High concentration of ghrelin in children with growth hormone deficiency and neurosecretory dysfunction

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Abstract

BACKGROUND: The role of endogenous ghrelin in the growth process of children is unclear. The aim of the present study was to assess ghrelin concentrations in children with growth hormone deficiency (GHD), neurosecretory dysfunction (NSD) and idiopathic short stature (ISS) in comparison to healthy controls.
MATERIAL: One hundred and forty seven children (61 girls and 86 boys), aged 3.7–16.8 years (mean±SD: 10.7±3.44 years) with short stature (below –2.0 SD) were qualified into the study. In each child, fasting ghrelin and insulin-like growth factor type I (IGF-I) concentrations were measured and growth hormone (GH) secretion was assessed after falling asleep and during two GH-stimulating tests. According to maximal GH concentrations, children were qualified into GHD, NSD and ISS group. Additionally, depending on biological development, the children were divided on younger and older subgroups. The control group consisted of 19 healthy children with normal height and body mass.
RESULTS: Ghrelin concentrations in GHD (1847.5±1444.3 pg/mL) and NSD (1809.3±983.5 pg/mL) were significantly higher than in ISS (1218.1±646.8 pg/mL) and in Controls (924.9±318.4 pg/mL). A comparison of ghrelin concentrations in older and younger children within the same diagnostic group, showed statistically higher ghrelin levels in younger than in older children (except of NSD group, in which the difference reached the border of statistical significance).
CONCLUSIONS: Ghrelin concentration is elevated in GHD and NSD children. Independently of GH and IGF-I secretion disorders type, ghrelin concentrations decrease with the children' age. The higher concentration of ghrelin in ISS than in Controls suggests the presence of GH-independent factors increasing ghrelin secretion by X/A cells in the gastric oxyntic mucosa.

ORIGINAL ARTICLE

INTRODUCTION

Ghrelin, a 28-amino-acid octanoylated peptide, predominantly produced by X/A cells in the gastric oxyntic mucosa, was discovered to be a natural ligand of the type 1a growth hormone (GH) secretagogue receptor. Thus, the peptide is considered as a natural GH secretagogue, exerting GH-releasing hormone (GHRH)-like effect. The GH-releasing action of ghrelin takes place both directly – by influence on pituitary cells and indirectly – through modulation of GHRH secretion from the hypothalamus; some functional anti-somatostatin actions have also been shown. Moreover, ghrelin significantly stimulates prolactin secretion, the hypothalamus-pituitary-adrenal axis and plays a relevant role in modulation of the hypothalamic-pituitary-gonadal function (Veldhuis & Bowers 2010; Lanfranco *et al.* 2010). It is also possible that the vagus nerve is essential for the stimulation of GH by ghrelin (Al-Massadi *et al.* 2011). However, many different factors influence the regulation of ghrelin secretion, as it is mainly an orexigenic hormone.

The role of endogenous ghrelin in the growth process of children is unclear. Ghizzoni *et al.* (2004) have reported that ghrelin secretion presents a pulsatile pattern, with maintained circadian rhythm and higher nocturnal concentrations, similarly as GH, although no direct correlation has been confirmed between them. In contrast to GH, ghrelin secretion is expressed also during the day. Its intensity is dependent on food intake, thus increasing in fasting state and decreasing after meals (Spiegel *et al.* 2011; Sangiao-Alvarellos & Cordido 2010). Whatmore *et al.* (2003) have demonstrated that ghrelin concentrations in healthy children decrease with age and with subsequent stages of puberty. The results of available studies, in which the authors have evaluated ghrelin concentrations in adult patients with GH secretion disorders, are rather divergent and no expected changes in ghrelin secretion are observed during GH therapy (Janssen *et al.* 2001; Jung *et al.* 2006; Lopez-Siguero *et al.* 2010). So far, very few studies have attempted to evaluate ghrelin concentrations in children with short stature, due to different etiology (Ghizzoni *et al.* 2004; Lopez-Siguero *et al.* 2010; Iniguez *et al.* 2010). Consequently, the goal of the reported study was an assessment of ghrelin levels in children with short stature, taking into consideration GH and insulin-like growth factor type I (IGF-I) concentrations, as well as the age of children and the pubertal stage.

MATERIAL AND METHODS

An approval for the study was obtained from the Bioethical Committee in the Polish Mother's Memorial Hospital – Research Institute (PMMH-RI).

One hundred and forty seven (147) children (61 girls and 86 boys) were qualified into the study group, their age ranged from 3.7 to 16.8 years (the mean age ± SD: 10.7±3.44 years). All of the patients presented with short stature, defined as body height below –2.0 SD from the mean value for child's age and sex, determined on the basis of actual population standards given by Palczewska & Niedźwiecka (2001).

Body height was assessed by using a stadiometer in all the children and height standard deviation score (Height SDS) was calculated for each of them. Next, based on the actual child's position on percentile charts, the height age (HA) was calculated (as the age, given for the 50th percentile for child's height). Body mass was assessed in all the qualified patients, followed by calculation of body mass index standard deviation score for chronological age (BMI SDS for CA) and for height age (BMI SDS for HA). The stage of puberty was assessed in each child by the Tanner's scale.

The children were recruited from the patients of the Outpatient Endocrinology Clinic and the Outpatient Gastroenterology Clinic, where they were referred due to short stature. In each child thyroid function was assessed. The children with hypothyroidism and with other chronic diseases, as well as with complaints of the gastrointestinal tract were not qualified into the study group. Subjects with Turner's syndrome were excluded by genetic tests. Moreover, bone age (BA) was assessed in each child, based on X-rays of non-dominant hand and wrist, according to Greulich-Pyle's standards. Next, children were referred to the Department of Endocrinology and Metabolic Diseases of PMMH-RI.

In each child a 3-hour nocturnal profile of GH secretion was obtained during sleep, with half-hour intervals, starting from the first hour after falling asleep. Then, two GH-stimulating tests were performed on subsequent days of hospitalisation: the oral clonidine test, with dose of 0.15 mg/m^2 and with GH measurements at 0, 30th, 60th, 90th and 120th minute of the test, and the test with intramuscular glucagon administration in dose of 30 μg/kg (not exceeding 1 mg), during which GH was measured at 0, 90th, 120th 150th and 180th minute. Peak GH concentration (GH_{max}) was determined in both tests and after falling asleep. Following individual GH_{max} values, the patients were qualified into the following groups:

GHD (growth hormone deficiency) – if GH_{max} <10 ng/ml (decreased) in both stimulating tests and during sleep;

NSD (neurosecretory dysfunction) – if GH_{max} <10 ng/ml (decreased) in sleep but >10 ng/ml (normal) in at least one stimulating test; with low IGF-I concentration;

ISS (idiopathic short stature) – if GH_{max} >10 ng/ml (normal) in sleep and in at least one stimulating test.

On the 2nd day of hospitalisation (before performing any stimulating tests), fasting serum concentrations of total ghrelin and IGF-I were measured. IGF-I concentrations were expressed by IGF-I SDS for sex and chronological age (IGF-I SDS for CA) and for HA and BA (IGF-I SDS for HA, IGF-I SDS for BA), according to reference data.

When GHD was identified, other pituitary hormone tests and MRI of the pituitary region were performed, however, isolated GHD was identified in all the cases, without any tumours in MRI images.

The lack of any pubertal features was identified in 92 out of 166 children, qualifying the patients to stage I of the Tanner's scale, while the other cases presented with puberty at stage II or more of the Tanner's scale. Consequently, the analysed group of children was divided into two subgroups, taking into consideration also BA in very short children:

the younger group – CA below 11 years, without pubertal features, BA below 9 years in boys and below 8 years in girls;

the older group – CA more than 11 years and/or with pubertal features and/or BA more than 9 years in boys and more than 8 years in girls.

The control group consisted of 19 healthy children (10 girls and 9 boys), aged from 5.5 to 14.8 years (mean ± SD: 11.1±2.70 years) with normal body height and normal body weight. In that group of children, fasting total ghrelin concentration was assessed, while no other hormonal measurements (GH stimulating tests, IGF-I concentration) were performed in any of the patients.

Growth hormone levels were measured by the immunometric method. The measurements were performed by IMMULITE, DPC assay sets, calibrated vs. the WHO IRP 80/505 standard set, with the following sensitivity level: 0.01 ng/ml, range: up to 40 ng/ml, the conversion index: ng/ml x 2.6 = mIU/l, the intra-assay CV: 5.3–6.5% and inter-assay CV: 5.5–6.2%.

IGF-I was assessed by Immulite, DPC assays; WHO NIBSC 1st IRR 87/518 standard was applied, with the analytical sensitivity of 20 ng/ml, calibration range up to 1600 ng/ml, intra-assay CV: 3.1–4.3% and inter-assay CV: 5.8–8.4%. For comparison of children with different age and sex, IGF-I concentrations were expressed as IGF-I SDS, according to reference data.

The total ghrelin concentration was measured by radioimmunometric assay by Millipore assay sets, with the following sensitivity level: 100–10.000 pg/ml, the intra-assay CV: 3.3–10.0% and inter-assay CV: 14.7–17.8%.

One-way ANOVA was applied for statistical analysis with post-hoc tests to account for median differences (because of different patient numbers in groups, Tukey's HSD [Honestly Significant Difference] test was used). The typical regression and correlation analyses were used to assess the relationships among parametric data. The level of significance at $p<0.05$ was accepted for all the performed tests and comparisons.

RESULTS

Following the obtained results, 15 patients were assigned into GHD group, 16 patients into NSD group and 116 into ISS group.

Table 1 presents auxological parameters of the children. It should be emphasized that degree of short stature (Height SDS) was similar in all groups of short children.

The body mass (expressed by BMI SDS for CA and BMI SDS for HA) in children from GHD group was significantly higher than in NSD or ISS group, while in NSD group significantly lower than in the Controls.

The IGF-I concentrations, also expressed as IGF-I SDS for CA and IGF-I SDS for HA and IGF-I SDS for BA, were significantly higher in ISS group than in NSD or GHD group.

Tab. 1. Auxological data and hormonal results in particular analyzed groups of short children and in Controls.

groups	GHD	NSD	ISS	Controls
nb of children (girls/boys)	15 (8/7)	16 (7/9)	116 (46/70)	19 (10/9)
CA (years)	10.51±2.88	9.78±3.08	10.58±3.51	11.02±3.53
HA (years)	8.00±2.43 [a]	7.14±2.33 [b]	8.03±2.89 [c]	10.56±3.71 [a,b,c]
BA (years)	8.75±3.07	7.47±2.81	8.56±3.53	–
Height SDS	–2.52±0.58 [d]	–2.81±1.15 [e]	–2.50±0.81 [f]	0.30±0.98 [d,e,f]
BMI SDS for CA	0.80±1.34 [g,h]	–0.72±0.73 [g,i]	–0.31±0.94 [h,j]	0.65±1.18 [i,j]
BMI SDS for HA	1.26±1.49 [k,l]	–0.37±0.95 [k,m]	0.05±1.07 [l]	0.71±1.23 [m]
GH_{max} (ng/mL) after clonidine	7.07±1.74 [n,o]	17.84±9.73 [n]	17.42±9.03 [o]	–
GH_{max} (ng/mL) after glucagon	5.84±2.26 [p]	8.77±4.80	11.70±8.00 [p]	–
GH_{max} (ng/mL) nocturnal profile	6.76±2.97 [r]	8.71±3.11 [s]	15.07±8.92 [r,s]	–
IGF-I (ng/mL)	145.65±65.56	100.17±64.28 [t]	196.77±113.15 [t]	–
IGF SDS for CA	–1.53±0.88 [u]	–1.98±1.31 [v]	–0.82±0.97 [u,v]	–
IGF SDS for HA	–0.69±0.81 [w]	–1.13±0.93 [x]	–0.02±0.82 [w,x]	–
IGF SDS for BA	–1.02±0.89 [y]	–1.44±1.10 [z]	–0.23±1.22 [y,z]	–

a–z: $p<0.05$

Fasting serum ghrelin concentrations in particular groups of children are presented in Table 2. Ghrelin concentrations in GHD and NSD were significantly higher than in ISS and/or in Controls (see Figure 1).

A significant negative correlation was observed between ghrelin concentration and CA, between ghrelin and HA as well as between ghrelin and BA (see Figures 2a, 2b and 2c).

There was no correlation between ghrelin concentrations and Height SDS (see Figure 3).

In turn, a significant negative correlation was observed between ghrelin concentrations and body weight, as well as between ghrelin concentrations and BMI SDS for HA, although somewhat weaker. No significant correlation was found between ghrelin concentration and BMI SDS for CA – being an evidence for the fact that higher ghrelin concentrations are observed in slimmer children, regardless of their chronological age (see Figures 4a, 4b, 4c). If such analysis was performed for particular diagnostic groups, it was found that the correlation between ghrelin concentrations and BMI SDS for HA occurred in ISS group and in Controls, but it was not observed either within GHD group or NSD group. In those groups of children, ghrelin secretion was not associated with body mass of the children (see Figure 4d).

No significant correlations were found between ghrelin concentrations and GH_{max} in the entire group of children, either during the clonidine stimulating test or during the glucagon stimulating test, or after falling asleep.

Taking into consideration the significant correlation between ghrelin concentration and CA, we decided to

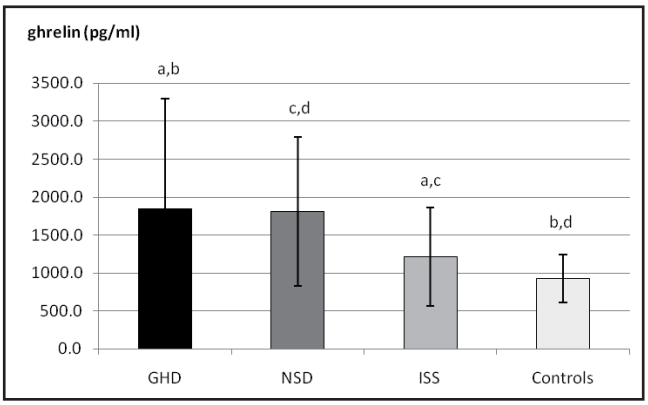

Fig. 1. Ghrelin concentrations in particular analyzed groups of short children and in Controls. a,b,c,d: $p<0.05$

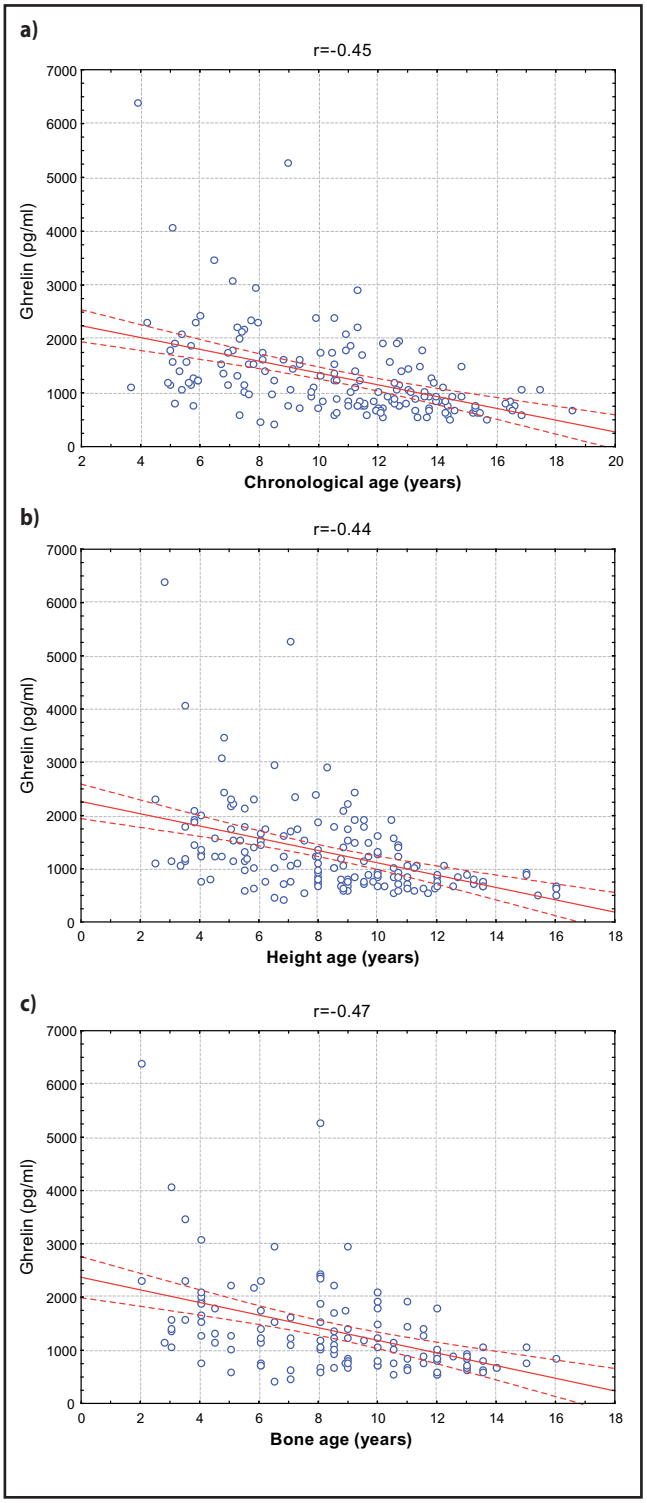

Fig. 2a, 2b, 2c. The correlation between ghrelin concentrations and: chronological age (2a), height age (2b), and bone age (2c) in the whole analyzed group of children.

Tab. 2. Ghrelin concentrations in particular analyzed groups of short children and in Controls.

groups	GHD	NSD	ISS	Controls
Ghrelin (pg/mL)	1847.45±1444.27 [a,b]	1809.28±983.47 [c,d]	1218.14±646.76 [a,c]	924.91±318.41 [b,d]

a–d: $p<0.05$

divide the analyzed group of children into two age subgroups: younger and older (see the inclusion criteria in Methods).

Eighty two (82) children (35 girls and 47 boys) were qualified into the younger group, their age ranged from 3.6 to 11.0 years (mean±SD: 7.80±2.09 years), while 84 children (36 girls and 48 boys) created the older group, their age ranged from 9.72 to 16.47 years (mean ± SD: 13.37±1.76 years) – see Table 3 and Table 4.

In younger children, ghrelin concentrations were clearly elevated in GHD and NSD groups in comparison to the control group: we observed significantly higher ghrelin concentrations in GHD group than in either ISS group or the control group. In turn, ghrelin concentrations in NSD group were also high but the differences between that group and either ISS group or the control group reached the border of significance (see Figure 5).

In older children, elevated ghrelin concentrations were also observed in GHD and NSD groups in comparison to the Controls. Significant differences between NSD group and ISS group, as well as between NSD group and Controls were observed. Ghrelin concentrations in GHD group were higher than those in either ISS group or the Control group, but without statistical significance (see Figure 6).

Summing up, ghrelin concentrations were generally higher in younger children and lower in older children. The comparison of ghrelin concentrations in older and younger individuals within the same diagnostic group, showed statistical differences within GHD, ISS and Controls, while in NSD group the differences reached only at the border of statistical significance (see Figure 7).

In turn, we did not find any statistical differences between the ghrelin concentrations in boys and in girls in whole group of children, as well as in younger and in older subgroups (Table 5).

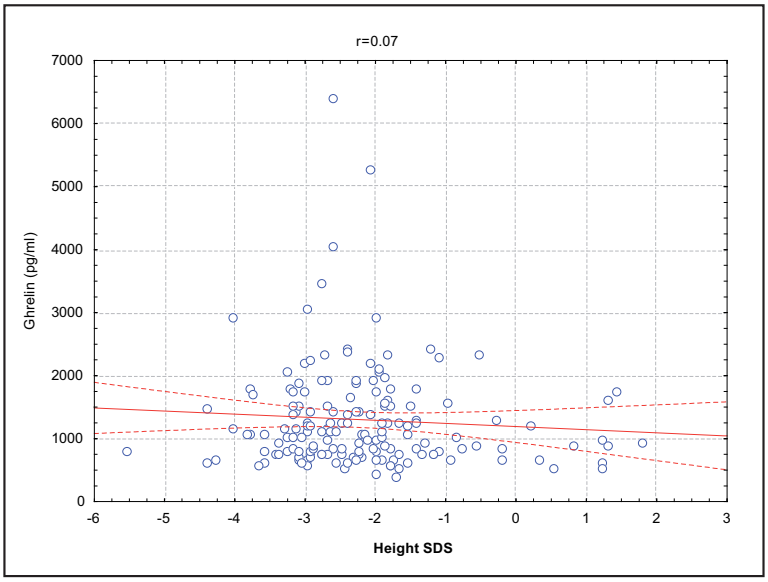

Fig. 3. The correlation between ghrelin concentration and Height SDS in the whole analyzed group of children.

Tab. 3. The younger subgroup – auxological data and hormonal results in particular groups of short children and in Controls.

groups	GHD	NSD	ISS	Controls
nb of children (girls/boys)	7	9	58	8
CA (years)	8.43±2.64	7.87±2.29	7.62±2.00	8.39±2.26
HA (years)	6.25±2.07	5.73±1.68	5.63±1.77	8.01±2.06
BA (years)	6.47±2.57	6.15±2.29	5.63±2.14	
Height SDS	–2.39±0.47 [a]	–2.62±1.19 [b]	–2.37±0.78 [c]	0.07±1.11 [a,b,c]
BMI SDS for CA	1.28±1.33 [d,e]	–0.84±0.47 [d]	–0.21±1.03 [e]	0.19±1.26
BMI SDS for HA	1.69±1.73 [f,g]	–0.68±0.63 [f]	–0.12±1.25 [g]	0.32±1.34
GH_{max} (ng/mL) after clonidine	7.40±2.15 [h]	22.86±9.59 [h]	17.75±8.91	
GH_{max} (ng/mL) after glucagon	5.96±2.37	7.56±4.38	10.63±7.39	
GH_{max} (ng/mL) nocturnal profile	6.82±2.97 [i]	8.95±3.43	13.64±6.86 [i]	
IGF-I (ng/mL)	150.91±87.68 [k]	57.50±23.3 [k,l]	128.35±47.24 [l]	
IGF SDS for CA	–0.88±0.74	–2.00±1.55 [m]	–0.55±0.78 [m]	
IGF SDS for HA	–0.20±0.81 [n]	–1.38±1.07 [n,o]	0.13±0.78 [o]	
IGF SDS for BA	–0.31±0.66	–1.57±1.28 [p]	0.03±0.88 [p]	
Ghrelin (pg/mL)	2564.82±1816.59 [r,s]	2102.81±1241.00	1490.27±720.36 [r]	1188.84±351.83 [s]

a–s: $p<0.05$

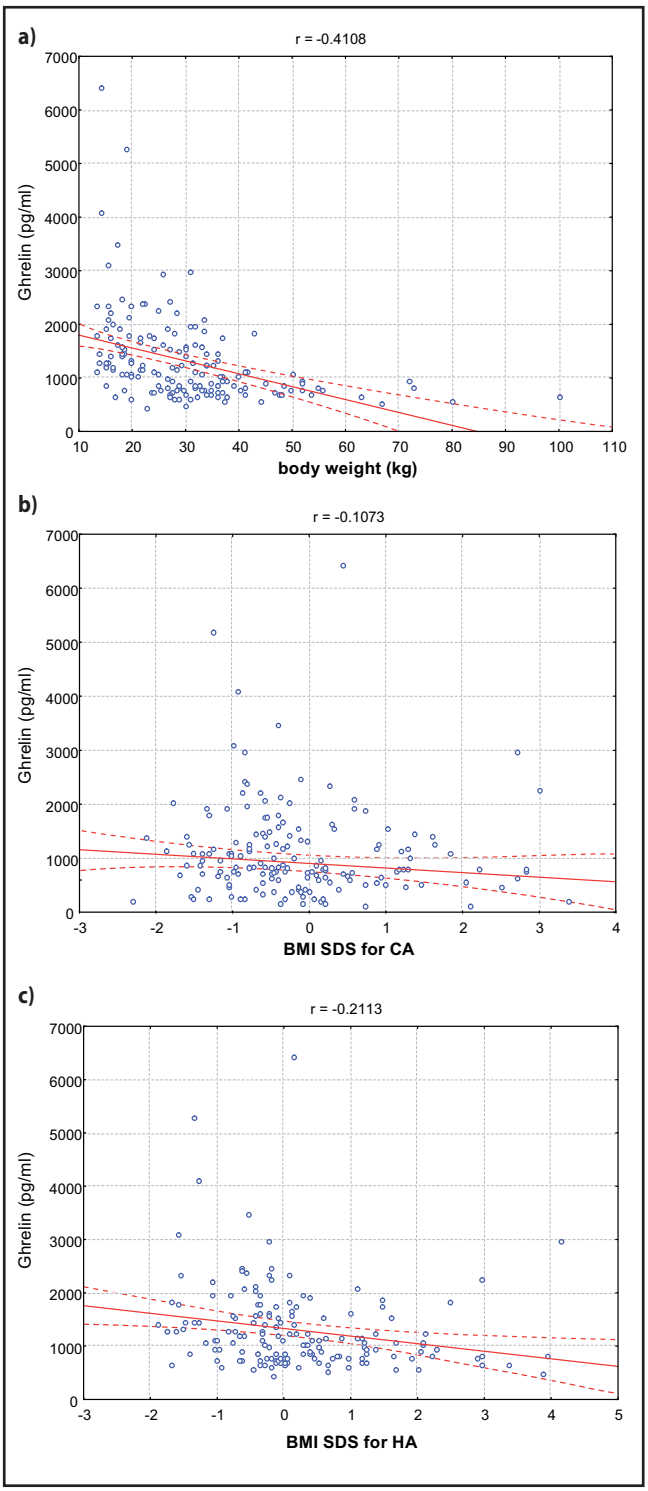

Fig. 4a, 4b, 4c. The correlation between ghrelin concentration and body weight (4a) and BMI SDS for CA (4b) and BMI SDS for HA (4c) in the whole analyzed group of children.

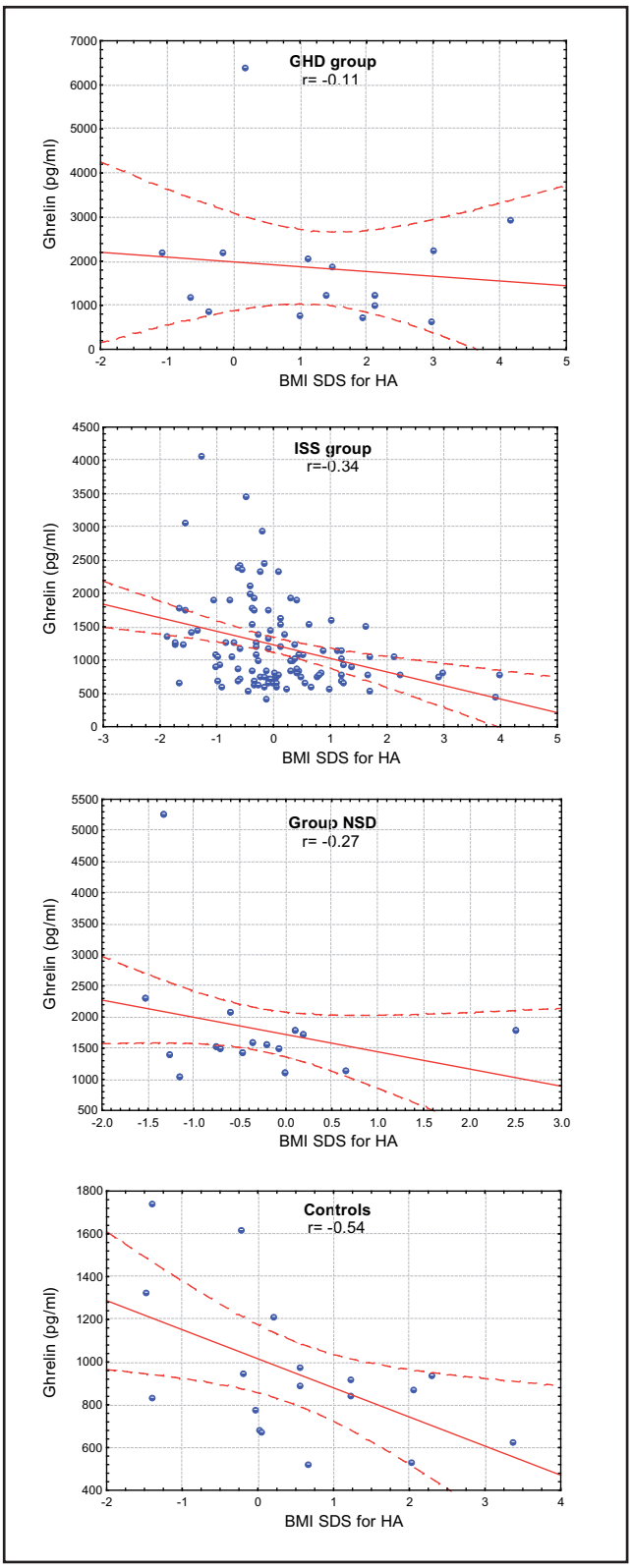

Fig. 4d. The correlation between ghrelin concentration and BMI SDS for HA in particular groups of short children and in Controls.

A statistically considerable dispersion of ghrelin concentrations was observed in all the diagnostic groups – see Figure 8a and 8b and it seems to be impossible to establish the critical value (the cut-off point) for healthy children with normal height, as well as for children with idiopathic short stature or with GHD and NSD.

Tab. 4. The older subgroup - auxological data and hormonal results in particular groups of short children and in Controls.

groups	GHD	NSD	ISS	Controls
nb of children (girls/boys)	8	7	58	11
CA (years)	12.32±1.61	12.51±1.65	13.54±1.75	13.83±1.77
HA (years)	9.52±1.58 [a]	9.15±1.47 [b]	10.35±1.55 [c]	14.15±2.11 [a,b,c]
BA (years)	10.75±1.85	10.10±1.63	11.31±2.04	
Height SDS	−2.63±0.67 [d]	−3.08±0.87 [e]	−2.62±0.83 [f]	0.46±0.90 [d,e,f]
BMI SDS for CA	0.36±1.26	−0.56±1.02 [g]	−0.41±0.85 [h]	0.97±0.1.07 [g,h]
BMI SDS for HA	0.88±1.23	0.06±1.21	0.23±0.84	0.99±1.12
GH_{max} (ng/mL) after clonidine	6.78±1.37 [i]	10.68±3.69	17.09±9.22 [i]	–
GH_{max} (ng/mL) after glucagon	5.73±2.32	10.32±5.21	12.87±8.54	–
GH_{max} (ng/mL) nocturnal profile	6.71±3.16 [k]	8.36±2.82	16.51±10.46 [k]	–
IGF-I (ng/mL)	141.05±44.22 [l]	161.14±53.22	262.76±119.13 [l]	–
IGF SDS for CA	−2.09±0.53	−1.93±1.01	−1.07±0.1.09	–
IGF SDS for HA	−1.12±0.55 [m]	−0.76±0.58	−0.18±0.84 [m]	–
IGF SDS for BA	−1.65±0.52	−1.18±0.66	−0.47±1.43	–
Ghrelin (pg/mL)	1219.75±615.12	1431.88±262.17 [n,o]	946.01±417.50 [n]	764.74±161.21 [o]

a–o: $p<0.05$

DISCUSSION

An evaluation of serum ghrelin levels in children is difficult to interpret because ghrelin concentrations negatively correlate with child's age and with stage of puberty, moreover, reference values are no available.

In the present study, a significant negative correlation was corroborated between the age of children and ghrelin concentrations, not only in the group of healthy children but also in children with ISS and in those suffering from GHD or NSD.

The present study confirms the observation that ghrelin concentration does not correlate with the maximal value of GH secretion, either in GH-stimulating tests or in nocturnal profile. However, our study has provided some evidence that ghrelin concentration is significantly higher in children with GHD or NSD than in children with ISS and – especially – in normal children (the control group). Similar results in children populations have been presented by other researchers (Ghizzoni *et al.* 2004; Lopez-Siguero *et al.* 2010 and Iniguez *et al.* 2010). Nevertheless, in the studies by Jung *et al.* (2006), including adult patients with GHD, the basal ghrelin concentration in Controls subjects did not differ from that in GHD group. It is tempting to speculate that in adult persons, GHD is usually present for a longer time and leads to the development of

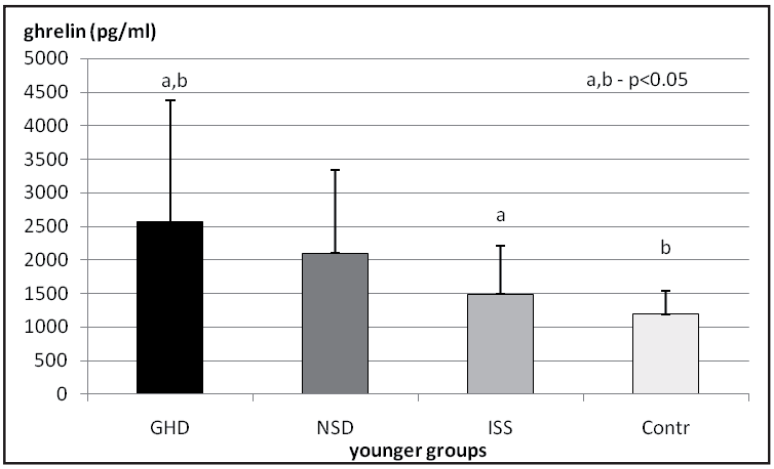

Fig. 5. The ghrelin secretion in particular groups of younger children.

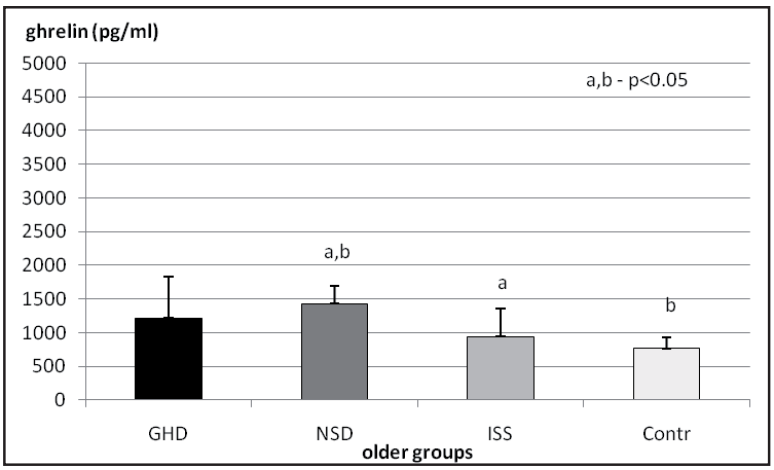

Fig. 6. The ghrelin secretion in particular groups of older children.

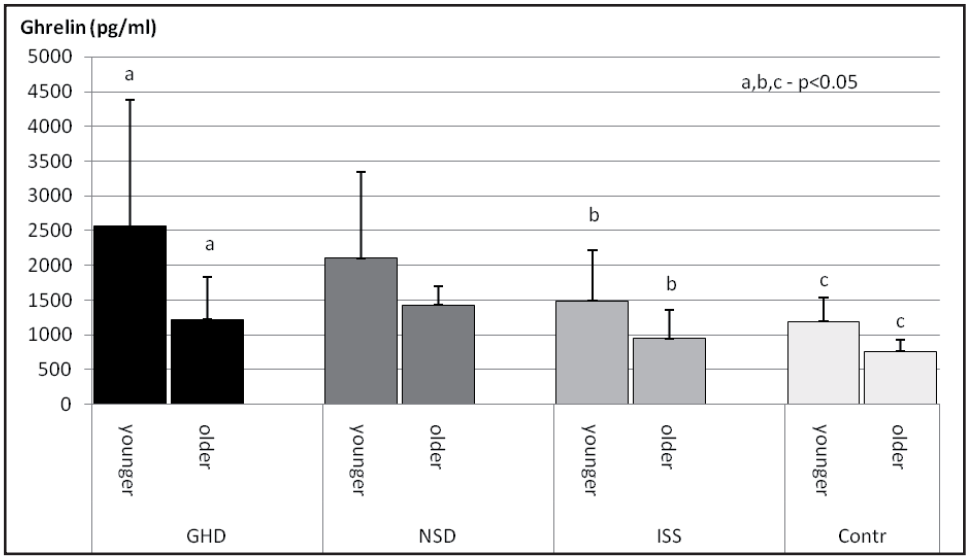

Fig. 7. Comparison of ghrelin concentrations in younger and older group of children with the same diagnosis and in Controls.

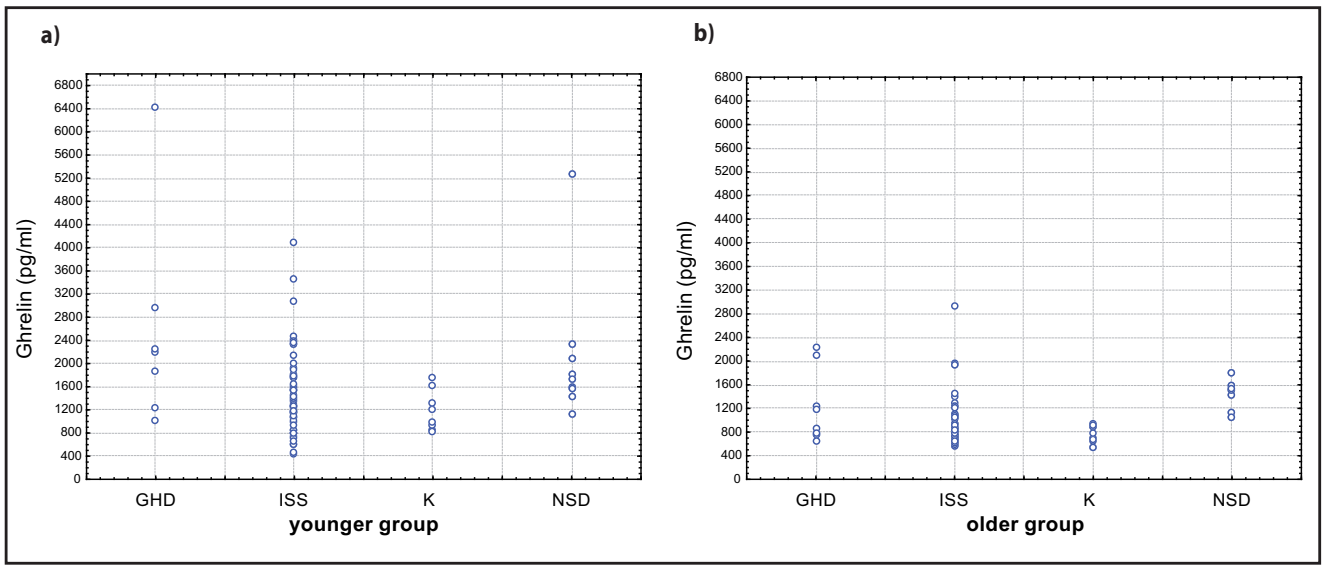

Fig. 8. Dispersion of ghrelin concentrations in younger and older children in the particular groups of examined children.

Tab. 5. The ghrelin concentration in boys and in girls in the whole analyzed group, as well as in younger and older groups of children.

Ghrelin (pg/mL)	girls	boys
Total group (n=166) Girls/boys: 71/95	1415.05±903.44	1375.68±823.62
Younger group (n=82) Girls/boys: (35/47)	1649.12±925.90	1695.82±1085.59
Older group (n=84) Girls/boys: 36/48	1059.34±451.46	994.33±432.61

obesity what can explain the observed reduction of originally higher ghrelin serum concentrations. Besides, in adult subjects severe GHD is usually recognized, while in the majority children the partial GHD is observed (thus, with less intense metabolic complications). In adult persons with GHD of childhood origin, the pituitary hypoplasia, pituitary stalk interruption syndrome (PSIS) or hypothalamo-pituitary tumours are frequently observed. When studying the patients with childhood-onset GHD, Maghnie *et al.* (2007), have demonstrated that GH response after ghrelin is significantly higher in patients with isolated GHD than in these with multiple pituitary hormone deficiency. Tauber *et al.* (2004) have postulated that ghrelin acts mainly at the hypothalamic level and a primary injury of that region and/or of its links with the pituitary stands at the base of so called the ghrelin-resistance syndrome, with very high ghrelin concentrations in patients with PSIS. Therefore, hyperghrelinemia, as observed in the above syndrome, does not increase GH secretion. In our group of children with GHD, PSIS has been observed in one child only and isolated hypoplasia of the pituitary gland – in two children.

In these cases, the basic ghrelin concentration has not been higher than in the other GHD children. It is possible that in patients with GHD or NSD, the partial "ghrelin-resistance syndrome" is observed, which may be related to functionally (not only anatomically) impaired integrity of hypothalamic-pituitary connections.

In our present study, significantly higher ghrelin concentrations have also been observed in NSD group vs. concentrations in question either in patients with ISS or in Controls. Interesting results, regarding children with NSD and ISS, have been presented by Ghizzoni *et al.* (2004) – though no differences between diurnal ghrelin concentrations have been found in each of studied groups, the nocturnal ghrelin concentrations have been significantly higher in children with NSD than in those with ISS. In our present study, ghrelin concentrations were measured in serum, which was collected at approx 6:00 a.m., immediately after waking. Thus, the measurements reflected nocturnal rather than diurnal ghrelin concentrations.

In our opinion, the results of ISS patients, may be considered fairly interesting, as higher ghrelin concentrations have been observed in that group than in Controls. In study by Iñiguez *et al.* (2010) in children with ISS and higher ghrelin levels, certain polymorphisms have been found in the ghrelin receptor. In our ISS group the dispersion of ghrelin concentrations was clearly marked. It may, then, be possible that in children with higher ghrelin concentrations, ghrelin receptor polymorphism is also present. It is also possible that in some ISS children the oligosymptomatic gastrointestinal disorders are present i.e. Helicobacter pylori infection, celiac disease or inflammatory bowel diseases. It has been proved that in these cases the secretion of ghrelin may be altered (Sakata & Sakai 2010, Selimoglu *et al.* 2006).

It is to be stressed that in the group of examined children, only total, and not acylated, ghrelin concentrations have been measured. As it is well known, ghrelin acylation is essential for its stimulatory effects on GH release and appetite and the total ghrelin reflects mainly the levels of unacylated ghrelin. However, Spiegel *et al.* (2011) provided some evidence that acylated ghrelin is important mainly for appetite control and orexigenic effect but not for GH-stimulating effect and that the acylated-to-total ghrelin ratio is lower during sleep than during waking.

Summing up, ghrelin concentrations have decreased with the age of children, independently of GH and IGF-I secretion disorders type. However, the relationship between body mass and ghrelin concentration is disturbed in children with GH secretion disorders.

It spite of the fact that no correlation between ghrelin and maximal GH secretion during stimulating tests is observed, fasting ghrelin levels are elevated in short children with GHD and NSD. In turn, higher ghrelin concentrations in ISS group than in Controls indicate the presence of GH-independent factors increasing ghrelin secretion from X/A cells in the gastric oxyntic mucosa.

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