Growth, Therapeutic Effectiveness, and Disparities in Pediatric Type 1 Diabetes: Lessons from Continuous Glucose Monitoring Use in Latin America

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Type 1 diabetes (T1D) is prevalent among children, with increasing incidence.[1] Daily management is burdensome for affected individuals and their caregivers, with few children reaching glycemic targets. Over the past decade, outcomes have been influenced positively by technological advances. One significant and widespread change has been the advances and subsequent rapid uptake of continuous glucose monitors (CGMs).[2] CGM use is associated with multiple benefits including improved glycemia (average blood glucose assessed by hemoglobin A1c, more time in target glucose ranges), less glucose variability, reduced hypoglycemia (particularly nocturnal hypoglycemia), and improved quality of life.[3]

In this issue of *The Journal*, Hirschler et al from the CODIAPED (Collaborative Diabetes in Pediatrics) study group provide an observational report of associations between CGM use, hemoglobin A1c, and linear growth over 3 years in 433 children with newly diagnosed T1D.[4] This study draws strength from broad Latin American collaboration, involving 19 centers across 6 countries. The 199 children who used CGM had lower mean hemoglobin A1c levels at follow-up and were more likely to achieve a target hemoglobin A1c of <7.0% than the 234 children who did not use CGM. Further, although height *z*-scores decreased over time in all children, the height decrease was smaller in those with lower hemoglobin A1c and smaller in CGM users than those without CGM.

Growth is a highly sensitive marker of child health and well-being,[5] so regular assessments of physical development (including height and weight) are an integral part of recommended pediatric care.[6] Often, when we think about the effects of diabetes on physical development, we concentrate on changes in weight. This bias is in large part because the onset of stage 3 T1D (ie, time of clinical diagnosis) is often characterized by profound weight loss. When Araeteus of Cappadocia coined the term "diabetes" in the first century AD, he noted that persons with the disease had "melting down of the flesh and limbs into urine." In December 1921, 13-year old Leonard Thompson became the first child treated with insulin (at the time, "Macleod's serum"); he presented for care to the Toronto General Hospital with a height of 71 inches and weight of only 65 pounds (giving him a body mass index [BMI] of 9 kg/m^2!).

Once insulin therapy became more widespread and enabled survival, reports emerged of poor linear growth in children with T1D. In 1930, Mauriac described a series of children treated with insulin (then still a "total pancreatic extract"), who were short with round facies and large livers, as "torn away" from death.[7] He questioned, "Can we predict for them a very long survival and normal development?" Nearly a century later, despite dramatic improvements in care, diabetes outcomes and life expectancy, both the eponymous Mauriac syndrome and other, milder examples of impaired growth linked to higher average glycemia are still reported. Overall, children with established T1D whose hemoglobin A1cs are closer to the target value of <7% have better linear growth than peers with higher A1cs.[8] Hirschler's report adds to those data for a cohort of youth with mean A1cs in the 8%-9% range 3 years after diagnosis.

Interestingly, at the time of clinical diagnosis (now known as stage 3 T1D), children with T1D are often taller than peers. This observation was first made by Drayer a half century after Mauriac's report,[9] and later confirmed in other studies. This might be because excessive weight and puberty can both accelerate height growth in children and increase insulin resistance, thereby hastening the progression from early stage T1D to clinical diabetes. It has been well-reported that children with higher BMIs at lower ages in the years immediately prior to diagnosis have a greater risk of progressing from early stage T1D to clinical diabetes,[10] although how much of these more recent data are driven by trends toward obesity in our children (compared with in Drayer's time) are not entirely clear. Hirschler's study also showed mean *z*-height at baseline was >0, despite mean *z*-BMI being only 0.04 ± 1.40 after diagnosis for the overall group. Although the BMI of their cohort was likely somewhat lower owing to the weight loss accompanying diagnosis, the relative lack of obesity in the Hirschler cohort suggests that other factors beside BMI might drive the modest increases observed in height in children at stage 3 diagnosis.

BMI	Body mass index
CGM	Continuous glucose monitors
CODIAPED	Collaborative Diabetes in Pediatrics
T1D	Type 1 diabetes

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https://doi.org/10.1016/j.jpedcp.2024.200137

Hirschler's study provides data suggesting that CGM use is accompanied by better outcomes even in settings where caregivers generally have low levels of formal education. It also adds to the evidence of disparities in care.[11] Even in a setting where uninsured children can get a CGM if processes are followed, like in the CODIAPED centers, not every child received a CGM. Hemoglobin A1cs were still well above target values in the cohort overall, even though all children had access to free insulin. When CGM is linked to an insulin pump in an automated insulin delivery system (artificial pancreas devices), height might be further optimized (owing to improved overall glycemia) while minimizing the weight gain that is sometimes associated with intensive therapy to achieve average glycemia near target values. Only 5% of children in the current study used artificial pancreas devices, in part likely because approvals of and access to automated insulin delivery systems varied across the countries represented in CODIAPED.

The CODIAPED group recently reported that *z*-BMI in a slightly different sample derived from the same population as the Hirschler cohort increased significantly in the year after diagnosis (from a baseline mean *z*-BMI of 0.03 ± 1.39 kg/m^2) and remained steady over the subsequent 2 years (at a mean *z*-BMI of 0.46 ± 0.95).[12] Because overweight and obesity are established independent risk factors for developing cardiovascular disorders, and the most common long-term, life expectancy-shortening complication of diabetes is macrovascular disease, any relationship between achieving glycemic targets and BMI is an important consideration. Access for children with T1D and their families to dietary counselling is critical, to ensure that the benefits of improved glycemia are not offset by increasing BMI.

Several limitations must be considered in generalizing from Hirschler's study. Most notably, it was not a randomized study of CGM, so baseline differences were likely between the children who received CGM and those who did not. In light of the cohort's ages (mean of 9.4 ± 3.7 years for the group not using CGM and 8.0 ± 3.5 years for those with CGM), it is expected that many of the participants experienced puberty or even completed puberty by the end of the study period and there is no way to know how this confounder impacted the observed differences in height and hemoglobin A1c *z*-scores over time. It is also hard to interpret height *z*-scores in the absence of data about midparental heights/genetic potential. The authors stated that there may be some inaccuracies in the data, including ones owing to recall bias and that families may not have disclosed all sources of employment to healthcare providers lest they lose government assistance.

This report demonstrating an association between technology use and improved diabetes outcomes as well as other aspects of child development and growth adds to the growing evidence that advanced technologies should be available for all children with T1D. More broadly, we also emphasize that all children with diabetes should have access to a full team of specialists, including diabetes care providers, dietitians, and diabetes educators, to ensure they receive the best possible care.[13] ■

CRediT authorship contribution statement

Linda A. DiMeglio: Writing – original draft. **Adda Grimberg:** Writing – review & editing.

Declaration of Competing Interest

L.A.D. has consulted for Tandem.

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