 Accepted Manuscript published as EC-22-0370.R1. Accepted for publication: 16-Feb-2023

Role of glucose variability on linear growth in children with Type 1 Diabetes

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Running Title: glycemic variability and growth in T1D

Keywords: Type 1 Diabetes, growth, glucose variability, children

Word count: 2725

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Abstract

Objective: Linear growth is impaired in children with type 1 diabetes (T1D) and poor metabolic control. A good metabolic control is a key therapeutic goal to prevent vascular complications but also for ensuring an appropriate anthropometric development during childhood. In this study, we aimed to identify and characterize the effects of glycemic variability on linear growth in children with T1D.

Methods: Data from 144 prepubertal children with T1D were evaluated. Anthropometric measurements (weight, weight-SDS, height, height-SDS, BMI, BMI-SDS) were collected and glycosylated hemoglobin (HbA1c) was measured at admission and every four months over a 2-year period. Glycemic variability indexes (glycemic coefficient of variation [CV], glycemic CV percentage [CV%] and the product between HbA1c-mean and HbA1c-SDS/100 [M*SDS-HbA1c/100]) were calculated. According to height-SDS changes after 2-years of follow up, the study population was divided into three tertiles groups and differences across groups were investigated for variables of interest.

Results: The three groups were similar in terms of age, gender and follow up period. After 2 years, all prepubertal children showed a significant positive trend of anthropometric data. Across the three tertiles groups, HbA1c-SDS, CV, CV% and M*SDS-HbA1c significantly decreased from the first to the third tertiles of height-SDS. During follow-up children with lower Δheight-SDS values, reported higher values of HbA1c-SDS, CV, CV% and M*SDS-HbA1c than subjects with higher linear growth.

Conclusions: Glycemic variability correlates with the linear growth in children with T1D. Low glycemic variability indexes were reported in higher height-SDS tertile. Δheight-SDS is inversely correlated with glycemic CV, CV% and M*SDS-HbA1c.

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Introduction

Type 1 Diabetes (T1D) and other chronic diseases are well recognized to adversely affect linear growth in childhood. Indeed, early studies have shown that suboptimal glycemic control and longer disease duration can impair anthropometric development in children with T1D (1,2). The Mauriac Syndrome, characterized by growth failure and hepatomegaly, constitutes the most critical growth-related condition characterized with long-term and poorly controlled T1D in relation to chronic under-insulinization (3). These effects are mainly related to the role of insulin in the regulation of the growth hormone (GH)/insulin like growth factor-1 (IGF-1) axis. In fact, normal insulin secretion and adequate portal insulin levels are necessary to obtain normal serum concentrations of IGF-1 and IGF-binding proteins (IGFBPs), thus indirectly ensuring physiological growth in children. In particular, many studies have demonstrated that insulin could influence GH receptor (GHR) expression in the liver and interacts with GH post-receptor signaling, thereby regulating the hepatic synthesis of IGF-1 and IGFBPs (4,5). Thus, in children with T1D, portal insulin deficiency frequently occurs and determines GH hypersecretion, low circulating concentrations of IGF-1 and IGFBP-3, with high serum levels of IGFBP-1 consequently. Indeed, exogenous subcutaneous insulin therapy seems not able to replace pancreatic insulin secretion in portal circulation (6). These impaired hormonal patterns have been largely described not only in an actually rare condition such as Mauriac Syndrome but also in many children and adolescents with poorly controlled T1D (7,8,9). In particular, many authors have detected an association between the lowest IGF-1 levels in those children with the highest glycated haemoglobin (HbA1c) levels (9,10). Other studies have also documented an inversely strictly correlation between height velocity and HbA1c value in prepubertal children with T1D (11). However, modern diabetes care, particularly intensified insulin regimens and novel technologies, can improve metabolic control in patients with T1D, therefore preventing abnormalities of the GH–IGF-I axis thus potentially leading to normal growth and final height similarly to unaffected peers (12). Bizzarri et al. described that HbA1c levels modulated the growth pattern in diabetic children and demonstrated that height velocity after T1D diagnosis was directly associated with pancreatic beta

cell residual activity, evaluated as C-peptide levels (8). However, although a large number of data have clearly shown that glucose variability strongly affects the risk of diabetes related microvascular and macrovascular complications (13-15) no data characterizing its effect on growth pattern are available. Therefore, the aim of the study was to identify and characterize the effects of glycemic variability on the linear growth in a well selected-group of prepubertal children with T1D, by using accurate glycemic variability indexes during a 2 year follow up period.

Material and Methods

Study Population

We performed a retrospective study evaluating charts of children with T1D at the Department of Pediatrics, University of Chieti, Chieti, Italy. In the outpatient clinic, subjects with T1D are followed every four months and during each visit data regarding weight, height, BMI and pubertal development are routinely evaluated and HbA1c values are measured. In particular, we included data of 144 prepubertal Caucasian children (76 Male/68 Female) with T1D, older than 5 years at onset. In addition, only children younger than 9 years and 10 years for female and male, respectively, thus without signs of pubertal development according to Tanner stage at baseline and during follow up, were included in order to avoid confounding effects of puberty on growth pattern. Only data after 6 months from diagnosis of T1D (T0) were included. In addition, only children with complete data during a 2 years (T24) follow up were included. Furthermore, in order to exclude the potential effects on growth, children with other autoimmune complications or genetic disorders, patients with chronic diseases (i.e. celiac disease, thyroid abnormalities) or using corticosteroid therapy or with genetic syndromes (i.e. Prader-Willi syndrome, Down syndrome) were excluded.

All children have had a diagnosis of T1D according to American Diabetes Association (ADA) criteria (16). All selected patients were treated with an intensive insulin therapy consisting in injections of rapid insulin (lispro or aspart) plus long-acting insulin (degludec) once a day. Periodical adjustments

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were made every 3 or 6 months. Children using continuous subcutaneous insulin infusion were not included.

Ethics approval for this study was not required, since i) it was a retrospective study confined to anonymised and unidentifiable data that are routinely collected at the outpatient clinic for T1D at the University Hospital in Chieti; and ii) the study findings would not affect patient care retrospectively.

Physical characteristics

Anthropometric measurements (height, height-SDS, weight, weight-SDS, BMI, BMI-SDS) were determined in all children, at admission (T0) and every 4 months during the 2 years follow-up (T24). Body weight was taken with a digital scale to the nearest ±0.1 kg. Height was evaluated in triplicate with a wall mounted Harpenden stadiometer to the nearest ±0.1 cm. BMI was used as fatness index and calculated as the ratio of weight (kg)/height^2 (m). Weight-SDS, Height-SDS, BMI-SDS for age and sex was also obtained using the reference data for Italian population (17). Pubertal stage was defined according to Tanner's stage for both sexes (18).

Laboratory procedures and glycemic variability indexes

In all subjects, HbA1c values were obtained at admission (T0) and every 4 months, during the 2 years (T24) by using High Performance Liquid Chromatography (HPLC) technique. Moreover, specific indexes to characterize the glycemic variations of T1D children were also calculated. In particular, according to HbA1c values during the follow-up, we calculated the glycemic mean evaluated as mean-HbA1c (M-HbA1c), the Standard Deviation Score of HbA1c (HbA1c-SDS), the Coefficient of Variation (CV) of HbA1c (CV=HbA1c-SDS/meanHbA1c), the Percentage of CV (CV%), the product between HbA1c-mean and HbA1c-SDS divided by 100 (M*SDS-HbA1c).

Statistical Analysis

Statistical analysis was performed using SPSS version 23.0 software for Windows (SPSS Inc., Chicago, Illinois, USA). Values were expressed as mean ± standard deviations (SD). A *P*-value <0.05 was considered statistically significant. The variations of the main anthropometric and laboratory parameters (weight, weigh-SDS, height, height-SDS, BMI, BMI-SDS, HbA1c) in the entire population between admission (T0) and 2-year period (T24) were calculated by using the Wilcoxon Test. In addition, in order to explore differences in term of glycemic variability, according to different growth patterns, the height-SDS changes after two years of follow up (height-SDS after 2 year - height-SDS at baseline) was calculated and the study population was then divided into three tertile groups (first tertile: height-SDS≤-0.29; second tertile: -0.29<height-SDS<0.20; third tertile: height-SDS≥0.20). Thus, differences across the three groups were investigated by Kruskal-Wallis test, while the U-Mann-Whitney test was used for post hoc analysis. In order to further characterized the variations of anthropometric SDS values across the three tertile groups, the delta changes for age, weight SDS, height SDS and BMI SDS were calculated as variables at follow (T24) - variable at baseline (T0) [Δ(T24-T0)] and differences across the three groups were investigated by Kruskal-Wallis test while the U-Mann-Whitney test was used for post hoc analysis. The Spearman test was also performed to evaluate the correlation between height-SDS and the glycemic variability indexes.

Results

Physical and biochemical characteristics at admission and during follow-up

The main anthropometric and biochemical characteristics of the study population including 144 prepubertal children with T1D, recruited and followed up for 2 years, at 4-month intervals are summarized in **Table 1**.

In particular, data from 76 boys and 68 girls were evaluated with a mean age at admission of 7.7±2.0 years. At admission, the mean value of HbA1c was 7.7±1.7%. In the entire population as expected after 2 years of follow-up (T24), mean weight (*P*<0.01) and weight-SDS (*P*=0.02), the mean height

 Accepted Manuscript published as EC-22-0370.R1. Accepted for publication: 16-Feb-2023

(P<0.01) and the mean BMI (P<0.01) significantly improved, while the BMI-SDS and height-SDS increased and the mean HbA1c decreased although they did not reach a significant value.

Main anthropometric and laboratory data of the study population divided according to changes in height-SDS at follow up (height-SDS tertiles)

The main data of the three groups divided into tertiles according to changes of height-SDS at follow up (height-SDS at T24 - height-SDS at T0), are reported in **Table 2**. In particular, at admission (T0) the three groups were similar in terms of the main anthropometric measurements (weight, weight-SDS, height, height-SDS, BMI and BMI-SDS) and in term of metabolic control as defined by HbA1c values (all P>0.05). Therefore, in order to characterize the variations of anthropometric SDS values across the three tertile groups, the delta changes were calculated and reported in **Table 3**. As expected, Δ-height-SDS resulted statistically different across the three groups, thus increasing from the first to the third tertile of height-SDS (P<0.001) during follow-up. In addition, no difference was reported for Δ-age and Δ-BMI-SDS across the three tertiles groups. In contrast, Δ-weight-SDS values were significantly different across the three groups (P<0.001).

Main glucose variability indexes in the study population divided according to changes in height-SDS at follow up (height-SDS tertiles)

Figure 1 shows data regarding the main glucose variability indexes across height-SDS tertiles (**Figure 1**). In detail, glucose variability indexes significant improved with the increasing of height-SDS tertiles. In fact, HbA1c-SDS significantly decreased from the first to the third tertile group (*P for trend*<0.001); in addition HbA1c-SDS was also higher in the second group than the third tertile (P=0.01) (**Figure 1A**). In addition, CV (*P for trend*<0.001; first tertile, 0.12, second tertile 0.11 and third tertile 0.09, P0) and the CV% significantly decreased from the first to the third group (*P for trend*<0.001), showing higher values in the second tertile compared to the third (P=0.01) and as well as in the second compared to the first tertile (P=0.16) (**Figure 1B**). Similarly, the M*SDS-HbA1c

progressively and significantly decreased across the three tertiles (*P for trend*=0.001), showing lower values in the third tertile compared to the second (*P*=0.02) and first (*P*<0.001) as well as in the second compared to the first tertile (*P*=0.19) (**Figure 1C**). Of note, no statistically significant difference in term of mean HbA1c values across the three tertiles (*P for trend*=0.99) was documented.

Correlation analyses

An indirect and statistically significant correlation was documented between HbA1c-SDS and Δ(T24-T0)-height-SDS values (*P*=0.006, β=-0.22). In particular, it was observed a higher HbA1c-SDS value in those children who had a lower Δ(T24-T0)-height-SDS (**Figure 2A**). In addition, Δ(T24-T0)-height-SDS correlated significantly and indirectly with CV (*P*=0.003, β=-0.24) and CV% (*P*=0.003, β=-0.24). Indeed, children with lower Δ(T24-T0)-height-SDS showed higher CV and CV% values (**Figure 2B**), thus the higher was the glucose variability the lower was the increased of height-SDS at follow up. Moreover, an indirect and statistically significant association between M*SDS-HbA1c and Δ(T24-T0)-height-SDS values (*P*=0.01, β=-0.22) was found. In particular, children with lower values of Δ(T24-T0)-height-SDS, reported higher values of M*SDS-HbA1c (**Figure 2C**). Of note, in contrast, no significant correlation was documented between mean-HbA1c and Δ(T24-T0)-height-SDS (*P*=0.74).

Discussion

In this study, by evaluating a highly selected population of only pre-pubertal children with T1D we showed for the first time a direct association between glycemic variability and linear growth. In fact, the worse was the increase of height SDS during a two year follow up the higher was the glucose variability during follow up, thus documenting a positive effect of low glucose variability in linear group.

Linear growth in children is a complex multifactorial physiological process influenced by nutritional, endocrinological and psychological elements. Many studies reported that T1D duration and its

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metabolic control could modulate children's linear growth pattern and final adult height (19). In particular, the GH-IGF-1 axis has been described to be impaired in these patients. These effects are directly related to low IGF-1 serum concentrations caused by low intraportal insulin concentration (4). Therefore, in poorly controlled T1D, exogenous subcutaneous insulin therapy could be unable to replace pancreatic insulin secretion in portal circulation, thus impairing linear growth in children (20). Previously, Van Sickle et al. confirmed that adolescents with T1D which reported higher HbA1c values, presented higher levels of interleukin-8 (IL-8) and lower IGF-1 serum concentrations than diabetic peers with better metabolic control (21). Bonfig et al. evaluating anthropometric parameters and glycemic control in children with T1D, demonstrated that children with HbA1c <7.0% had a better final adult height-SDS, while the groups with HbA1c 7.0-8.0% and suboptimal metabolic profile (HbA1c>8.0%) reported a worst final adult height-SDS (22). In addition to these previous studies, we were able to confirm that not only metabolic control defined by HbA1c values but also glucose variability is related to growth pattern. In fact, in our study we have confirmed an indirect and statistically significant association between indexes of glycemic variability and height-SDS values in prepubertal children with T1D during the prepubertal period. In particular, children with lower height-SDS values at follow up reported higher glycemic variability indexes, namely HbA1c-SDS, CV, CV%, and M*SDS-HbA1c. Interestingly, correlations were also found between glycemic index (HbA1c-SDS, CV, CV% and M*SDS-HbA1c) and Δheight-SDS, confirming the possible link between gluco-metabolic profile and linear growth in pediatric population with T1D during pre-puberty. Therefore, these data suggest a potential link between glycemic control and growth parameters. To date several studies have shown the direct correlation of these indexes with the risk of microvascular and macrovascular complication (23,24). Of note, these indexes independently of the overall HbA1c values better predict the risk of complications. In fact, it is largely known that children with similar mean glucose or HbA1c levels can reported differences in terms of both the number and degree of glucose excursions that have been largely associated with diabetic complications (25). It is important to highlight that in our study delta in weight-SDS and height SDS

overtime significantly increased across the three tertile groups, although no differences in term of overall adiposity was documented as expressed by no statistically significant differences in terms of in BMI-SDS. Thus, since weight might also drive height, in order to properly characterize whether the differences could be due to higher weight and not necessarily the glycemic control itself, or the two effects are independent it is necessary to confirm our result in further studies including a larger population thus allowing to categorize the tertile groups according to the degree of weight gain.

We are aware of some limitations of the present study related to the retrospective nature of the study which strongly affect the availability of data regarding food diary or physical activity. In addition, a relevant limitation is the absence of IGF-1, IGFBP3 and ALS measurement able to show a direct effect of glucose variability on hormonal pattern. In addition, a longer follow up evaluating data up to the final height are needed in order to confirm our results. As well, evaluating a highly selected population it is not possible to extend these data to other ethnic groups, therefore further studies in this sense will be necessary to confirm such results according to this relevant factor. Finally, the lack of data regarding of parental height and especially bone age might not offer a complete view regarding its relevant effects on growth and particularly do not allow to differentiate fast growers (bone age>calendar age) from late bloomers (bone age<calendar age). A strength of our study is the highly selected population of prepubertal children with a close age-range evaluated. In fact, by evaluating data of subject older than 5 years and with absence of signs of pubertal development during the entire follow up we were able to minimize several hormonal effects on growth related to puberty. In addition, by excluding subjects with other disease able to affect growth such as celiac disease or thyroid dysfunction we were able to strongly minimize additional confounding factors on growth.

Conclusions

In conclusion, not only metabolic control but also glucose variability is able to affect growth pattern in prepubertal children with T1D. Therefore, new insulin regimes and new technologies able to minimize glucose variability are needed in children with T1D in order to improve linear growth in prepubertal children with T1D.

 Accepted Manuscript published as EC-22-0370.R1. Accepted for publication: 16-Feb-2023

Conflict of Interest Statement

The authors declare that the research was performed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

All the authors contributed to the research of the articles and to the writing of the manuscript.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Legends

Tables

Table 1. Clinical and biochemical characteristics of all children with T1D at admission (T0) and after 2 years follow-up (T24).

Table 2. Main clinical and biochemical characteristics at admission (T0) and after 2 years follow-up (T24) of children with T1D divided according to height-SDS tertile.

Table 3. Delta values (T24-T0) of the main anthropometric variables in the three groups of height-SDS tertiles.

Figure 1. ***Main glucose variability indexes across height-SDS tertiles***.

HbA1c-SDS (1A), CV percentage (CV%) (1B), M*SDS-HbA1c (1C) across the three tertiles of heigh-SDS.

Figure 2. ***Association between Δheight-SDS and main glucose variability indexes***
2 A. Association between Δheight-SDS and HbA1c-SDS (P=0.006). **2 B.** Association between Δheight-SDS and CV% (P=0.003). **2 C.** Association between Δheight-SDS and M*SDS-HbA1c (P=0.01).

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Table 1. Clinical and biochemical characteristics of all children with T1D at admission (T0) and after 2 years follow-up (T24).

Variables	Admission (T0)	Follow-up (T24)	*P-value*
Sample size	144	144	
Gender (Male/Female)	76(53%)/68(47%)	76(53%)/68(47%)	
Age (years)	7.7±2.0	9.8±2.0	
Weight (kg)	30.8±8.7	40.5±11.6	**<0.01**
Weight-SDS	0.44±0.99	0.55±1.0	**0.02**
Height (cm)	127.6±12.5	139.6±12.8	**<0.01**
Height-SDS	0.25±1.0	0.26±1.1	0.82
BMI (kg/m^2)	18.5±2.6	20.4±3.4	**<0.01**
BMI-SDS	0.50±0.92	0.61±0.95	0.07
HbA1c (%)	7.7±1.7	7.3±1.2	0.07

BMI: body mass index; HbA1c: glycosylated haemoglobin.

Table 2. Main clinical and biochemical characteristics at admission (T0) and after 2 years follow-up (T24) of children with T1D divided according to height-SDS tertile.

	Height-SDS 1° TERTILE Height-SDS≤-0.29		**Height-SDS 2° TERTILE -0.29<Height-SDS<0.20**		**Height-SDS 3° TERTILE Height-SDS≥0.20**		***P-value (at T0)***
	T0	**T24**	**T0**	**T24**	**T0**	**T24**	
Sample size	48		48		48		
Gender (Male/Female)	27/21		27/21		27/21		0.69
Age (years)	8.2±2.0	10.2±2.0	7.6±2.0	9.6±2.0	7.4±1.9	9.5±1.9	0.14
Weight (kg)	32.4±8.6	40.8±11.4	30.5±10.1	39.7±12.9	29.7±7.2	41.0±10.5	0.24
Weight-SDS	0.43±0.96	0.30±1.0	0.39±1.0	0.52±0.97	0.49±0.93	0.83±0.92	0.83
Height (cm)	130±12	139±12	126±12	138±12	125±12	141±14	0.18
Height-SDS	0.29±0.95	-0.18±0.98	0.28±0.95	0.21±0.92	0.18±1.1	0.76±1.2	0.87
BMI (kg/m^2)	18.7±2.5	20.5±3.5	18.4±3.2	20.3±3.8	18.6±2.1	20.3±2.8	0.66
BMI-SDS	0.48±0.87	0.52±0.99	0.39±1.0	0.59±0.97	0.63±0.81	0.71±0.89	0.51
Mean HbA1c (%)	7.3±1.4	7.2±0.9	7.6±1.5	7.3±1.6	7.6±1.4	7.4±0.9	0.19

Data are expressed as Mean±SD. P significant <0.05.
BMI: body mass index; HbA1c: glycosylated haemoglobin.

 Accepted Manuscript published as EC-22-0370.R1. Accepted for publication: 16-Feb-2023

Table 3. Delta values (T24-T0) of the main anthropometric variables in the three groups of height-SDS tertiles.

	Height-SDS 1° TERTILE Height-SDS≤-0.29	**Height-SDS 2° TERTILE -0.29<Height-SDS<0.20**	**Height-SDS 3° TERTILE Height-SDS≥0.20**	***P-value***
Δ(T24-T0)-age (years)	2.0±0.14	1.9±0.10	2.0±0.16	0.10
Δ(T24-T0)-weight-SDS	-0.13±0.36	0.13±0.55	0.33±0.43	**<0.001**
Δ(T24-T0)-BMI-SDS	0.04±0.45	0.19±0.71	0.07±0.51	0.60
Δ(T24-T0)-height-SDS	-0.47±0.17	-0.04±0.14	0.57±0.29	**<0.001**

Figure 1 A.

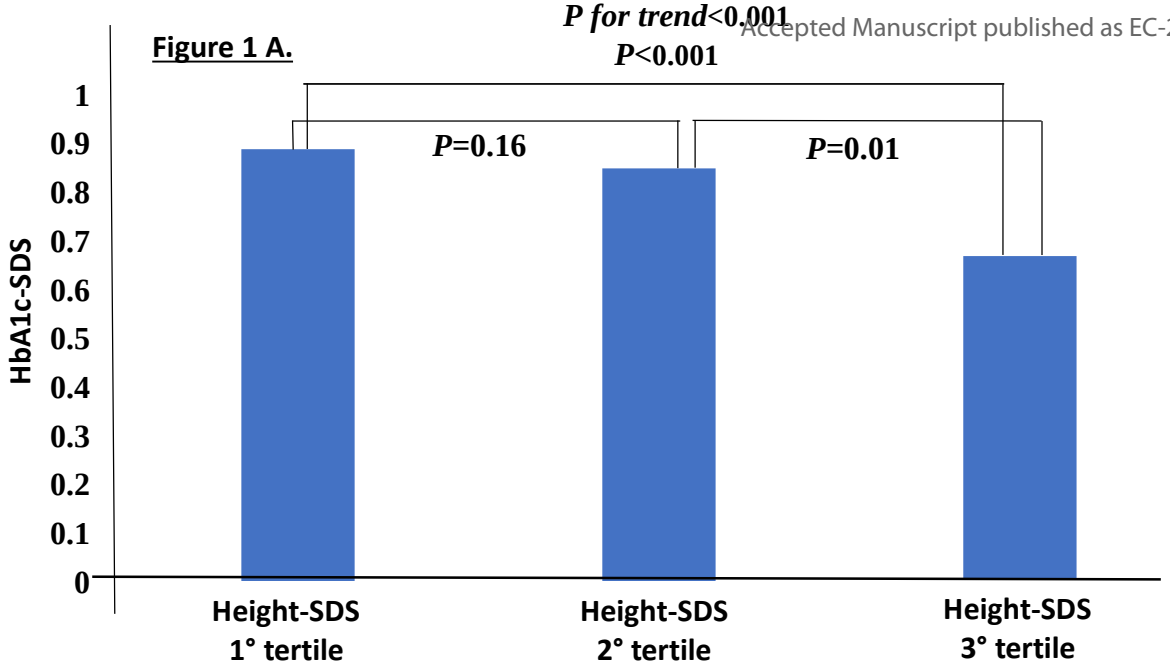


Figure 1 B.

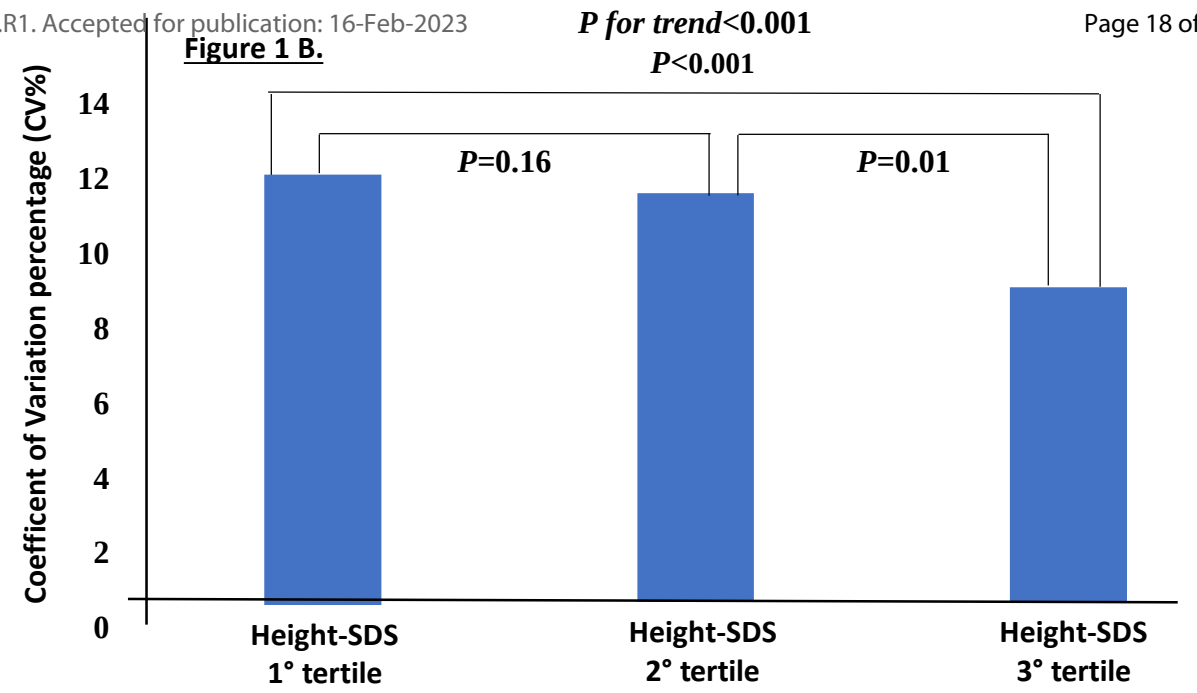
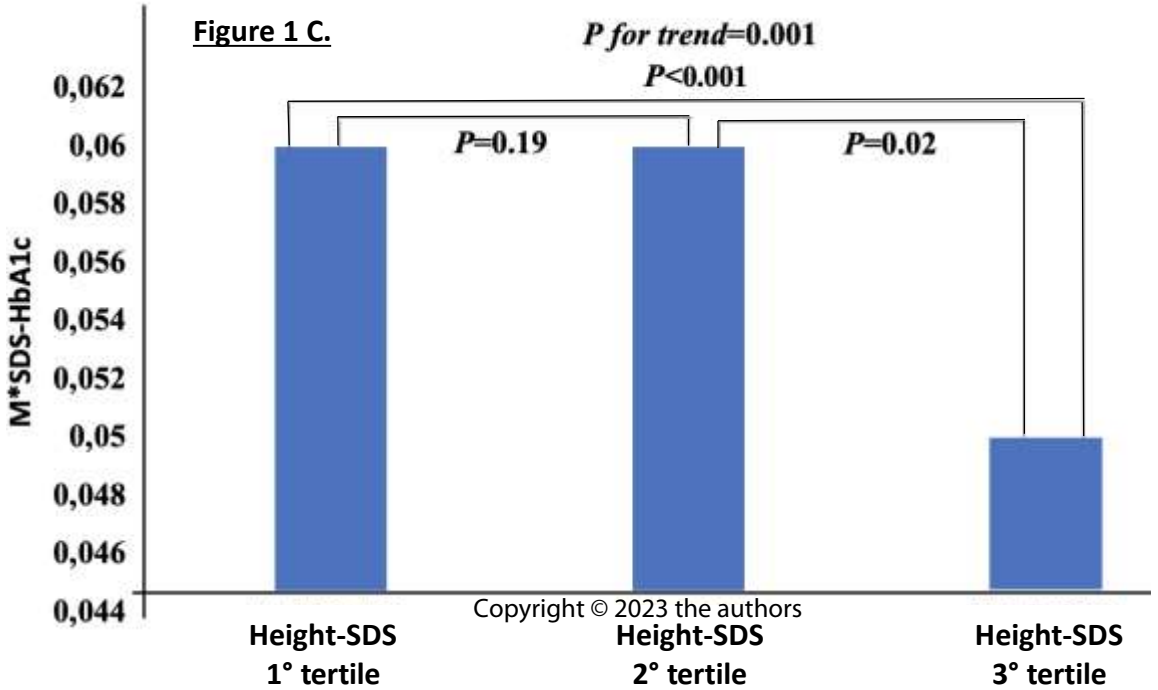


Figure 1 C.



Accepted Manuscript published as EC-22-0370.R1. Accepted for publication: 16-Feb-2023

Figure 2 A.

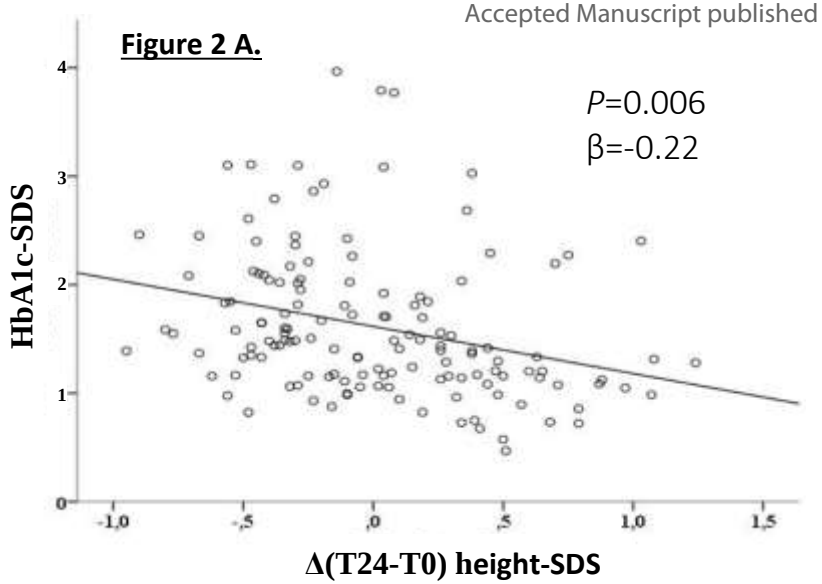


Figure 2 B.

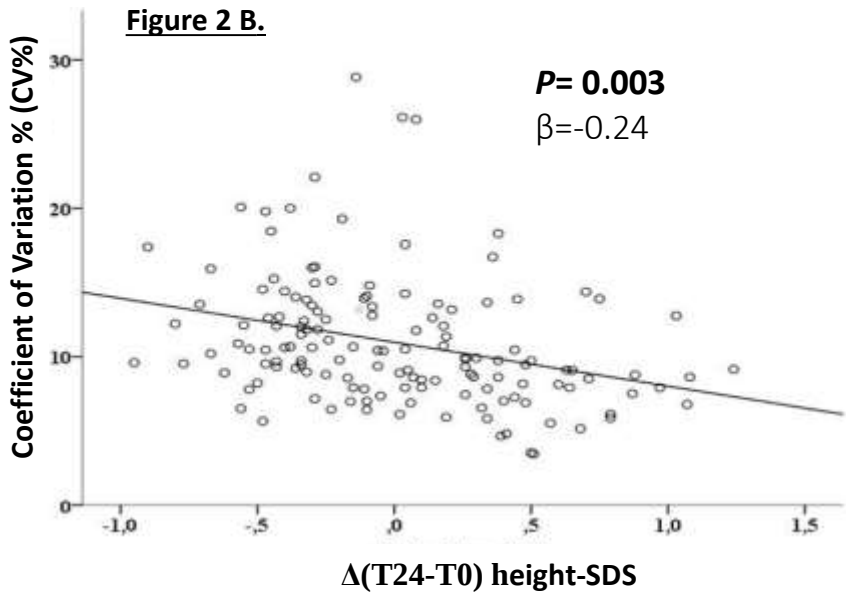


Figure 2 C.

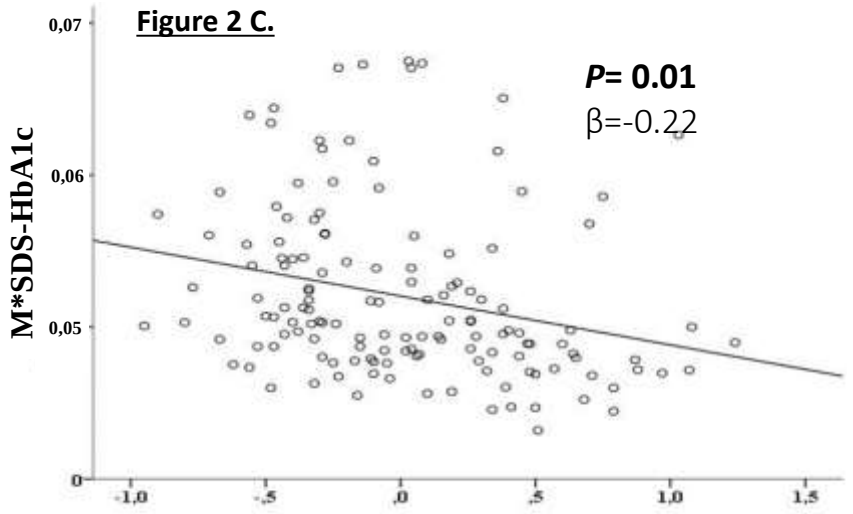


Figure 2 A**.** Association between Δheight-SDS and HbA1c-SDS (*P*=0.006).
Figure 2 B**.** Association between Δheight-SDS and CV% (*P*=0.003).
Figure 2 C**.** Association between Δheight-SDS and M*SDS-HbA1c (*P*=0.01).