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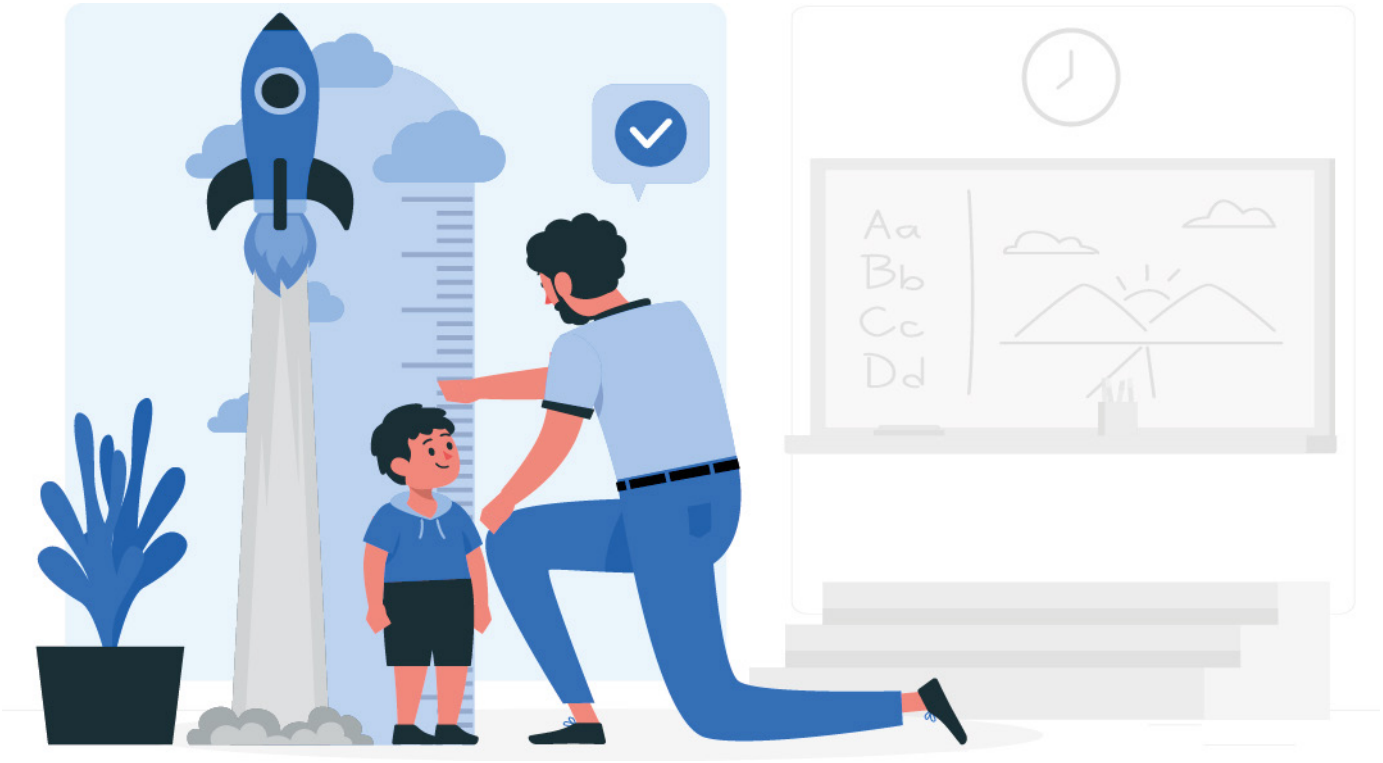


Impact of type 1 diabetes on growth during childhood and adolescence

Growth is a biological phenomenon that begins at conception and continues until the end of puberty, when adult height is achieved. During this process, individuals increase their body mass and acquire physical and psychological maturity. Adult height is influenced by genetic and hormonal factors, particularly the growth hormone and growth factors axis ("GH/IGF-1"), in which growth hormone (GH) from the anterior pituitary directly affects bones and indirectly stimulates the liver's receptors (GHR) to produce peripheral factors (insulin-like growth factor 1 (IGF-1), IGF-binding protein 3 (IGFBP-3), and acid-labile subunit (ALS)). Other factors affecting growth include nutrition, puberty, sleep, psychosocial environment, physical activity, healthy lifestyle habits, and exposure to drugs/toxins. Chronic illness, especially when poorly controlled, negatively impacts growth patterns. According to the World Health Organization, growth is the best indicator of children's and adolescents' health and well-being.

Insulin plays an essential role in normal growth by regulating the GH/IGF-1 axis. Normal insulin secretion and adequate levels in the portal vein (which carries blood from the intestines, spleen, pancreas, and gallbladder to the liver) are crucial for maintaining normal blood levels of IGF-1 and IGFBPs. Several studies have shown that insulin stimulates the expression of GH receptors (GHR) in the liver, increases the availability of these cellular receptors, and promotes post-receptor GH signaling, regulating liver synthesis of IGF-1 and IGFBPs. ***Figure 1*** schematically shows the hormonal factors of the growth axis, as well as the disorders found in patients with type 1 diabetes mellitus (T1DM).

In T1DM linear growth can be negatively impacted by several factors, such as the course of the disease and poor metabolic control (something that will be discussed below).

Some studies have shown a correlation between the **course** of T1DM and adult height and poorer growth in patients with longer disease progression. Growth rate seems to be influenced by the age of onset of T1DM, with the most severe growth impairment seen in children diagnosed in early childhood. Several studies have demonstrated that children with T1DM experience a reduction in height and growth rate after disease onset during the prepubertal period. Although some researchers have found no influence of metabolic control on pubertal growth in patients with T1DM, others have shown that high levels of glycated hemoglobin (HbA1c) and poor glycemic control correlate with reduced height growth in adolescents with T1DM. Research on the deterioration of the pubertal growth spurt comparing female vs male adolescents shows contradictory results. On the other hand, Bizzarri et al. demonstrated that the growth rate after the diagnosis of T1DM was directly associated with the residual activity of pancreatic beta cells, evaluated as C-peptide levels.

Height at the time of T1DM diagnosis in children is discussed in the literature. Many studies indicate that children are taller than their non-diabetic peers at diagnosis, while others have not confirmed this. The "accelerator" hypothesis suggests that increased growth rates and excess adiposity lead to insulin resistance, promoting beta-cell hyperfunction and increased antigen expression, ultimately leading to autoimmunity and acceleration of beta-cell failure. Furthermore, many recent studies have confirmed that rapid height, weight, and body mass index increases in early childhood seem to be associated with the development of islet autoimmunity and subsequent onset of T1DM in children.

Poor **metabolic control** in children with T1DM correlates with impaired linear growth. Various authors have detected an association between lower IGF-1 levels in children and higher HbA1c levels. Poor glycemic control in T1DM is also associated with tissue resistance to GH action. An extreme example of how poor diabetic control negatively impacts growth is Mauriac syndrome. This syndrome, characterized by growth retardation, pubertal delay, and hepatomegaly with lipid abnormalities, is the most critical growth-related condition linked to long-standing, poorly controlled T1DM. It results in reduced GH responsiveness, leading to low IGF-1 levels. Fortunately, in Spain, given the accessible means for T1DM control, Mauriac syndrome cases and their severe growth effects are rare. Additionally, poor metabolic control can delay the onset and/or progression of puberty, potentially leading to suboptimal pubertal growth and final height impact.

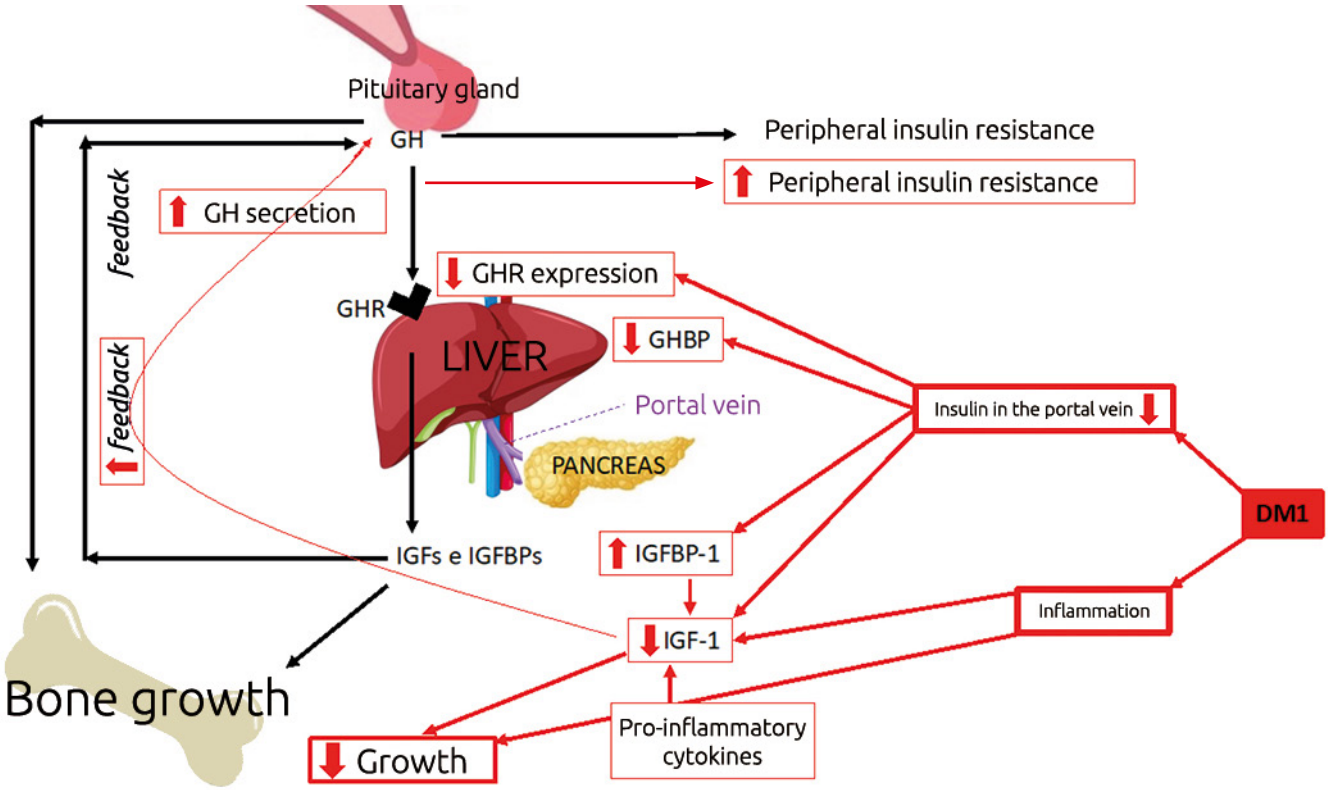
In T1DM children, insulin deficiency in the portal vein often occurs, resulting in GH hypersecretion, low circulating levels of IGF-1 and IGFBP-3, and consequently elevated blood levels of IGFBP-1. Elevated IGFBP-1 levels may inhibit the bioactive free fraction of IGF-1 (the one that acts on target tissues). Additionally, low IGF-1 levels increase negative feedback to the pituitary gland, leading to GH hypersecretion, which significantly contributes to insulin resistance during puberty in adolescents with T1DM. GH binding proteins (GHBPs) are formed by the proteolytic cleavage of the transmembrane GH receptor (GHR), and children with T1DM exhibit low GHBP levels due to low portal insulin levels.

Additionally, suboptimal growth in the T1DM population likely reflects a continuous metabolic disorder related to the traditional **microvascular complications** of diabetes, particularly diabetic nephropathy. It has been reported that patients with T1DM have elevated circulating in- »

INSULIN PLAYS AN ESSENTIAL ROLE IN THE PHYSIOLOGY OF NORMAL GROWTH BY REGULATING THE GH/IGF-1 GROWTH AXIS

POOR METABOLIC CONTROL IN CHILDREN WITH T1DM IS ASSOCIATED WITH AN IMPAIRED LINEAR GROWTH

FIGURE 1. Changes in the GH/IGF-1 axis in patients with type 1 diabetes mellitus.



The red arrows indicate changes that occur in the GH/IGF-1 axis in patients with type 1 diabetes mellitus (T1DM); an upward arrow is indicative of increases, while a downward arrow is indicative of decreases. GH, growth hormone; GHR, growth hormone receptor; GHBP, growth hormone binding proteins; IGFs, insulin-like growth factors; IGFBPs, insulin-like growth factor binding proteins.

» flammatory markers, including interleukins-1beta, 6, and 8, as well as tumor necrosis factor-alpha, C-reactive protein, and fibrinogen. These and other proinflammatory cytokines may affect growth both through direct effects on the bone growth plate and by locally suppressing IGF-1 actions, either by inducing resistance to IGF-1 action or lowering its blood levels.

Similarly, **glucose variability** strongly impacts the risk of diabetes-related microvascular and macrovascular complications. Glucose variability correlates with linear growth in children with T1DM, with lower variability indexes observed in children with the highest height percentiles.

Based on the above, improving glycemic control can lead to better IGF-1 levels, reduced tissue resistance to GH action, and consequently, improved linear growth.

Other factors associated with poor linear growth in T1DM include the addition of **another poorly controlled illness** (often co-occurring, such as celiac disease) as well as **dietary transgressions**. Same as it happens in other chronic diseases, patients with T1DM are also more susceptible to developing eating disorders, which can detrimentally affect pubertal development and longitudinal growth. Some studies suggest that increasingly popular very low-carbohydrate diets, if not carefully managed, may increase the risk of attenuated linear growth in individuals with T1DM.

In recent years, despite technological »

» advances in T1DM treatment, there are contradictory results in the literature regarding its effect on growth and adult height. This discrepancy between studies may be due to differences in methodology, diagnosis duration, study and control populations, including ethnic and socioeconomic differences. Conventional subcutaneous insulin therapy does not seem capable of replacing pancreatic insulin secretion into the portal vein circulation. Although some studies have shown increased blood IGF-1 levels after improvement with intensive insulin therapy, reaching normal or slightly reduced final height compared with unaffected peers, continuous subcutaneous insulin infusion (CSII) therapy also does not seem to improve chronic hepatic hypoinsulinemia and does not appear to influence the linear growth pattern compared to multiple daily injections (MDI) therapy. In an interesting study by Hainaire-Broutin et al., the GH/IGF-1 axis was evaluated in T1DM patients on conventional subcutaneous insulin therapy vs CSII. Although subjects on CSII had lower HbA1c levels vs the conventional therapy group, there was no difference in GHBP levels. Patients who received CSII were then treated with continuous portal insulin infusion (CPII) via an implanted pump. Although there were no significant differences in HbA1c between CSII and CPII, there was a greater increase in GHBP, almost normalization of IGF-1, and normalization of IGFBP-3. Subsequently, other authors also confirmed similar results on the beneficial effects of CPII therapy on the GH/IGF-1 axis. These results suggest that it is not only glycemic control that influences the GH/IGF-1 axis in T1DM but that the presence of even small amounts of residual insulin in portal circulation is crucial for the proper functioning of the GH/IGF-1 axis. Whether it is feasible to implement CPII therapy in T1DM remains to be determined.

In recent years, other circulating factors in the peripheral GH/IGF-1 axis, known as papalysins and stanniocalcins, have been discovered, and their study in children with T1DM may help better understand the impact of the disease on the growth of these children. D

CONCLUSION

Despite advances in understanding the GH/IGF-1 axis, many questions remain regarding its impairment in diseases like T1DM. There are contradictory data on the impact of intensive insulin therapy regimens on growth and adult height, suggesting that biochemical abnormalities in the GH/IGF-1 axis persist in children with T1DM, although they seem to reach normal adult height or heights similar to their reference population.

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