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Sizes of abdominal organs in adults with severe short stature due to severe, untreated, congenital GH deficiency caused by a homozygous mutation in the GHRH receptor gene

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Summary

Objective—To assess the sizes of intra-abdominal organs of adult subjects with untreated severe congenital isolated GH deficiency (IGHD) due to lack of functional GHRH receptor (GHRH-R), and to verify whether there is proportionality between size of organ and adult stature and body surface area (BSA).

Subjects and methods—By using ultrasound, we studied the sizes (absolute and corrected by height, weight and BSA) of the intra-abdominal organs of 18 adult subjects with IGHD (eight females, IGHD group) who have never received GH replacement therapy. They were all homozygous for the same null mutation (IVS1 + 1G → A) in the GHRH receptor gene (*GHRH-R*). They were compared with normal controls from the same region.

Results—After correction for BSA, subjects lacking a functional GHRH-R have normal prostate and ovaries size, small spleen and uterus, and large liver, pancreas and kidney.

Conclusions—Size of individual abdominal organs is influenced in different ways by severe and congenital lack of GH due to a *GHRH-R* mutation.

Introduction

The growth of individual organs depends on several and still not completely known circulating or locally produced factors. The sizes of some organs (e.g. liver and kidney) correlate closely with body weight and body surface area (BSA),[1,2] while some other organs (e.g. pancreas and spleen) do not.[3] The role of GH and its effector IGF-1 in determining the size of individual organs in humans is not well elucidated. No data is available to our knowledge, about the sizes of intra-abdominal organs in GH deficient (GHD) subjects who reached adult age without receiving GH replacement.

In Itabaianinha County, in the north-eastern Brazilian state of Sergipe, we have identified an extended pedigree with approximately 100 individuals over seven generations with severe isolated GHD (IGHD) due to a homozygous null mutation (IVS1 + 1G → A) in the GHRH receptor (GHRH-R) gene (*GHRH-R*). All these subjects have very low serum GH and IGF-1 levels at birth, resulting in severe short stature, with adult height ranging from 107 to 136 cm

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(-9·6 to -5·2 SD below normal).[4-6] As many of the adult subjects from this kindred have never received GH treatment, they offer a unique opportunity to evaluate the final size of abdominal organs in the almost complete absence of GH and IGF-1. We have already shown that these subjects have decreased limb size[6] and head circumference, reduced pituitary volume,[7] decreased thyroid volume[8] and decreased cardiac size.[9,10] As stature reflects mostly the size of the bones,[11] the size of the abdominal organs may not be reduced proportionally to height.

Ultrasonography is often used for evaluation of the sizes of abdominal organs.[12,13] It uses reference values from population with normal stature which may not be necessarily applicable to subjects with severe short stature. In this study, we used ultrasonography to measure the absolute and corrected sizes of abdominal organs of the subjects with mutated *GHRH-R*, with the objective of verifying whether there is proportionality between size of organ and adult stature.

Subjects and methods

Subjects

Subjects were recruited by advertising in the local health clinic and by word of mouth. They were submitted to clinical examination and blood analyses to exclude systemic disease (blood cell count, fasting glucose, serum creatinine and serum liver enzymes) that could interfere with size of organ. One IGHD male subject and one male control were excluded due to liver and renal diseases. They were all genotyped for the IVS1 + 1G → A *GHRH-R* mutation by denaturing gradient gel electrophoresis from buccal swabs DNA, as previously published.[4]

Eighteen GH-naive GHD adult patients from the Itabaianinha cohort, all homozygous for the IVS1 + 1G → A *GHRH-R* mutation (eight women; *GHRH-R* mutant group) and 18 subjects with normal stature from the same community (Control A, 18 subjects, 10 women) were compared to assess pancreas, spleen, kidney, prostate, uterus and ovaries. The assessment of pancreas size was possible in 11 *GHRH-R* mutant and 14 control subjects. As liver was not measured in the first control group, we enrolled a second control group, Control B (18 subjects, seven women) to compare the liver size. All the control subjects were homozygous for the wild-type *GHRH-R* allele.

This study was approved by the Ethics Committee of the Federal University of Sergipe and all subjects gave written informed consent.

Study protocol

Height and weight were measured, and BSA was calculated using the formula: BSA (m^2) = $w^{0·425} \times h^{0·725} \times 71·84 \times 10^{-4}$, where w is the weight in kilograms, and h is the height in centimetres.[14] BMI was calculated by dividing body weight (kg) by the square of height (m).[15]

Sizes of abdominal organs were estimated by ultrasound (Medison-AS6000C Digital Color MT) after 10 h fasting and bladder emptying. The examinations were all performed by the same operator (E.O.M.C.). The sizes of the organs were measured three times and the average was calculated. Liver was measured in two sections: mid-clavicular line (right lobe) and the mid-abdominal line (left lobe).[12,16] Anterior-posterior size of the head, body and tail of pancreas were measured individually.[12] Spleen, prostate, uterus and ovaries volumes were estimated by the ellipsoid formula: volume = 1/6 π × length × width × thickness (cm^3).[12,13,17] Both ovaries were measured and the mean value was used. Longitudinal and transversal lengths of the left and right kidneys (cm) were measured and the mean of the left and right longitudinal data ('longitudinal kidney'), and the left and right transversal data ('transversal kidney') were calculated.[12]

To correct for the effect of stature, weight and BSA, we divided the measurements by height (m), weight (kg) and BSA, which we called the corrected size for stature (CDs), for weight (CDw) and for BSA (CDbsa).

Normal sizes of organs were used to determine the Brazilian references values using the same ultrasonography methods[12,13] generated by the University Hospital of Federal University of Sergipe.

Statistical analysis

Statistical analysis was performed using the statistical software SPSS/PC 12·0 (SPSS, Inc., Chicago, IL). Values are expressed in mean ± SD, and *t*-student and Mann-Whitney tests were used to compare groups when indicated. For the correlation between sizes of organs, height, weight and BSA, Pearson and Spearman tests were used for the data with normal distribution and not for the normal one, respectively. Probability values $\leq 0{\cdot}05$ were considered statistically significant.

Results

Age, sex and BMI of *GHRH-R* mutant group did not differ from control subjects. As expected weight, height and BSA in *GHRH-R* mutant subjects were lower than in the two control groups (Table 1).

Sizes of abdominal organs were within the reference values used by the University Hospital[12,13] (Table 2). *GHRH-R* mutant subjects had reduced absolute size of liver, spleen, kidney, prostate and uterus when compared to the control group. Ovaries and pancreas absolute size were similar in the two groups (Table 2).

When we calculated the corrected sizes, the CDs, CDw and CDbsa of liver, pancreas and kidneys were larger in *GHRH-R* mutant subjects than in the control group. The CDs of uterus and spleen in *GHRH-R* mutant group remained smaller than in the control group. Uterus CDbsa was smaller and spleen CDbsa has a trend to be smaller in *GHRH-R* mutant subjects than in the control group ($P = 0{\cdot}071$). (Table 3).

The correlation coefficient between height, weight, BSA and sizes of organs in the pooled groups are showed in Table 4. Liver size correlated with height, weight and BSA; spleen size correlated with height; both kidney measurements correlated with height, weight and BSA; prostate size correlated with height; uterus size correlated with height. Analysis limited to the *GHRH-R* mutant subjects showed only correlations of longitudinal kidney size with height ($r = 0{\cdot}585$; $P = 0{\cdot}011$), right liver lobe with weight and BSA ($r = 0{\cdot}499$; $P = 0{\cdot}035$ and $r = 0{\cdot}555$; $P = 0{\cdot}017$, respectively).

Discussion

Despite the general believe that GH is important for organ development, to date no data is available to our knowledge on the size of individual organs in subjects with IGHD who have never received GH replacement therapy. Studying a highly homogeneous group of patients who have severe IGHD due to a homozygous *GHRH-R* mutation, we found that the absolute sizes of liver, spleen, kidneys, prostate and uterus are smaller in the *GHRH-R* mutant group (while pancreas and ovaries are similar in both groups), but all of them are within reference values of normal subjects.[12,13] When corrected by height and BSA, only spleen and uterus sizes remain smaller, while pancreas, liver, and kidneys are actually bigger than controls. Pancreas, liver and kidney remain bigger also when corrected for weight. This indicates that

the growth of these three organs is less dependent from an intact GH-IGF-1 axis than the longitudinal bone growth.

In a mouse model of GH resistance, lack of GH effects seems to have important consequences on the development of pancreatic islets, but the relative pancreatic volume (corrected for body weight) is not affected.[18] We have shown that adult subjects with mutated *GHRH-R* have evidence of increased insulin sensitivity,[10] but we did not find evidence of reduced pancreatic endocrine function. Nevertheless, most of the pancreatic mass represents the exocrine pancreas. Hence, it seems that the development of the exocrine pancreas do not require an intact GH-IGF-1 axis.

Similarly to the pancreas, we have previously shown that in GHD mice (with ablation of the GHRH gene), while the absolute weight of the kidney is reduced, it is not different from control animals when corrected by body weight.[19] Conversely, in the same mouse model, liver remained smaller than controls even when corrected by weight. A similar result (for both liver and kidney) has been observed in a mouse with ablation of the GH receptor.[20] Interestingly, mice with liver-specific knock out of the IGF-1 gene (resulting in low serum IGF-1 and high serum GH) have increased liver size.[21] All these data suggest that in mice GH has a direct effect on liver growth, independent from circulating IGF-1. Here we found that, similarly to pancreas, the both kidney and liver are not different when normalized by body size. Therefore, while the kidney result is similar to the GHD mouse models, the liver result is discordant. It is possible that liver growth in humans is less dependent from an intact GH-IGF-1 axis than in rodents, or that the degree of GHD is different. Interestingly, kidney measurements are the ones that in our study have the strongest correlation with height, weight and BSA, suggesting that body size is an important determinant of kidney growth.

Contrary to the findings in liver, pancreas and kidney, spleen and uterus volumes are reduced beyond the reduction in longitudinal growth. Uterus and spleen are therefore added to the group of organs (pituitary and thyroid)[7,8] with significant absolute and relative reduction of their size in these *GHRH-R* mutant subjects. While the reduction of anterior pituitary size is likely due to hypoplasia of the somatotroph cells that require GHRH for their proliferation,[22] the effects on the other organs are likely due to reduction of circulating GH, and circulating and/or locally produced IGF-1. These findings seem to point to a particularly important role of GH-IGF-1 in determining the growth of the uterus, thyroid and spleen. The spleen finding is not unexpected, as in mice with ablation of the GHRH gene weight-corrected spleen is smaller than controls.[19] Accordingly, a previous study has shown that normal rats treated with recombinant GH display increased spleen mass.[23] As GH plays an important role in controlling haemato-lymphopoiesis,[24] and the GH receptor is a member of cytokine receptor super family (type I receptor) and shares intracellular pathways with other similar receptors,[25] we hypothesize that low GH serum levels caused reduced proliferation of splenic tissue. The effect of GHD on the uterus has been reported previously in the literature in a small group of women with IGHD of various aetiologies, who had previously received GH therapy (and therefore had presumably normal body size).[26] In addition to the effect of lack of GH, our *GHRH-R* mutant women tend to have lower number of children (because of the need for caesarean sections due to cephalic-pelvic disproportion) (average 2·0 *vs.* 5·5 gestations/lifetime),[27] factor that may also contribute to reduce uterine size.

Prostatic volume correlated with height, weight and BSA. GH-IGF-1 axis has a likely effect on prostatic development, and also in prostatic neoplasia development. In mice, lack of GH causes significant delay in prostate cancer progression.[28] Accordingly, a correlation between serum IGF-1 levels and prostatic cancer risk has been reported in humans, as subjects with IGF-1 in the highest quartile (and lower IGF-binding protein 3) levels have prostate cancer risk that is 4·3 times higher than subjects in the lowest quartile.[29] In addition, acromegalic

subjects have a high prevalence of prostatic hyperplasia.[30] When we adjusted prostatic volume for height, weight and BSA, the reduction observed in the *GHRH-R* mutant subjects disappeared. Further studies concentrating on older males will evaluate a possible protective effect of GHD on the development of prostatic hyperplasia or cancer.

All our patients have the same mutation, and therefore may differ from subjects who have IGHD due to mutations in other genes (e.g. GH), or who have GH resistance. While we hypothesize that the effects on size of organ are (with the exception of the anterior pituitary) a reflection of low GH and IGF-1 levels, we cannot exclude a specific effect of the lack of GHRH action. Indeed, splice variants of the GHRH-R are found in several tissues,[31] and one could hypothesize that some of the effects on organ development are a direct consequence of lack of GHRH. Only similar studies performed in subjects who have IGHD due to mutations in different genes could conclusively answer this question. On the other hand, it is likely that in these patients GHRH transcription is up-regulated (due to lack of negative feed back by GH and IGF-1)[32] and such increase in GHRH may have additional effects mediated by another receptor.

In conclusion, our data demonstrate that subjects with untreated lifetime IGHD and severe short stature due to a homozygous mutation in the *GHRH-R* have smaller spleen and uterus and bigger liver, kidney and pancreas adjusted size, pointing to different roles of the GH-IGF-1 axis on the growth of individual organs.

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Table 1

Demographic and anthropometric data of 18 *GHRH-R* mutant (*GHRH-R* mut.) individuals and two control groups. Control B was used only for liver size

Variable	*GHRH-R* mut.	Control A	Control B
Sex (F/M)	8/10	10/8	11/7
Age (years)	46·1 ± 13·0	52·3 ± 11·6	43·9 ± 10·9
Height (m)	1·23 ± 0·08	1·55 ± 0·08*	1·64 ± 0·08*
Weight (kg)	36·4 ± 5·6	57·8 ± 12·1*	65·6 ± 15·8*
BMI (kg/m^2)	24·4 ± 5·1	23·9 ± 13·8	24·1 ± 4·9
BSA (m^2)	1·14 ± 0·11	1·59 ± 0·24*	1·72 ± 0·19*

*$P < 0·0001$ in comparison to *GHRH-R* mutant group. Values are means ± SD. BMI, body mass index; BSA, body surface area.

Table 2

Absolute sizes of organs in *GHRH-R* mutant (*GHRH-R* mut.) and control subjects

	***GHRH-R* mut.**	**Control**	***P***
Liver right lobe (cm)	12·02 ± 1·31	13·18 ± 1·54	**0·003**
Liver left lobe (cm)	7·67 ± 1·5	8·7 ± 1·25	**0·032**
Head of pancreas (cm)	2·15 ± 0·42	2·13 ± 0·38	0·893
Body of pancreas (cm)	1·2 ± 0·41	0·95 ± 0·37	0·136
Tail of pancreas (cm)	1·74 ± 0·4	1·51 ± 0·037	0·169
Spleen (cm^3)	63·26 ± 19·63	126·5 ± 83·46	**0·006**
Longitudinal kidney (cm)	8·33 ± 0·5	9·86 ± 0·97	**< 0·0001**
Transversal kidney (cm)	3·58 ± 0·39	4·7 ± 0·78	**< 0·0001**
Prostate (cm^3)	13·61 ± 4·26	26·98 ± 15·85	**0·005**
Uterus (cm^3)	34·92 ± 15·59	88·8 ± 60·66	**0·001**
Ovary (cm^3)	3·41 ± 0·94	4·84 ± 1·92	0·07

Values are means ± SD. Significant correlations are in bold characters.

Table 3

Abdominal sizes of organs corrected by stature (S), weight (W) and body surface area (BSA) in patients with *GHRH-R* mutant (*GHRH-R* mut.) and control subjects

	Corrected by	*GHRH-R* mut.	Control	*P*
Liver right lobe	S (cm/m)	9·8 ± 1·21	8·02 ± 0·95	< **0·0001**
	W (cm/kg)	0·33 ± 0·04	0·21 ± 0·04	< **0·0001**
	BSA (cm/m^2)	10·56 ± 0·99	7·7 ± 0·94	< **0·0001**
Liver left lobe	S (cm/m)	6·26 ± 1·31	5·29 ± 0·69	**0·01**
	W (cm/kg)	0·21 ± 0·05	0·14 ± 0·03	< **0·0001**
	BSA (cm/m^2)	6·77 ± 1·41	5·11 ± 0·83	< **0·0001**
Head of pancreas	S (cm/m)	1·77 ± 0·35	1·4 ± 0·24	**0·007**
	W (cm/kg)	0·06 ± 0·01	0·04 ± 0·01	**0·005**
	BSA (cm/m^2)	1·84 ± 0·41	1·43 ± 0·33	**0·015**
Body of pancreas	S (cm/m)	0·98 ± 0·33	0·62 ± 0·23	**0·004**
	W (cm/kg)	0·03 ± 0·01	0·02 ± 0·01	**0·003**
	BSA (cm/m^2)	1·02 ± 0·36	0·63 ± 0·22	**0·003**
Tail of pancreas	S (cm/m)	1·43 ± 0·31	0·99 ± 0·23	**0·001**
	W (cm/kg)	0·04 ± 0·01	0·03 ± 0·01	**0·001**
	BSA (cm/m^2)	1·48 ± 0·35	1·0 ± 0·21	< **0·0001**
Spleen	S (cm^3/m)	51·26 ± 15·06	82·83 ± 55·53	**0·031**
	W (cm^3/kg)	1·78 ± 0·59	2·48 ± 1·96	0·159
	BSA (cm^3/m^2)	55·69 ± 16·84	87·1 ± 67·75	**0·071**
Longitudinal kidney	S (cm/m)	6·78 ± 0·4	6·36 ± 0·5	**0·008**
	W (cm/kg)	0·23 ± 0·04	0·18 ± 0·04	< **0·0001**
	BSA (cm/m^2)	7·35 ± 0·73	6·31 ± 0·92	**0·001**
Transversal kidney	S (cm/m)	2·91 ± 0·31	3·03 ± 0·41	0·521
	W (cm/kg)	0·1 ± 0·02	0·08 ± 0·02	**0·003**
	BSA (cm/m^2)	3·16 ± 0·42	3·0 ± 0·47	0·161
Prostate	S (cm^3/m)	10·7 ± 3·66	16·58 ± 9·7	0·315
	W (cm^3/kg)	0·39 ± 0·11	0·4 ± 0·24	0·364
	BSA (cm^3/m^2)	11·94 ± 3·59	15·07 ± 9·03	0·962
Uterus	S (cm^3/m)	29·96 ± 12·37	59·36 ± 41·53	**0·015**
	W (cm^3/kg)	1·02 ± 0·43	1·97 ± 2·1	0·107
	BSA (cm^3/m^2)	31·96 ± 13·19	65·2 ± 57·76	**0·025**
Ovary	S (cm^3/m)	2·93 ± 0·86	3·23 ± 1·31	0·813
	W (cm^3/kg)	0·09 ± 0·04	0·11 ± 0·06	0·740
	BSA (cm^3/m^2)	3·04 ± 1·09	3·51 ± 1·68	0·505

Significant correlations are in bold characters.

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Table 4

Correlation between sizes of organs and height; sizes of organs and body surface area (BSA) of all the subjects (pooled *GHRH-R* mutant and control subjects)

	Height	Weight	BSA
Liver right lobe	*r* = 0·417	*r* = 0·625	*r* = 0·607
	***P* = 0·011**	***P* < 0·0001**	***P* < 0·0001**
Liver left lobe	*r* = 0·398	*r* = 0·343	*r* = 0·374
	***P* = 0·016**	***P*** = 0·04	***P* = 0·025**
Head of pancreas	*r* = 0·04	*r* = 0·026	*r* = -0·004
	P = 0·849	*P* = 0·9	*P* = 0·987
Body of pancreas	*r* = -0·131	*r* = 0·029	*r* = -0·007
	P = 0·533	*P* = 0·891	*P* = 0·974
Tail of pancreas	*r* = -0·146	*r* = 0·055	*r* = 0·034
	P = 0·486	*P* = 0·795	*P* = 0·874
Spleen	*r* = 0·411	*r* = 0·217	*r* = 0·178
	P = **0·013**	*P* = 0·203	*P* = 0·299
Longitudinal kidney	*r* = 0·813	*r* = 0·758	*r* = 0·786
	***P* < 0·0001**	***P* < 0·0001**	***P* < 0·0001**
Transversal kidney	*r* = 0·807	*r* = 0·695	*r* = 0·735
	***P* < 0·0001**	***P* < 0·0001**	***P* < 0·0001**
Prostate	*r* = 0·502	*r* = 0·686	*r* = 0·651
	***P* = 0·040**	***P* = 0·002**	***P* = 0·005**
Uterus	*r* = 0·593	*r* = 0·389	*r* = 0·387
	***P* = 0·002**	*P* = 0·054	*P* = 0·056
Ovary	*r* = 0·175	*r* = 0·072	*r* = 0·072
	P = 0·503	*P* = 0·782	*P* = 0·783

Values are means ± SD. Significant correlations are in bold characters.