Pediatric Research and Child Health

RESEARCH ARTICLE

Human Immunodeficiency Virus Infected Children Show Poor Growth Associated To Abnormalities in Insulin Growth Factor System Even With Low Viral Load

Marcelo Amaral Ruiz[1], Raphael Del Roio Liberatore Junior[1], Bento Vidal de Moura Negrini[2], Soraya Lopes Sader[1], Rodrigo Jose Custodio[1], Maria Célia Cervi[2], Carlos Eduardo Martinelli Junior[1]

[1]Section of Endocrinology. Department of Pediatrics. Ribeirão Preto Medical School. University of São Paulo. Brazil. Av. Bandeirantes, 3900, Ribeirão Preto, state of São Paulo, Brazil.
[2]Section of Infectious Diseases. Department of Pediatrics. Ribeirão Preto Medical School. University of São Paulo. Brazil. Av. Bandeirantes, 3900, Ribeirão Preto, state of São Paulo, Brazil.

Abstract

Objective: To correlate serum concentration of IGF-1, IGF-2, IGFBPs and interleukins in a population of HIV-infected children with height and viral loud (VL).

Study design: Thirty-seven pre-pubertal children vertically infected with HIV, aged 5-11 years, in good clinical condition were allocated into 2 groups: VL>1000 (VL>1000 copies/mL, n= 20) and VL<1000 (VL<1000 copies/mL, n=17). Thirty age-matched non-infected children were studied as controls (CG). Anamnesis and physical examination were performed at the inclusion in the study, 6 and 12 months after. Fasting blood sample were collected for IGF-1, IGF-2, IGFBP-1, IGFBP-3, interleukin 2 (IL-2), interleukin 6 (IL-6), tumour necrosis factor-alpha (TNF-α), and insulin analysis.

Results: Children in both HIV-infected groups were shorter than the CG ($p<0.01$). IGF-1 and IGFBP-3 concentrations were lower in VL>1000 compared with CG ($p<0,01$). IGF-2 concentrations were lower in VL>1000 and VL<1000 compared with CG ($p<0,01$). IGFBP-1 concentrations were not different among groups. However, insulin concentrations were lower in the VL>1000 group ($p<0.01$) and a negative correlation was observed between insulin and IGFBP-1 concentrations ($r=-0.41$; $p<0.01$). IL-6 and TNF-alfa concentrations were higher in VL>1000 and VL<1000 compared with CG ($P<0.01$).

Conclusion: HIV-infected children were shorter than no infected children despite good disease control. The growth failure is associated with reduced concentrations of IGF-1, IGF-2 and IGFBP-3 in relation to IGFBP-1 leading to an imbalance that could decrease IGF bioactivity. High inflammatory cytokine concentrations in VL<1000 group demonstrates that good control is not enough to extinguish the inflammatory process that can affect growth by regulating the IGF system.

Keywords: HIV, children, IGF-1, IGF-2, IGFBP-3, interleukins, viral load, growth.

Abbreviations and Acronyms

BMI: body mass index; CG: control group; CI: confidence interval; GH: growth hormone; GHD: growth hormone deficiency; HAART: highly active antiretroviral therapy; hGHr: recombinant human growth hormone; HIV: Human Immunodeficiency Virus; HOMA-IR: homeostatic model assessment insulin resistance; IGF-1: insulin-like growth factor one; IGF-2: insulin-like growth factor two; IGFBPs: insulin-like growth factor binding proteins; IGFBP-1: insulin-like growth factor binding protein one; IGFBP-2: Insulin-like growth factor protein two; IGFBP-3: Insulin-like growth factor protein three; IL-2: interleukin two; IL-6: interleukin six; SDS: standard deviation score; TNF-α: tumour necrosis factor alfa; VL: viral loud

Introduction

Acquired Immunodeficiency Syndrome in childhood due to Human Immunodeficiency Virus (HIV) infection continues to be a public health problem, especially in developing countries. About 1500 new children are contaminate on a daily basis [1].

Until the 1990s, HIV-infected patients were treated with antiretroviral schemes with low efficacy on immunity and disease control. Children suffered multiple and severe infections, chronic diarrhea, malabsorption and anemia, that could explain the deficient weight-height gain [2, 3].

The advent of highly active antiretroviral therapy (HAART) permitted a satisfactory maintenance of immunity and reduction of complications, mainly regarding infections, with an important improvement of survival and quality

***Correspondence to:** Marcelo Amaral Ruiz, Professor of Pediatrics. Ribeirão Preto Medical School. University of São Paulo. Brazil. Av. Bandeirantes, 3900, Ribeirão Preto, state of São Paulo, Brazil. Email: marceloamaralruiz[AT] gmail[DOT]com

Received: Feb 18, 2020; **Accepted:** Feb 24, 2020; **Published:** Feb 26, 2020

of life, especially among children [2]. However, despite a better control of the disease, several studies still show that a significant number of HIV-infected children continue to have short stature [2, 3].

HIV-infected children have high cytokine and reduced IGF-1 concentrations, and high levels of IGF-binding proteins (IGFBPs), especially IGFBP-1 and IGFBP-2[4-7].Studies on children have been limited to the analysis of one or two components of the IGF system.

The objective of the present study was to describe stature, serum concentration of components of IGF system and proinflammatory interleukin according to viral loud (VL) in HIV-infected children and compare with non-HIV –infected children.

Methods

Study population

Thirty-seven pre-pubertal children (22 boys and 15 girls) vertically infected with HIV, aged 5 to 11 years, were included in this study. They were further allocated to 2 groups according to viral load (VL): Group VL>1000 (VL higher than 1000 copies/mL, n= 20) and Group VL<1000 (VL lower than 1000 copies/mL, n=17). The cut-off value of 1000 copies/mL was used since it represents good control of HIV infection. None of the children studied showed signs or symptoms of systemic disorders, chronic diarrhoea, or opportunistic infections, and none of them used corticosteroids or reached puberty during the 12 months of the study.

Thirty non-infected children (17 boys and 13 girls) matched for age and sex were studied as control group (CG).

The study was approved by Local Ethics Committee and written informed consent obtained from all participants and guardians before inclusion in the study.

Study Design

Detailed anamnesis and physical evaluation was performed at inclusion in the study, after 6 months and after 1 year by the same observer. Height, body weight, and BMI were recorded. All participants were evaluated by a nutritionist and their caloric intake, as well as micro and macronutrient distribution, was adjusted for age.

At the time of clinical evaluation, fasting peripheral blood samples were collected for IGF-1, IGF-2, IGFBP-1, IGFBP-3, interleukin 2 (IL-2), interleukin 6 (IL-6), tumour necrosis factor alpha (TNF-α), glucose and insulin analysis. Serum was stored at -60°C until analysis.

Assays

IGF-1, IGF-2, IGFBP-1, IGFBP-3 (DSL, Diagnostic Systems Laboratories, Webster, TX, USA), and insulin (Siemens, USA) were determined by specific immunoassays. All samples were analysed in duplicate. The intra- and inter-assay coefficients of variation were 4.5% and 8.8% for IGF-1, 3.5% and 7.7% for IGF-2, 2.5% and 6.2% for IGFBP-1, 7.3% and 10.4% for IGFBP-3, and 5.8% for insulin. Assay sensitivity was 5 ng/ml for IGF-1, 30 ng/ml for IGF-2, 5 ng/ml for IGFBP-1, 100 ng/ml for IGFBP-3, and 0.5 µIU/ml for insulin.

Serum concentrations of IL-2, IL-6 and TNF-α were determined by Luminex® xMAP® technology using commercial HCYTOMAG-60K-03 kits (Millipore Corp., St. Charles, MO, USA). The intra-assay coefficient of variation was 2.1% for IL-2, 2.0% for IL-6, and 2.6% for TNF-α.

Plasma HIV-1 RNA was quantitated directly using the commercial VERSANT HIV-1 RNA 3.0 (bDNA) kits (Bayer Corporation, USA).

Statistical analysis

The values utilized for statistical analysis were those obtained at the inicial evaluation. HOMA-IR [glycemia (mmol/L) x insulin (µIU/mL) / 22.5] was used for the determination of insulin resistance. Variables are expressed as medians and interquartile ranges or means and standard deviation. The Kruskal-Wallis test with Dunn's post-test and Spearman coefficient were used when appropriated. The level of significance was set at 5% ($P \leq 0.05$). Statistical analysis was performed using the GraphPad Prism 7.0 software (GraphPad Software Inc., San Diego, CA, USA).

Results

Anthropometric data

Seventeen out of 37 HIV-infected children had VL<1000 copies/mL while 20 had VL>1000 copies/mL. The anthropometric data are presented in Table 1.

A significant difference in stature was observed among the two patient groups and the control group (p<0.01) (Table 1, Figure 1), with no difference in BMI among the three groups (p=0.49).

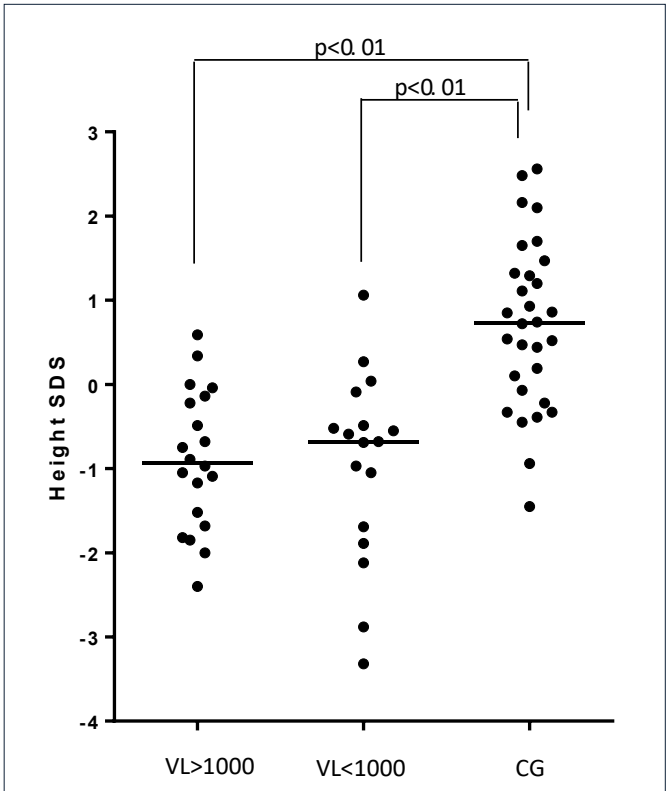

Figure 1: A significant difference in stature was observed among the two patient groups and the control group (p<0.01)

IGF-1 and IGF-2

The VL>1000 group had lower IGF-1 (129ng/mL) than CG (245ng/mL) (P<0.01), while the values of the VL<1000 (173ng/mL) group did not differ from either VL>1000 or CG (Figure 2A).

The serum IGF-2 concentrations were lower in VL>1000 (599ng/mL) and in VL<1000 (641ng/mL) groups compared to CG (901ng/mL) (P<0.01) (Figure 2B).

IGFBP-1 and IGFBP-3

Serum IGFBP-1 concentrations did not differ among the three groups. VL>1000 (129ng/mL); VL<1000 (173ng/mL) and CG (245 ng/mL) (Figure 2C).

Table 1: Median and interquartile age range (years), standard deviation score for height, weight and BMI of patients vertically infected with HIV with a viral load of more than 1000 copies/ml (VL>1000), less than 1000 copies/ml (VL<1000), and control group (CG).

	VL>1000(n=20)	VL<1000(n=17)	CG(n=30)
Age (yrs)	7.75 (6.14 a 8.60)	9.0 (7.38 a 10.5)	6.75 (5.80 a 8.50)
Height-SDS	-0.93 (-1.64 a -0.16)[a]	-0.68 (-1.79 a -0.29)[a]	0.73 (-0.11 a 1.36)
Weight-SDS	-0.54 (-1.15 a -0.19)[a]	-0.68 (-1.30 a 0.25)[a]	0.49 (-0.01 a 0.95)
BMI -SDS	-0.10 (-0.53 a 0.38)	-0.16 (-0.68 a 0.44)	-0.04 (-0.41 a 1.03)

a=p<0.01 compared to control.

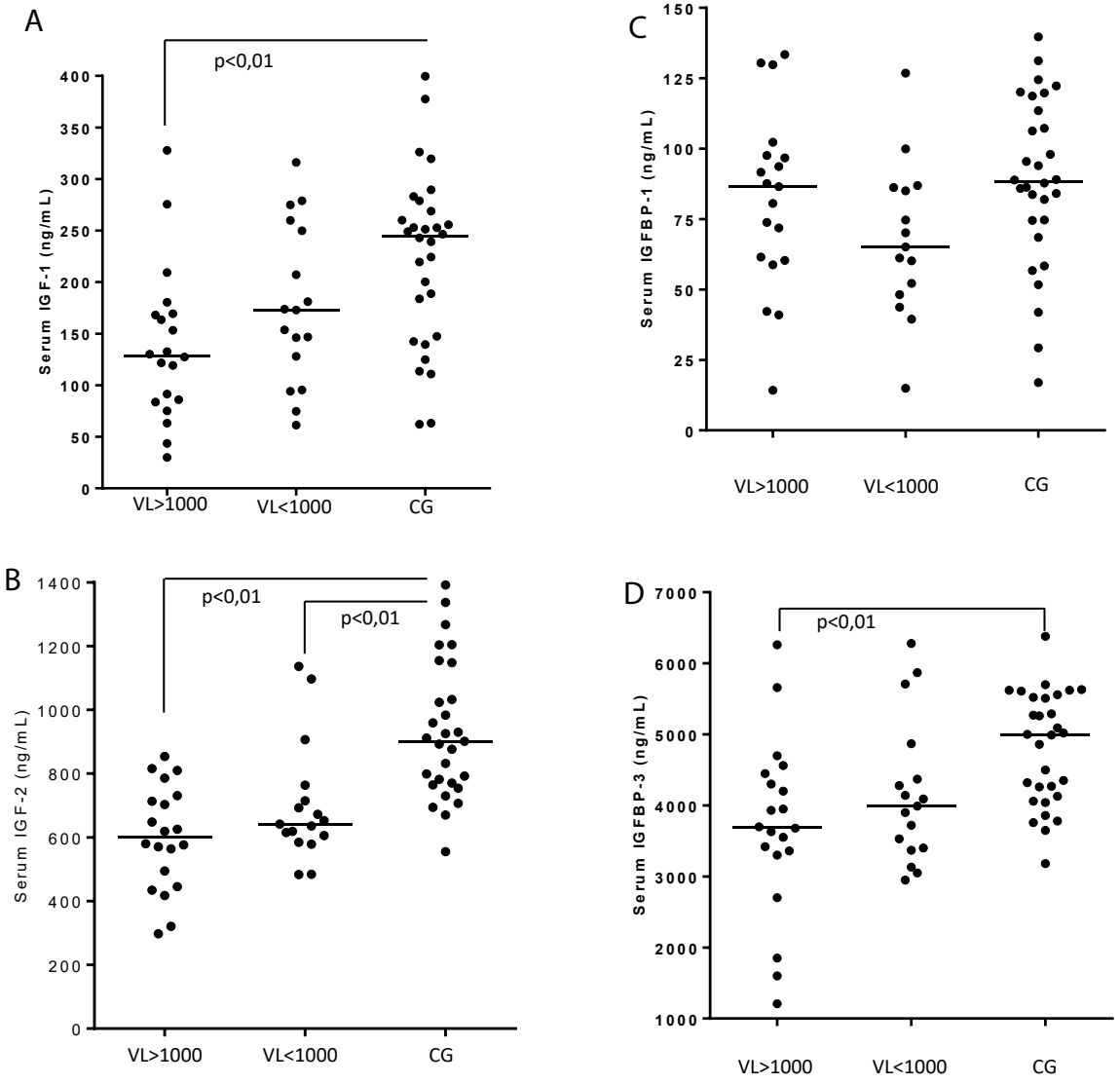

Figure 2: a) The VL>1000 group had lower IGF-1 (129ng/mL) than CG (245ng/mL) (P<0.01), while the values of the VL<1000 (173ng/mL) group did not differ from either VL>1000 or CG. **b)** The serum IGF-II concentrations were lower in VL>1000 (599ng/mL) and in VL<1000 (641ng/mL) groups compared to CG (901ng/mL) (P<0.01). **c)** Serum IGFBP-1 concentrations did not differ among the three groups. VL>1000 (129ng/mL); VL<1000 (173ng/mL) and CG (245 ng/mL). **d)** Serum IGFBP-3 concentrations were lower in the VL> 1000 group (3690ng/mL) compared to CG (4995ng/mL) (P<0.01). The values of the VL<1000 group (3990ng/mL) did not differ from the other two groups

Serum IGFBP-3 concentrations were lower in the VL> 1000 group (3690ng/mL) compared to CG (4995ng/mL) (P<0.01). The values of the VL<1000 group (3990ng/mL) did not differ from the other two groups (Figure 2D).

Insulin, glycaemia and Homa-IR

Serum insulin concentrations were lower in the VL>1000 group (2, 1µUI/mL) than in the VL<1000 and CG (respectively 5,4 and 4,6µUI/mL) (p<0.01). No difference was observed between the VL<1000 group and CG.

There was no difference in glycaemia among the three groups and the HOMA-IR index was lower in the VL>1000 group (0, 42) compared to the VL<1000 and CG (respectively 1,07 and 0,85) (p<0.01). No difference was observed between the VL<1000 group and CG (Figure 3A).

A negative correlation was found between serum insulin and serum IGFBP-1 concentrations (r = -0.41; p<0.01; Figure 3B).

IL-2, IL-6 and TNF-α

IL-2 values were higher in the VL>1000 group compared to control, but many children showed values below the detection limit of the method in all groups. We considered it may be some dosing method problem.

Higher IL-6 levels were observed both in the VL>1000 group (1.24pg/mL) (P<0.01) and the VL<1000 group (2.77pg/mL) (P<0.01) compared to CG (0.08pg/mL) (Figure 4A).

Serum TNF-α concentrations were also higher in the VL>1000 (12.3pg/mL) (P<0.01) and VL<1000 (14.6pg/mL) groups (P<0.01) compared to CG (7.85pg/mL) (Figure 4B). No significant differences in IL-6 or TNF-α were observed between the VL<1000 and VL>1000 groups.

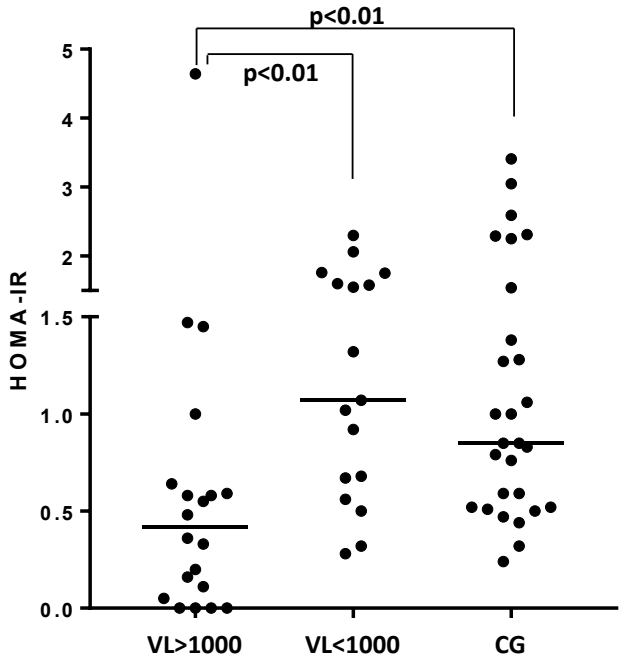

Figure 3a: There was no difference in glycaemia among the three groups and the HOMA-IR index was lower in the VL>1000 group (0, 42) compared to the VL<1000 and CG (respectively 1,07 and 0,85) (p<0.01). No difference was observed between the VL<1000 group and CG

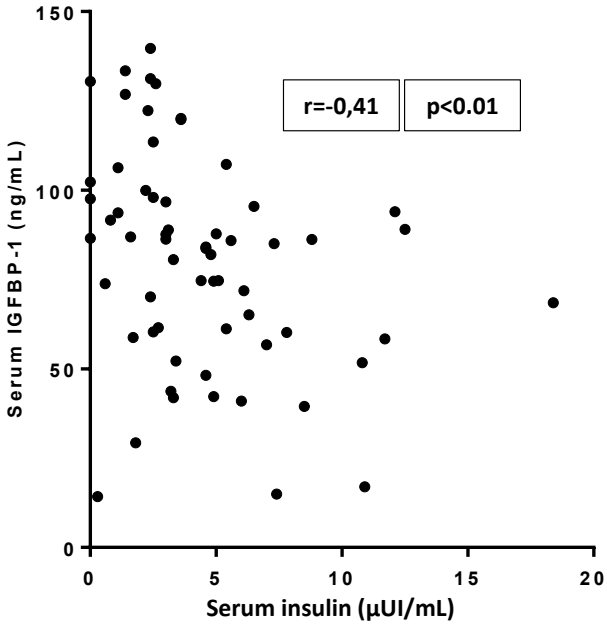

Figure 3b: A negative correlation was found between serum insulin and serum IGFBP-1 concentrations

Discussion

The present study demonstrated for the first time in children that multiple changes in the IGF-IGFBP system are associated with poor height growth in HIV-infected patients even after the introduction of new antiretroviral treatments. Reduced IGF-1, IGF-2 and IGFBP-3 concentrations have been reported, suggesting a state of partial deficiency or insensitivity to growth hormone related to clinical control and higher inflammatory cytokine concentrations.

It has been known for several decades that HIV-infected children have a deficient weight and height gain. Mckinney et al [8]. Detected a reduction of weight and length in HIV-infected infants even before 24 months of age. In a study of HIV-infected children in Ruanda, Lepage [9] observed that, after 5 years of life, more than half of HIV infected children had short stature and one third had low weight for age.

With new antiretroviral medications and new therapeutic schemes, the rates of opportunistic and severe infections have decreased. Today, patients with good adherence to treatment are able to maintain high TCD4+ lymphocyte concentrations and a low viral load. Good disease control and appropriate nutrition are essential to allow children growth [10]. This was demonstrated by Ran et al [11]. In a study of Chinese children conducted before and after the beginning of antiretroviral therapy, weight and height Z-scores increased by 0.052 and 0.014 respectively, after two years of treatment.

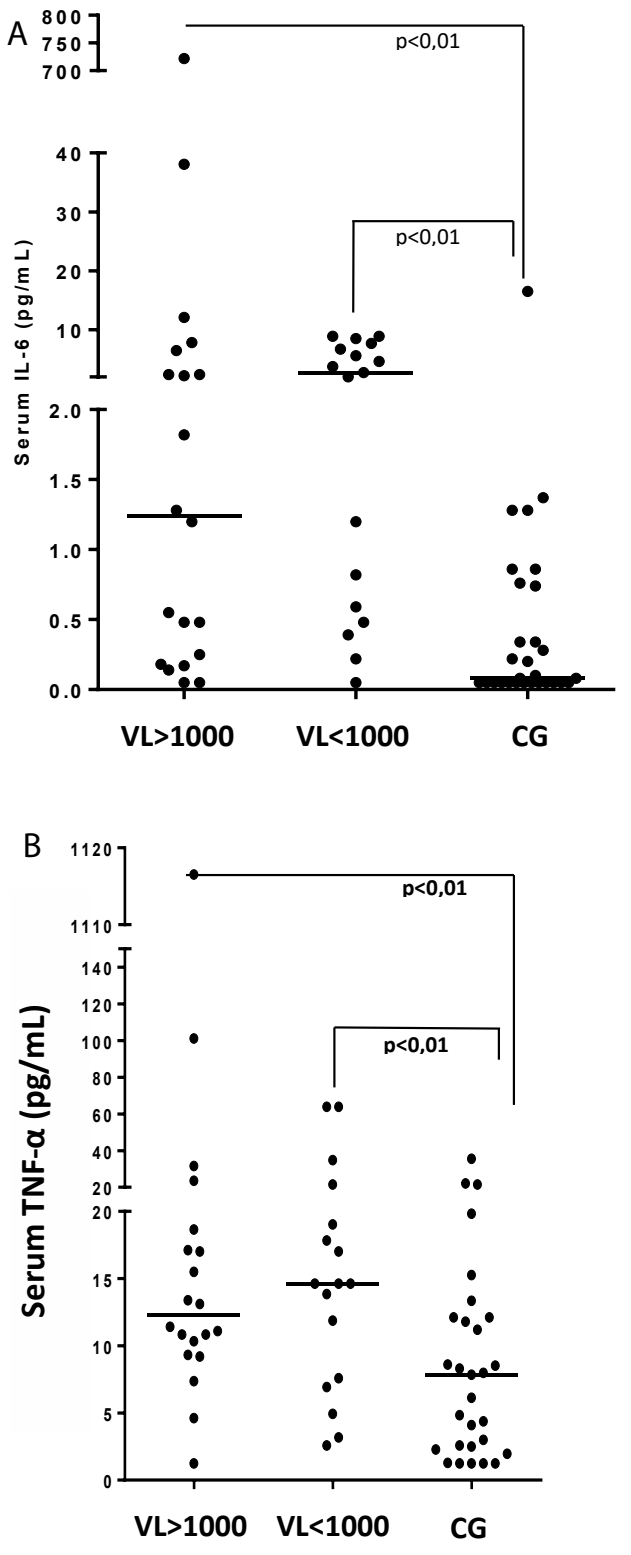

Figure 4: a) Higher IL-6 levels were observed both in the VL>1000 group (1.24pg/mL) (P<0.01) and the VL<1000 group (2.77pg/mL) (P<0.01) compared to CG (0.08pg/mL)

b) Higher IL-6 levels were observed both in the VL>1000 group (1.24pg/mL) (P<0.01) and the VL<1000 group (2.77pg/mL) (P<0.01) compared to CG (0.08pg/mL)

However, several studies have shown that, even with a good control of HIV infection, these children are shorter than non-infected children. In a study from Uganda, Achan et al [12]. observed that the beginning of antiretroviral therapy improved the Z-scores of height for age although the values continued to be lower than control.

Joel et al. In Botswana, reported that the prevalence of a short stature did not significantly differ among HIV children with an undetectable viral load and from that with treatment failure. This finding was also observed in the present study. Although 17 patients had a viral load of less than 1000 copies/mL they remain shorter than the non-infected children.

In this study, all children were clinically stable and showed no severe or opportunistic infection during the study period. They had no adverse reactions to the medications and all received an appropriate protein-calorie supply. This observation suggests that, among HIV-infected children, a good control of the disease was not sufficient to guarantee normal growth.

This findings could be partially explained by the lower IGF-1 concentrations observed in HIV-infected children especially in those with VL>1000. Moreover, IGF-2 concentrations were also reduced in HIV-infected children as previously described in adults [13].

No difference was observed in serum IGF-1 concentrations during the pubertal growth spurt between HIV-infected adolescents and non-HIV-infected controls, although they did observe a difference in the final adult height [14]. The present study data suggest that height impairment and changes in the IGF-IGFBP system could start early and maybe the late puberty is not the ideal time for the identification of changes in the IGF-IGFBP system.

Poor control of the disease has also been linked to higher proteolytic activity of IGFBP-3. However, the lower IGFBP-3 described in the present paper, in parallel mainly to the chances in IGF-I, can be better explained by decreased GH stimulus due to a growth hormone deficiency or insensitivity.

In this study we showed that the three main growth-stimulating components of the IGF-IGFBP system, IGF-1, IGF-2 and IGFBP-3, are reduced in HIV-infected children, with this reduction being more evident in the VL >1000 copies/mL subjects.

Another finding that contribute to explain the growth impairment is the lower insulin concentration in the VL>1000 group associated with the negative correlation between IGFBP-1 and insulin. This could sign to a higher inhibition of IGF actions by IGFBP-1.

On this basis, a broad view of the IGF-IGFBP system reveals that, in the present study, HIV-infected children had reduced IGF concentrations, with IGFs being proportionally more linked to IGFBP-1 than to IGFBP-3, with consequent impairment of their growth-stimulating activities even in children with good disease control. Kessler et al. described similar IGF-I concentrations in patients and controls, although IGFBP-1 was proportionally elevated among the patients.

These changes in the IGF system seem to be linked to changes in the immunological/inflammatory system and with cytokine

concentrations in particular. Zamboni et al. detected reduced IGF-I levels in patients with lower T CD4 + lymphocyte counts and high IL-6 levels. In a vitro study, Wolf et al. [15], observed that TNF-α and IL-1β inhibit GH stimulation and the synthesis of IGF-1 in culture cells. In a study of children just before the HAART, Van Rossum et al. [16] detected high TNF-α levels and low IGF-1 and IGFBP-3 levels, with the levels returning to normal after 24 weeks of therapy. Kelley [17] reported that IL-6 reduce IGF-1 concentrations and the expression of hepatic GH receptors in animals and *in vitro*, characterizing a state of partial GH insensitivity. He also demonstrated that TNF-α, even at low concentrations, inhibited the anabolic action of IGF-I in murine neurons and myoblasts and in human epithelial cells, indicating a double insensitivity to GH and IGF-1.

Studies in adults demonstrated high prevalence of growth hormone deficiency (GHD) among HIV infected lipodystrophic patients [18, 19]. The mechanisms involved in GHD in HIV adults patients remains uncertain [20]. The antivirus drugs seems do not reduce de GH secretion in vitro[21] Adults with GHD demonstrated high levels of cytokines than controls and the cytokines levels reduced during GH replacement [22].

The results of the present study go in the same direction. So, HIV-infected children have high concentrations of inflammatory cytokines, even when VL is less than 1000 copies/mL. The presence of inflammatory markers and reduced growth has been reported in other studies [23].

The state of GH deficiency or resistance may explain in part the reduced IGF and IGFBP-3 levels. It may also explain the proportionally elevated IGFBP-1 levels, since the lack of a GH stimulus increases IGFBP-1 concentrations especially when associated with lower insulin concentrations. Increased levels of inflammatory cytokines and reduced growth are also observed in children with other diseases such as juvenile idiopathic arthritis [24, 25]. In addition, TNF-α in particular, seems to have an inhibitory effect on the action of IGF-I at cellular level. Thus, a reduced IGF-1 activity could be speculated.

In summary, HIV-infected children were shorter than no infected children despite good disease control. This growth failure is associated with changes in the GH-IGF axis, with reduced concentrations of IGF-I, IGF-II and IGFBP-3 in relation to IGFBP-1 and with a consequent imbalance that reduce the bioactivity of IGFs and their growth-stimulating action.

The presence of high inflammatory cytokine concentrations even in children with VL<1000 copies/mL demonstrates that good disease control is not sufficient to abolish the inflammatory process and it can negatively affect growth by the regulation of the IGF system.

Although this study included one of the largest numbers of patients prospectively investigated, this number is still small and more studies are need to confirm a probable state of GH deficiency or resistance, that could led to a proposal of intervention.

References

1. Prendergast A, Tudor-Williams G, Jeena P, Burchett S, Goulder P. International perspectives, progress, and future challenges of paediatric HIV infection. *Lancet.* 370: 68–80. [View Article]
2. Arico M, Azzini M, Caselli D. AIDS: Outcome of children born to HTLV-III/LAV infected mothers. *Helv Paediatr Acta.* 41:477-486. [View Article]
3. Laue L, Pizzo PA, Butler K, Cutler Jr GB. Growth and neuroendocrine dysfunction in children with acquired immunodeficiency syndrome. *J Pediatr*. 117:541-5. [View Article]
4. Rondanelli M, Solerte SB, Fioravanti M, Scevola D, Locatelli M, Minoli L, Ferrari E. Circadian secretory pattern of growth hormone, insulin-like growth factor type I, cortisol, adrenocorticotropic hormone, thyroid-stimulating hormone, and prolactin during HIV infection. *AIDS Res Hum Retroviruses*. 13:1243-9. [View Article]
5. Congote LF. Monitoring Insulin-like Growth Factors in HIV infection and AIDS. *Clinica Chimica Acta* 361:30-53. [View Article]
6. Johann-Liang R, O'Neill L, Cervia J, Haller I, Giunta Y, Licholai T, Noel GJ. Energy balance, viral burden, insulin-like growth factor-1, interleukin-6 and growth impairment in children infected with human immunodeficiency virus. *AIDS*. 14:683-90. [View Article]
7. Zamboni G, Antoniazzi F, Bertoldo F, Lauriola S, Antozzi L, Tato L. Altered bone metabolism in children infected with human immunodeficiency virus. *Acta Pediatric*. 92:12–16. [View Article]
8. McKinney Jr RE, Wilfert CM, Katz SL.The effect of human immunodeficiency virus (HIV) infection on growth of children less than 24 months old. *Pediatr Res*. 31:170A. [View Article]
9. Lepage P, Van de Perre P, Van Vliet G, Nsengumuremyi F, Van Goethem C, Kestelyn P, et al. Clinical and endocrinologic manifestations in perinatally human immunodeficiency virus type 1 Infected children aged 5 years or older. *Am J Dis Child*. 145:1248-51. [View Article]
10. Joel DR, Mabikwa V, Makhanda J, Tolle MA, Anabwani GM, Ahmed SF. The prevalence and determinants of short stature in HIV-infected children.13:529-33. [View Article]
11. Hu R, Mu W, Sun X, Wu H, Pang L, Wang L et al. Growth of HIV-Infected Children in the Early Stage of Antiretroviral Treatment: *A Retrospective Cohort Study in China. AIDS Patient Care and STDs*. 30: 365-370. [View Article]
12. Achan J, Kakuru A, Ikilezi G, Mwangwa F, Plenty A, Charlebois E et al. Growth Recovery Among HIV-Infected Children Randomized to Lopinavir/Ritonavir or NNRTI-Based Antiretroviral Therapy. *Pediatr Infect Dis J*.35:1329-1332. [View Article]
13. Helle SI, Ueland T, Ekse D, Froland SS, Holly JMP, Lonning PE, Aukrust P. The insulin-like growth factor system in human immunodeficiency virus infection: relations to immunological parameters, disease progression and antiretroviral therapy. *J Clin Endocrin Metabl*. 86:227-83. [View Article]

14. Kessler M, Kaul A, Santos-Malavé C, Borkowsky W, Kessler J, Shah B. Growth Patterns in Pubertal HIV-infected Adolescents and their Correlation with Cytokines, IGF-I, IGFBP-1 and IGFBP-3. *J Pediatr Endocrinol Metab*. 26: 639–644. [View Article]

15. Wolf M, Böhm S, Brand M, Kreymann G. Proinflammatory cytokines interleukin 1 beta and tumor necrosis factor alpha inhibit growth hormone stimulation of insulin-like growth factor I synthesis and growth hormone receptor mRNA levels in cultured rat liver cells. *Eur J Endocrinol*. 135(6):729-37. [View Article]

16. Van Rossum AM, Gaakeer MI, Verweel S, Hartwig NG, Wolfs TF, Geelen SP, et al. Endocrinologic and immunologic factors associated with recovery of growth in children with human immunodeficiency virus type 1 infection treated with protease inhibitors. Pediatr Infect Dis J. 22(1):70-6. [View Article]

17. Kelley KW. From hormones to immunity: the physiology of immunology. *Brain Behav Immun*. 18:95– 113. [View Article]

18. Zirilli L, Orlando G, Carli F, Madeo B, Cocchi S, Diazzi C, Carani C, Guaraldi G, Rochira V. GH response to GHRH plus arginine is impaired in lipoatrophic women with human immunodeficiency virus compared with controls. *Eur J Endocrinol*. 166:415-24. [View Article]

19. Brigante G, Diazzi C, Ansaloni A, Zirilli L, Orlando G, Guaraldi G, Rochira V. Gender differences in GH response to GHRH+ARG in lipodystrophic patients with HIV: a key role for body fat distribution. *Eur J Endocrinol*. 170:685-96. [View Article]

20. Rochira V, Guaraldi G. Growth hormone deficiency and human immunodeficiency virus. Best Pract Res Clin Endocrinol Metab.31:91-111. [View Article]

21. Brigante G, Riccetti L, Lazzaretti C, Rofrano L, Sperduti S, Potì F, Diazzi C, Prodam F, Guaraldi G, Lania AG, Rochira V, Casarini L. Abacavir, nevirapine, and ritonavir modulate intracellular calcium levels without affecting GHRH-mediated growth hormone secretion in somatotropic cells in vitro. Mol Cell Endocrinol. 482:37-44. [View Article]

22. Serri O, St-Jacques P, Sartippour M, Renier G. Alterations of monocyte function in patients with growth hormone (GH) deficiency: effect of substitutive GH therapy. J Clin Endocrinol Metab. 84:58-63. [View Article]

23. Prendergast AJ, Rukobo S, Chasekwa B, Mutasa K, Ntozini R, Mbuya MN et al. Stunting is characterized by chronic inflammation in Zimbabwean infants. PLoS One.9:e86928. [View Article]

24. Drozdova EA, Yadykina EV, Mezentseva EA, Nikushkina KV. Cytokine profile changes in children with juvenile idiopathic arthritis-associated uveitis. Vestn Oftalmol. 133(1):27-31. [View Article]

25. Frittoli RB, Longui BS, Silva AM, Filho AA, Monteiro MÂ, Appenzeller S.Effects of the use of growth hormone in children and adolescents with juvenile idiopathic arthritis: a systematic review.Rev Bras Reumatol . 57(2):100-106. [View Article]

Citation: Ruiz MA, Junior RDRL, de Moura Negrini BV, Sader SL, Custodio RJ, et al. (2020) Human Immunodeficiency Virus Infected Children Show Poor Growth Associated To Abnormalities in Insulin Growth Factor System Even With Low Viral Load. Pediatr Res Child Health 3: 001-007.