Growth Hormone & IGF Research xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Growth Hormone & IGF Research

journal homepage: www.elsevier.com/locate/ghir

Growth hormone and insulin-like growth factor-I axis in type 1 diabetes

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ARTICLE INFO

Keywords:
Type 1 diabetes
Growth hormone
Insulin like growth factor-I
Portal hypoinsulinization
Height

ABSTRACT

The precise mechanisms relating type 1 diabetes (T1D) and poor glycemic control to the axis of growth hormone (GH), insulin like growth factor- I (IGF-I), and IGF binding protein-3 (IGFBP-3) remain to be definitively determined. GH resistance with low IGF-I as is frequently seen in patients with T1D is often related to portal hypoinsulization, and lack of upregulation of GH receptors. There are conflicting reports of the effect of a dysregulated GH/IGF-I axis on height in children and adolescents with T1D, as well as on chronic complications. This brief review discusses some of the interactions between the GH/IGF-I axis and T1D pathology, and vice-versa.

1. Introduction

The GH/IGF-I/IGFBP-3 axis acts in concert and modulate growth in children. IGF-I and its binding proteins (IGFBPs 1–6) are produced from the liver and are regulated by pituitary GH. Of the six, IGFBP-3 is the major binding protein, and both IGF-I and IGFBP-3 are complexed to acid labile subunit (ALS), a hepatic glycoprotein produced under the action of GH, to form a circulating 150 kDa ternary complex. Almost 80% of IGF-I in the circulation are bound to this ternary complex and the biologically active, free fraction in circulation constitutes < 1% [1]. This complex prevents the premature degradation of IGF-I by circulating IGF-I proteases and its extravasation into the extravascular space, thus prolonging the half-life and helping in efficient transport to target tissues respectively, and allowing it to carry out its growth promoting effects. Numerous factors including nutritional status, chronic inflammation, hypothyroidism, hypercortisolism have all been reported to affect the functioning of the axis [2–5]. In poorly controlled T1D, marked by hyperglycemia and chronic inflammation, derangements in the GH/IGF-I/IGFBP-3 axis can lead to poor linear growth. A classic example of extreme growth retardation in children with poorly controlled T1D is Mauriac syndrome. With the introduction of fast acting insulin analogs, convenient methods of insulin delivery such as pen devices or insulin pumps, and the use of continuous glucose monitoring system, Mauriac syndrome has decreased in frequency but still reported in both children and adults [6,7]. This brief review discusses some of the interactions between the GH/IGF-I axis and T1D.

2. The GH/IGF-I/IGFBP-3 axis in T1D

Although GH and insulin have been traditionally recognized as metabolically antagonistic hormones, insulin has been reported to have a permissive role in mediating the action of GH. In-vitro studies have shown that insulin in the portal circulation upregulates hepatic GH receptor (GHR) expression, and increases net cell surface receptor availability [8]. The binding of GH to the GH receptor (GHR) mediates downstream production of growth promoting IGF-I and its binding protein (IGFBP-3). GH binding proteins (GHBPs) are formed by the proteolytic cleavage of transmembrane GHR, and children with T1D have been reported to have low levels of GHBP secondary to low levels of portal insulin [9].

In contrast to IGFBP-3 which is regulated by GH, IGFBP-I is regulated by insulin (Fig. 1). Insulin downregulates the production of IGFBP-1; the portal hypoinsulinization characterizing T1D leads to higher amounts of IGFBP-1, which in turn decreases the available, free bioactive fraction of IGF-I [10]. Compounding these effects is the concomitant chronic inflammation accompanying T1D [11]. Higher levels of proinflammatory cytokines such as TNF-α and IL-1β have been reported to induce IGF-I resistance [12], and studies have shown that higher levels of IL-8 (another inflammatory mediator) in T1D, have been associated with lower IGF-I levels in adolescents [13].

Interestingly, the portal hypoinsulinization in T1D, and its dysregulatory effect on GH/IGF-I/IGFBP-3 axis is not ameliorated with conventional subcutaneous routes of insulin delivery. Hedman et al. in 2004 had studied the GH/IGF-I axis in adults with long standing T1D (disease duration 17.8 ± 14.6 years). Total IGF-I and free IGF-I were

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https://doi.org/10.1016/j.ghir.2017.12.005
Received 9 October 2017; Received in revised form 7 December 2017; Accepted 9 December 2017

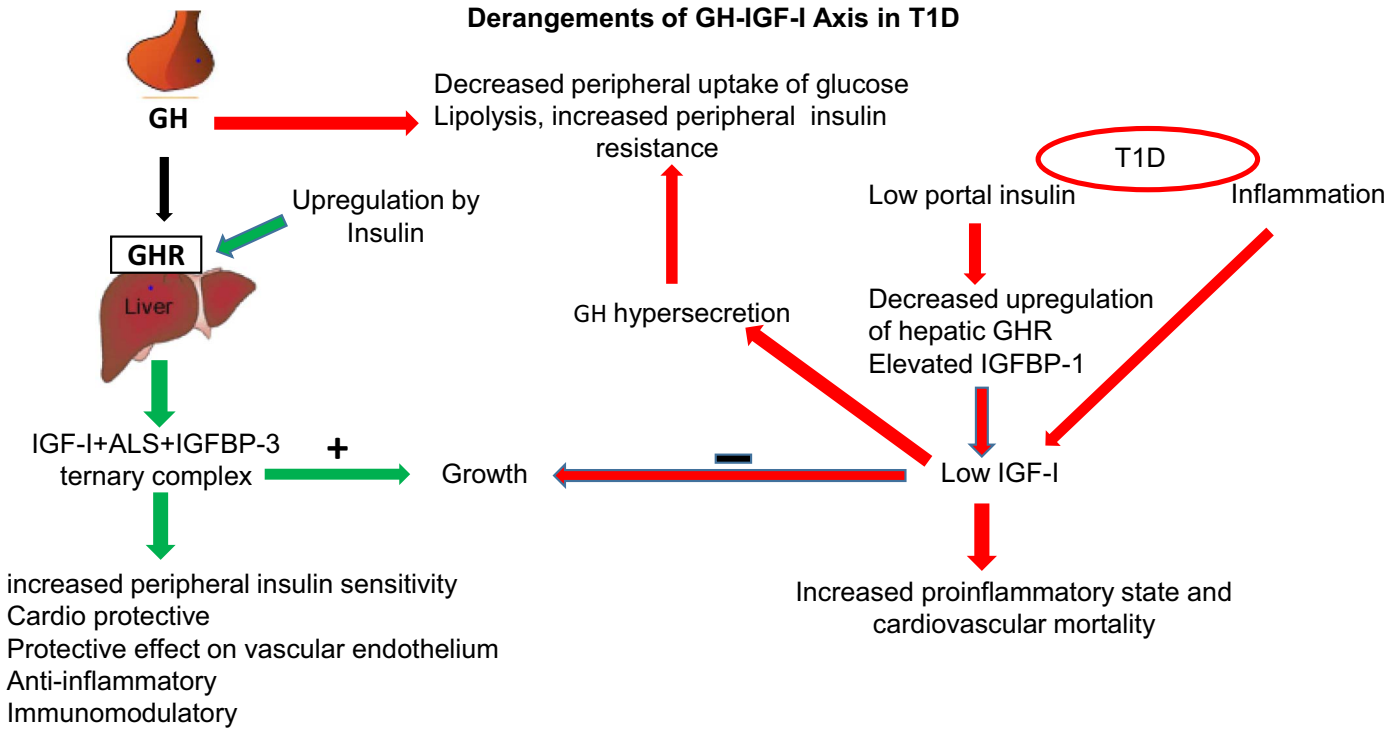

Fig. 1. Portal hypoinsulinization leading to low IGF-I compounded further by inflammation in T1D. Low IGF-I not only leads to poor growth in children but may also have a role in insulin resistance and poor metabolic and cardiovascular outcomes.
Green arrows: Beneficial outcomes of GH/IGF-I axis. Red arrows: Detrimental effects of deranged GH/IGF-1 axis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

higher, while IGFBP-1 was lower in those with detectable overnight fasting C-peptide (≥ 100 pmol/L) compared to those with undetectable C-peptide. For both groups, the average HbA1c and plasma free insulin were not different [14]. The same year, Hainaire-Broutin et al. evaluated the GH-IGF-I axis in T1D patients on conventional subcutaneous insulin therapy versus intensive continuous subcutaneous insulin infusion (CSII) [15]. Even though subjects on CSII had a lower A1c compared to the group on conventional therapy, there was no difference in GHBP levels. The patients who received CSII were then administered continuous portal insulin infusion (CPII) via an implantable pump. Although there was no significant difference in the HbA1c between CSII and CPII, there was a greater increase in GHBP, near normalization of IGF-I, and normalization of IGFBP-3. Later, Hedman et al. [16] and van Dijk et al. [17] also reported similar findings on the beneficial effects of CPII therapy on the GH/IGF-I/IGFBP-3 axis. These findings suggest that it is not solely glycemic control that influences GH/IGF-I axis in T1D, and the presence of even low amounts of residual insulin in the portal circulation is important for functioning of the GH/IGF-I axis. The precise relationship between portal hypoinsulinization, glycemic control and derangements in the GH/IGF-I/IGFBP-3 axis in T1D requires further study. It also remains to be determined whether CPII will actually become feasible in T1D.

Additionally, abnormalities in the GH/IGF-I/IGFBP-3 axis have been associated with increased risk for type 2 diabetes [18] as well as associated long term complications. The anti-atherosclerotic effects of IGF-I on the vascular endothelium, and increased risk for cardiovascular mortality in those with lower IGF-I have been reported [19,20].Studies have also shown that exogenous administration of rhIGF-I improves insulin sensitivity and decreases insulin requirements in T1D patients [21,22]. It was previously hypothesized that GH hypersecretion in T1D contributes to microangiopathic complications, and indeed studies have shown that T1D patients with GH deficiency have decreased rates of retinopathy [23,24]. However, other growth factors including IGF-I have also been implicated in microangiopathy in T1D [25,26]. TheT1D cohort who received higher dose of IGF-I in the 'rhIGF-I in the IDDM Study group' had worsening of early retinopathy [21]. Contradictory to this school of thought, other authors have hypothesized a protective role of IGF-I in preventing microangiopathic complications in T1D [27]. Thus, the clinical implications of low IGF-1 on longterm metabolic and vascular outcomes in patients with T1D remain unclear.

3. Growth and growth factors in children with T1D

Hoskin and co-workers compared the height of T1D patients at diagnosis with their unaffected monozygotic twin as controls. For children diagnosed before 19 years of age, 50% (8/16) were shorter than their twins at diagnosis with a mean difference of 3.4 cm (± SEM 0.62 cm). The authors also reported that there was at least 29 weeks of growth arrest before the patient developed symptoms. For those diagnosed after 25 years of age, there was no significant difference in height between the twins (0.08 cm ± 0.3 cm) [28]. Brown et al. similarly reported decreased height at the time of diagnosis in young T1D children under 5 years of age [29].

In contrast, other studies have reported that children with T1D may be taller [30,31], or no different than age-matched controls at the time of diagnosis [32]. Songer et al. reported that children with T1D diagnosed between 5 and 9 years of age were significantly taller than the national average, and similar to non-diabetic siblings of the same age group. However, those diagnosed at 14–17 years were significantly shorter compared to national averages. The authors speculated that a taller height in the younger group may have been related to higher body mass, whereas those in the older age group may have had a longer insulin-deficient prediabetic phase [30]. It remains to be determined if these age variations in height may also be related to age related heterogeneity in T1D and/or associated disease pathogenesis.

A prospective study by Larsson et al. [33] in children developing T1D before 6 years of age, reported significantly increased linear