109109.

24. Hoffman RP, Vicini P, Sivitz WI, Cobelli C. Pubertal adolescent male-female differences in insulin sensitivity and glucose effectiveness determined by the one compartment minimal model. Pediatr Res 2000;48:384-8.
25. Moran A, Jacobs DR Jr, Steinberger J, Hong CP, Prineas R, Luepker R, et al. Insulin resistance during puberty: results from clamp studies in 357 children. Diabetes 1999;48:2039-44.
26. Kim S, Song K, Lee M, Suh J, Chae HW, Kim HS, et al. Trends in HOMA-IR values among South Korean adolescents from 2007-2010 to 2019-2020: a sex-, age-, and weight status-specific analysis. Int J Obes (Lond) 2023;47:865-72.
27. Travers SH, Jeffers BW, Bloch CA, Hill JO, Eckel RH. Gender and Tanner stage differences in body composition and insulin sensitivity in early pubertal children. J Clin Endocrinol Metab 1995;80:172-8.
28. Foster NC, Beck RW, Miller KM, Clements MA, Rickels MR, DiMeglio LA, et al. State of type 1 diabetes management and outcomes from the T1D exchange in 2016-2018. Diabetes Technol Ther 2019;21:66-72.
29. Teo E, Hassan N, Tam W, Koh S. Effectiveness of continuous glucose monitoring in maintaining glycaemic control among people with type 1 diabetes mellitus: a systematic review of randomised controlled trials and meta-analysis. Diabetologia 2022;65:604-19.
30. Lin R, Brown F, James S, Jones J, Ekinci E. Continuous glucose monitoring: a review of the evidence in type 1 and 2 diabetes mellitus. Diabet Med 2021;38:e14528.
31. Hermanns N, Heinemann L, Freckmann G, Waldenmaier D, Ehrmann D. Impact of CGM on the management of hypoglycemia problems: overview and secondary analysis of the HypoDE study. J Diabetes Sci Technol 2019;13:636-44.
32. Lockhart MJ, Smith D. Should continuous glucose monitoring systems be offered to all patients with type 1 diabetes mellitus? Ir J Med Sci 2022;191:957-60.
33. Hovind P, Tarnow L, Rossing P, Jensen BR, Graae M, Torp I, et al. Predictors for the development of microalbuminuria and macroalbuminuria in patients with type 1 diabetes: inception cohort study. BMJ 2004;328:1105.
34. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group. J Pediatr 1994;125:177-88.
35. Morales A. A better future for children with type 1 diabetes: review of the conclusions from the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications study. J Ark Med Soc 2009;106:90-3.
36. Burger W, Hövener G, Düsterhus R, Hartmann R, Weber B. Prevalence and development of retinopathy in children and adolescents with type 1 (insulin-dependent) diabetes mellitus. A longitudinal study. Diabetologia 1986;29:17-22.
37. Cho YH, Craig ME, Donaghue KC. Puberty as an accelerator for diabetes complications. Pediatr Diabetes 2014;15:18-26.
38. Danne T, Kordonouri O, Enders I, Hövener G, Weber B. Factors modifying the effect of hyperglycemia on the development of retinopathy in adolescents with diabetes. Results of the Berlin Retinopathy Study. Horm Res 1998;50 Suppl 1:28-32.
39. Nordwall M, Fredriksson M, Ludvigsson J, Arnqvist HJ. Impact of age of onset, puberty, and glycemic control followed from diagnosis on incidence of retinopathy in type 1 diabetes: the VISS study. Diabetes Care 2019;42:609-16.
40. Sosenko JM, Miettinen OS, Williamson JR, Gabbay KH. Muscle capillary basement-membrane thickness and long-term glycemia in type I diabetes mellitus. N Engl J Med 1984;311:694-8.