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Increased circulating IL-8 is associated with reduced IGF-1 and related to poor metabolic control in adolescents with type 1 diabetes mellitus

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Abstract

Background—A dysregulated growth hormone (GH)/insulin-like growth factor 1 (IGF-1) axis is well-recognized in children and adolescents with type 1 diabetes mellitus (T1DM). Decreased IGF-1 levels can also be found in chronic inflammatory diseases, while hyperglycemia promotes inflammatory cytokine production. Therefore, inflammatory cytokines may link poor metabolic control with GH/IGF-1 axis changes. This study examined the relationship between serum inflammatory cytokines and IGF-1 in adolescents (age 13–18) with T1DM in chronic poor (n=17) or favorable (n=19) glucose control. Poor control (PC) was defined as ≥ 3 , consistent HbA1C > 9% during the previous 2 years, while favorable control (FC) was consistent levels of HbA1C < 9%.

Results—HbA1C (FC: $7.5 \pm 0.6\%$; PC: $10.5 \pm 0.9\%$, $p < 0.001$) and interleukin (IL)-8 (FC: 3.7 ± 4.0 pg/ml; PC: 7.4 ± 4.3 pg/ml, $p = 0.01$) were increased and IGF-1 (FC: 536.5 ± 164.3 ng/ml; PC: 408.9 ± 157.1 ng/ml, $p = 0.03$) was decreased in patients with poor control compared to patients with favorable control. Moreover, IL-8 was inversely correlated with IGF-1 ($r = -0.40$, $p = 0.03$) and positively correlated with HbA1C ($r = 0.36$, $p = 0.03$).

Conclusions—In adolescents with T1DM and chronic, poor glucose control, increased serum IL-8 is associated with reduced IGF-1 suggesting a pro-inflammatory milieu that may contribute to alterations in the GH/IGF-1 axis.

Keywords

diabetes; adolescence; metabolic control; IGF-1; IL-8

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1. Introduction

Dysregulation of the growth hormone (GH)/insulin-like growth factor 1 (IGF-1) axis is well-recognized in children and adolescents with type 1 diabetes mellitus (T1DM) [1–3]. Reduced IGF-1 levels in patients with poor glucose control may contribute to complications such as poor linear growth and low bone mineral content given that IGF-1 is a major anabolic regulator of bone growth and metabolism [2,4,5]. IGF-1 levels peak during the rapid growth of adolescence with 90–95% of peak bone mass accrued by the end of the second decade [6]. Therefore, poor blood glucose control during these critical years may have a significant life-long impact on bone health. Indeed, postmenopausal women with T1DM have a more than 10-fold increased risk for hip fractures than women without diabetes [7], and the basis for this may begin during adolescence, as several recent studies have reported that poor metabolic control in adolescents with T1DM is associated with decreased bone mineral density [8–10].

The mechanisms that could link poor blood glucose control with reduced IGF-1 levels are not entirely clear. Circulating IGF-1 is produced primarily by the liver and decreased levels in T1DM may result from reduced hepatic delivery of insulin [11,12]. However, IGF-1 is also produced locally in muscle and bone tissue. IGF-1 mediates important paracrine effects on bone metabolism with its local production regulated by hormones, growth factors and inflammatory cytokines [4]. Recent studies describe T1DM as a chronic, subclinical pro-inflammatory state characterized by elevated circulating pro-inflammatory molecules [13, 14], even from early childhood [15]. Both acute and chronic hyperglycemia increase inflammatory cytokine production and markers of inflammation in cultured human blood cells [16,17], as well as in humans with abnormal glucose metabolism [13,18,19]. Moreover, many diseases with chronic inflammation, including inflammatory bowel disease, juvenile idiopathic arthritis and cystic fibrosis, are associated with decreased IGF-1 levels [20,21], while anti-cytokine therapy normalizes levels of circulating IGF-1 in adults with inflammatory bowel disease [22]. Together, these data suggest an interaction between inflammatory mediators and the IGF system that may be central to understanding dysfunction of the GH/IGF-1 axis in T1DM and its relationship to growth and skeletal complications of diabetes.

A recent study by Moyer-Mileur and colleagues [23] demonstrated that poor metabolic control in adolescent girls with T1DM predicted alterations in the GH/IGF-1 axis and was associated with changes in bone geometry and reduced bone density. Previous studies from this same group showed that poor metabolic control was also associated with decreased trabecular bone mineral density (9, 10). Trabecular bone abnormalities have similarly been reported in animal models of chronic inflammation [24] and, in one study, appeared to be caused, at least in part, by systemic and local disruption of the IGF system [25]. Therefore, the aim of the present study was to investigate the association between inflammatory cytokine and IGF-1 levels and the relationship to metabolic control in a cohort of adolescents with T1DM.

2. Materials and methods

2.1 Participants

Adolescents (age 13–18) with T1DM for ≥ 3 years, at least 1 autoantibody consistent with T1DM (anti-islet cell antibody or anti-GAD65 antibody) and on insulin therapy were recruited from the Pediatric Clinic in the Eskind Diabetes Center at Vanderbilt Medical Center. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Vanderbilt University Medical Center Institutional Review Board. Informed consent was obtained from each participant's parent/legal guardian, and informed assent was obtained from each participant prior to beginning the study. Participants were categorized by the degree of glucose control. Poor control (PC) was defined as 3 or more HbA1C measurements $> 9\%$ and favorable control (FC) was defined as all HbA1C measurements $< 9\%$ during the previous 2

years. Participants were excluded for the following: presence of microalbuminuria, retinopathy or neuropathy; pre-existing bone disease, cystic fibrosis or celiac disease; eating disorder; estrogen-progesterone or testosterone treatment including oral contraceptives; smoking; pregnancy; amenorrhea; polycystic ovarian syndrome as previously diagnosed by a pediatric endocrinologist based upon irregular menses and hirsutism; obesity (BMI > 95th percentile for age and sex); short stature (< 3rd percentile for age and sex); or delayed/precocious puberty.

2.2 Collection of samples

Venous blood samples were collected after an overnight fast (~10 h). Participants received their usual evening insulin glargine dose the night prior or were continued on their insulin pump at the usual basal rate. For each participant, serum for cytokine and IGF-1 measures were stored at -70°C until later analysis.

2.3 Assay methods

Serum concentrations of IL-1 β , IL-6, IL-8, IL-10, MCP-1 and TNF- α were measured using the Cytometric Bead Array multiplex system (CBA assay; BD Biosciences, San Jose, CA, USA) as previously reported [26]. Inter- and intra-assay coefficients of variation were 6.1–8.0% and 4.6–6.6%, respectively, with a limit of detection at 0.1 pg/mL. Serum concentration of total IGF-1 was measured by radioimmunoassay (ALPCO Diagnostics, Salem, NH, USA). Inter- and intra-assay coefficients of variation were 3.4–4.2% and 2.6–4.1%, respectively. HbA1C was measured by point-of-care immunoassay using the DCA Vantage Analyzer (Siemens Healthcare Diagnostics, Deerfield, IL, USA).

2.3 Statistical Analysis

Statistical analysis was done using SPSS 15.0 for Microsoft Windows (SPSS Inc., Chicago, IL, USA). The results were expressed as the means $\pm$ SD or as median (range). The χ^2 -test was used to investigate differences between the groups regarding gender. Differences between groups for other variables were compared by MANOVA for normally distributed data or Mann-Whitney *U* tests if data were not normally distributed. Correlations were determined using Spearman's rank order analysis. Statistical significance was defined as a *p* value < 0.05.

3. Results

3.1 Demographic characteristics

The study population includes 36 participants, 19 with favorable glucose control and 17 with poor glucose control during the 2 years prior to study participation. Clinical and biochemical features of the study population are summarized in Table 1. No significant differences between groups were detected for age, gender, BMI or duration of diabetes. As expected based upon selection criteria, the average HbA1C during the two years prior to study in the poor glucose control group was significantly higher than that in the favorable glucose control group.

3.2 Serum Cytokine and IGF-1 measures

IGF-1 was significantly lower in the group with poor glucose control compared to those with favorable glucose control (Table 1). Serum IL-8 in the poor glucose control group was significantly higher than in the favorable glucose control group (Table 1). While IL-8 was undetectable in 26% patients with favorable control (5/19), it was detected in all those in the poor control group (Fig. 1). No differences between the groups were detected for any of the other cytokines measured (IL-6, IL-10, TNF- α or MCP-1); however a non-significant trend was noted for MCP-1 with higher levels in the poor glucose control group (Table 1). Due to the many values for IL-1 β in both groups that were below the limit of detection of the assay, analysis of this cytokine was not performed.

Next, associations between demographic and biochemical measures were investigated. The degree of blood glucose control as measured by average HbA1C demonstrated a significant, moderate inverse relationship with IGF-1 ($r=-0.43$, $p=0.02$; Fig. 2a). Additionally, there was a significant, positive correlation between HbA1C and IL-8 ($r=0.36$, $p=0.03$; Fig. 2b) suggesting a relationship between the degree of glucose control and this inflammatory cytokine level. Serum IL-8 also demonstrated a significant, positive association with MCP-1 ($r=0.49$, $p=0.003$) and IL-10 ($r=0.46$, $p=0.005$) but a significant, inverse relationship with IGF-1 ($r=-0.40$, $p=0.03$; Fig. 2c). There were no other significant associations among age, BMI, duration of diabetes, and biochemical measures.

4. Discussion

The findings in our study confirm the work of others that have demonstrated that the degree of metabolic control in patients with T1DM can influence inflammatory cytokine levels [13, 19] or the GH/IGF-1 axis [1,2]. However, to our knowledge, this is the first study to report a significant relationship between markers of inflammation and the GH/IGF-1 axis within the same cohort of patients with T1DM in regard to the degree of metabolic control. The data presented in this study are consistent with a role for inflammation in regulating the GH/IGF-1 axis in adolescents with T1DM and chronic, poor metabolic control.

The elevation of IL-8 and the trend towards increased MCP-1 observed in this study may represent a general, pro-inflammatory environment related to poorly controlled diabetes or, alternatively, may represent specific regulation of these inflammatory mediators. Increased serum levels of IL-1 β , TNF- α , IL-6 and IL-8 have been reported in adults with T1DM when compared to non-diabetic subjects [13,14], however these changes are less consistent within studies of pediatric subjects with T1DM [29,30]. Absence of detectable differences in TNF- α and IL-6 in the present study is not unexpected given the age of the subjects and lack of comparison to subjects without T1DM. Moreover, the finding of increased IL-8, and lack of changes in other cytokines, could argue that the degree of metabolic control has a more specific influence on the regulation of particular inflammatory mediators rather than on the general, pro-inflammatory state associated with T1DM. Indeed, IL-8 has most consistently been shown to be increased in both adults [27,28] and children [29,30] with T1DM. Additionally, MCP-1 was also increased in adults and children with T1DM and was associated with worse metabolic control [31,32]. Mechanistically, the possibility that increased IL-8 and its inverse relationship to HbA1C was specifically regulated in the current study is supported by previous work that hyperglycemia can induce transcription of the gene for IL-8 in human endothelial cells [33] and that hyperglycemia and ketosis (acetoacetate) regulate production of IL-8 and MCP-1 in cultured monocyte [34]. Although not measured, it is plausible to expect that study participants with chronic, poor glucose control might have periodic episodes of ketone production that could promote production of specific inflammatory cytokines, in addition to those produced in response to hyperglycemia alone.

Inflammatory cytokines and GH bind cell surface receptor complexes that involve activation of the Janus kinase (JAK) family of tyrosine kinases. Activation of JAKs ultimately results in recruitment of signal transducers and activators of transcription (STAT) proteins which migrate to the nucleus and regulate gene expression, IGF-1 being the most important product of GH receptor activation. Negative feedback control of inflammatory cytokine and GH actions occurs via production of a number of proteins including the family of suppressors of cytokine signaling (SOCS). Generally, transcription of the genes encoding SOCS proteins, which have been mostly characterized in vitro, is low in un-stimulated cells but can be rapidly induced upon exposure to cytokines and hormones [35]. GH induces a number of SOCS proteins with SOCS-2 playing a pivotal role in the negative feedback of GH signaling [36]. Induction of SOCS expression by inflammatory cytokines has also been shown to influence GH activity in

vitro. IL-1 β and TNF- α have been shown to increase GH-mediated SOCS expression [37] and reduce IGF-1 mRNA production [38] in hepatic tissues suggesting receptor cross-talk may be an important site for regulation of cytokine- and GH-stimulated gene expression. Cross-talk between shared signaling pathways is well-recognized for cytokines and GH [reviewed in 39] and may be a key determinant of circulating IGF-1 levels. However, local regulation of IGF-1 production in muscle and bone may also be important for mediating GH effects in these tissues and could utilize additional intracellular signaling mechanisms. Indeed, studies in cultured skeletal muscle cells demonstrated that inflammatory cytokines, in addition to the classic JAK-STAT pathway [40], can regulate IGF-1 production in these cells by the mitogen-activated protein kinase (MAPK) pathway [41]. To date, no studies have reported a role for IL-8 in these processes of GH-cytokine receptor cross-regulation; however, the results of the present study suggest a need to investigate a role for IL-8 in regulating hepatic, skeletal or muscle production of IGF-1, particularly in models of diabetes where the role of hyperglycemia in these processes can be delineated.

Finally, the potential therapeutic relevance of the association of increased IL-8 and reduced IGF-1 in adolescents with T1DM and chronic, poor metabolic control remains to be explored. Foremost, improved metabolic control is most desirable, yet interventions that target inflammation could have additional benefits. Nutritional and pharmacological therapies can reduce inflammation and improve IGF-1 levels in patients with inflammatory bowel disease [22,42]; however, studies evaluating the long-term benefits of these interventions on growth or skeletal complications are lacking. In a study of adults with T1DM, treatment with the lipid-lowering drug simvastatin reduced baseline and stimulated markers of inflammation that were independent of metabolic control [43], but measures of IGF-1 were not investigated. The effects of this inflammation reducing therapy on the GH/IGF-1 axis are therefore unknown. It is worthwhile to investigate these therapeutic possibilities, as targets beyond optimal blood glucose control may be required to reduce the increased fracture risk observed in adult women with T1DM [7] to that of adult women without diabetes. Moreover, intervention during the period of peak bone mass acquisition during adolescence may be necessary, and worth exploring, if benefits in bone health are to be realized.

In summary, increased serum IL-8 is associated with reduced IGF-1 in adolescents with T1DM and chronic, poor glucose control. These results suggest an interaction between inflammatory mediators and the IGF system that may be important to understanding dysfunction of the GH/IGF-1 axis in T1DM and its relationship to growth and skeletal complications of diabetes. It will be important to establish whether IL-8 specifically, versus inflammatory cytokines in general, drives this interaction and whether regulation of IGF-1 occurs primarily in the liver or also in local sites such as bone. Additional studies will be needed to evaluate the physiologic role of these observations and delineate the cellular mechanisms involved in IGF-1 regulation, as these could represent potential therapeutic targets to improve growth and skeletal complications, not only in T1DM, but also more widely in other chronic inflammatory diseases.

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Fig. 2.
Relationships among HbA1C, IGF-1 and IL-8 in adolescents with T1DM.

Table 1

Clinical and biochemical features of subjects with Type 1 DM

	Favorable Control (n=19)	Poor Control (n=17)	<i>p</i> value
Age (years)	15.9 ± 1.8	16.1 ± 1.6	0.73
Gender (M/F)	10/9	8/9	0.98
Duration diabetes (years)	6.7 ± 2.2	7.4 ± 3.3	0.42
BMI (kg/m ²)	23.5 ± 4.1	23.3 ± 4.9	0.88
HbA1C (%)	7.5 ± 0.6	10.5 ± 0.9	<0.001*
IGF-1 (ng/dL)	536.5 ± 164.3	408.9 ± 157.1	0.03*
IL-6 (pg/mL)	1.8 (0–8.6)	3.7 (0–31.2)	0.38
IL-8 (pg/mL)	2.2 (0–13.8)	7.3 (1.2–16.3)	0.01*
IL-10 (pg/mL)	2.1 (0–13)	2.9 (0–6.2)	0.49
MCP-1 (pg/mL)	26.6 (6.2–144)	46.3 (7.8–279)	0.07
TNF- α (pg/mL)	3.0 (0–9.4)	3.4 (0–5.3)	0.97

Values represent mean ± SD or median (range)

BMI, body mass index; HbA1C, hemoglobin A1C; IGF-1, insulin-like growth factor-1; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin 10; MCP-1, monocyte chemoattractant protein-1; TNF- α , tumor necrosis factor α ;