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Erstveröffentlichung in / First published in:

Journal of Pediatric Endocrinology and Metabolism. 2015, 28(9/10), S. 1047 – 1055 [Zugriff am: 31.01.2020]. De Gruyter. ISSN 2191-0251.

DOI: https://doi.org/10.1515/jpem-2015-0005

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Abstract: In a cross-sectional study of 54 patients with adolescence-onset hypogonadism (33 females, 21 males; age range: 19–40 years), medical care, quality of life, and health status were assessed. Most patients had received adequate medical care with short cumulative periods of interruption of hormone replacement. The prevalence of the metabolic syndrome was 27% in females and 19% in males. In comparison to the general population, females had both a lower bone mineral density (dual-energy X-ray absorptiometry, Z-score=−0.8, p<0.001) and a higher prevalence of obesity (age 19–29 years: study population 35%, general population 4%). The body fat percentage (dual-energy X-ray absorptiometry) was significantly elevated (age 19–29 years: females Z-score=+1.8, p<0.001, males Z-score=+2.4, p=0.001). Quality of life (SF-36) was normal. Despite adequate treatment, patients with early-onset hypogonadism are prone to develop signs and symptoms consistent with inadequate hormone replacement. A successful transition from pediatric to adult medicine seems important to optimize treatment outcomes.

Keywords: body composition; bone density; hypogonadism; metabolic cardiovascular syndrome; quality of life.

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DOI 10.1515/jpem-2015-0005
Received January 7, 2015; accepted February 26, 2015; previously published online April 18, 2015

Introduction

Hypogonadotropic hypogonadism is caused by abnormalities within the pituitary gland or the hypothalamus, whereas primary gonadal failure results in hypergonadotropic hypogonadism (1). A long-term substitution of sex hormones is essential for both male (1, 2) and female (1, 3) patients to prevent health problems associated with sex hormone deficiency. These include the reduction of bone mineral density (4, 5) and the development of a metabolic syndrome in men (6) or some of its components, such as dyslipidemia or an increase in central fat in women (7). Non-adherence or insufficient medical care have been observed for women with Turner syndrome (8–10), possibly contributing to the abovementioned health problems. Similar health issues have been reported for the Klinefelter syndrome. However, very few studies have been conducted to analyze the long-term consequences of adolescence-onset hypogonadism of diverse origins. The objectives of our study were to evaluate endocrine, metabolic, and skeletal parameters and to assess quality of life in patients with hypogonadism of various causes that manifested in adolescence.

Materials and methods

This clinical cross-sectional study was conducted at the University Hospital Dresden, Dresden, Germany. Inclusion criteria for study participation were manifestation of hypogonadism at the age of <18 years and the presence of hypogonadism at the time of re-examination in adulthood. Exclusion criteria were severe chronic diseases. Figure 1 shows the participant flow.

Fifty-four Caucasian patients (33 females, 21 males; age range: 19–40 years) with hypogonadism of mixed etiology (Table 1) were included in the analysis. Informed, written consent was obtained from all participating patients. The study was approved by the Ethics Committee of the Dresden University of Technology (EK 66022010) and was conducted in accordance with the Declaration of Helsinki.

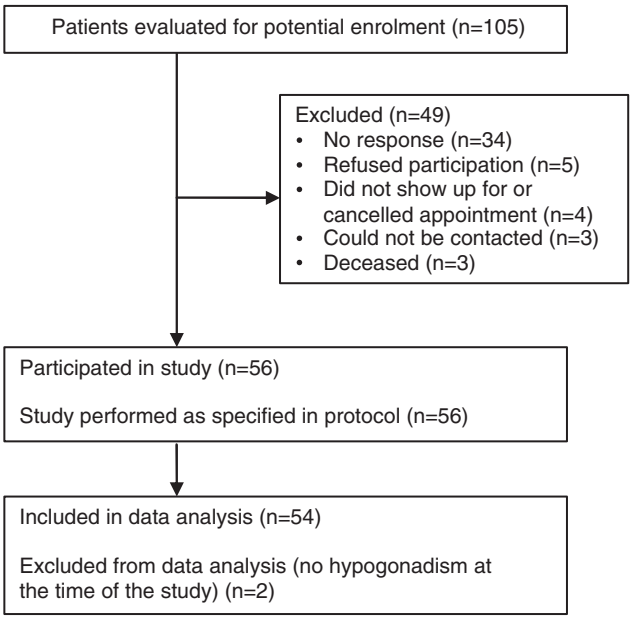

Figure 1: Study enrolment diagram.

A standardized medical history was obtained from patient files, as well as an interview and correspondence with the attending physician to collect information on past and present medical care, including age at initiation of sex hormone substitution and adherence to hormone replacement therapy (HRT). A physical examination including the measurement of height, weight, waist circumference, and blood pressure was performed. A fasting blood sample was collected to measure sex hormones and parameters of lipid and glucose metabolism. For all study participants, a dual-energy X-ray absorptiometry (DXA) using the Lunar Prodigy™ device (GE Medical Systems, Madison, WI, USA) was performed. Bone mineral density (BMD) was measured at the lumbar spine (L1 to L4), both femoral necks and both total hips and Z- and T-scores were provided by the DXA software based on a reference population. Measurements were evaluated according to the positions of the International Society for Clinical Densitometry (11). Osteopenia and osteoporosis were defined according to the definition of the World Health Organization (WHO), that is, osteoporosis was diagnosed when the lowest T-score was lower than –2.5 and osteopenia when the lowest T-score was lower than –1.0 but equal to or >–2.5 (4). The body mass index (BMI) was calculated and every patient was assigned to a weight category based on the WHO classification (12). Weight class frequency distributions based on data collected through the Telephone Health Survey 2003 allowed a comparison with the German general population (13). A Z-score for each measurement of body fat percentage was based on the reference population derived from the DXA software. For diagnosis of a metabolic syndrome, the joint definition of multiple organizations, for example the American Heart Association, from 2009 was applied (14). The prevalence of the metabolic syndrome in our study population was compared to that of the general population using data collected in a Germany-wide cross-sectional study (15). Health-related quality of life (QoL) was assessed using the SF-36 Health Survey. The data were analyzed following the instructions of the appropriate manual and compared to the norm sample from 1994 (16).

All statistical analyses were performed with IBM SPSS Statistics for Windows Version 19.0 and 22.0 (IBM Corp., Armonk, NY, USA). To test for normal distribution, the Kolmogorov-Smirnov test or the Shapiro-Wilks test were used. For comparisons of the study population and the general population, a one-sample t-test was employed for samples with normal distribution and a Wilcoxon test for samples with no normal distribution. To compare two normally distributed groups, a t-test for independent samples was applied. For samples that were not normally distributed, a Mann-Whitney U-test was used. For comparisons of frequency distributions in the study population and the general population, a χ^2-test was performed. The level of significance was set to p-value=0.05 in all analyses.

Results

Medical care

Out of 54 patients, 48 (89%) had been treated in the Department of Pediatric Endocrinology of the University Hospital Dresden for hypogonadism in their youth. Five patients (9%) had not received medical care concerning

Table 1: Characteristics of the study population.

	Male patients (n=21)	Female patients (n=33)
Age (years), mean±standard deviation	27.1±6.3	25.6±4.8
Hypergonadotropic hypogonadism, n (%)	9 (42.9)	27 (81.8)
Ullrich-Turner syndrome, n (%)	–	26 (78.8)
Klinefelter syndrome, n (%)	6 (28.6)	–
Gonadectomy, n (%)	2 (9.5)	1 (3.0)
Others, n (%)	1 (4.8)	–
Hypogonadotropic hypogonadism, n (%)	12 (57.1)	6 (18.2)
Status post brain tumor, n (%)	4 (19.0)	3 (9.1)
Multiple pituitary hormone deficiency, n (%)	4 (19.0)	–
Kallmann syndrome, n (%)	1 (4.8)	1 (3.0)
Prader-Willi syndrome, n (%)	–	1 (3.0)
Others, n (%)	3 (14.3)	1 (3.0)

hypogonadism in childhood or adolescence. More than 80% of the study participants had experienced either a spontaneous or sex-hormone-induced puberty before their 16th birthday. One male patient with Kallmann syndrome had remained without hormonal replacement until the age of 25 years. In 82% of the female patients and 48% of the male patients, puberty had to be initiated by HRT.

At the time of the study, all male patients and 88% of the female patients were receiving HRT. In males, testosterone replacement therapy was performed using intramuscular injection of testosterone undecanoate (n=11), intramuscular injection of testosterone enanthate (n=4), or transdermal testosterone gel (n=6). The medical treatment concerning hypogonadism in male study participants was provided by an adult endocrinologist in 62%. Twenty-four percent were in urological care and 10% were under the care of their general practitioner. In females, diverse therapeutic regimens of HRT with equine or synthetic estrogens variably combined with progestogens were applied. Sixty-four percent were treated by a gynecologist and 21% by an endocrinologist. One woman was treated by a general practitioner. Twelve percent of the female patients did not currently receive any medical care concerning hypogonadism.

The average cumulative period of interruption of HRT amounted to 0.4 years (SD=0.8) for male patients and 1.3 years (SD=3.3) for female patients. Seventy-one percent of the male and 67% of the female study participants had not had any relevant interruptions of HRT. The longest period of interruption in the male study population was 3.0 years, whereas 15% percent of the female patients discontinued HRT for more than 3 years. Of these, two women (6%) interrupted HRT for more than 10 years.

Bone mineral density

The female patients had a significantly lower mean BMD at lumbar spine and total hip than the female reference population of the same age (Table 2). Nineteen female study participants (58%) were diagnosed with osteopenia and one (3%) with osteoporosis. The average BMD of male patients was not significantly decreased in comparison with the control group for both lumbar spine and total hip (Table 2). Seven male patients (33%) had osteopenia and two men (10%) had osteoporosis.

BMI

On average, female study participants were pre-obese while male study participants exhibited a mean BMI in the normal range. For both men and women, only slight differences between the age groups 19–29 years and 30–40 years were found (Table 2).

Figure 2 illustrates the prevalence of the WHO BMI categories in the study population in comparison to the German general population (13) for the different age groups and genders. Female study participants had a higher prevalence of obesity when compared to the German general female population for both age groups.

Table 2: Bone mineral density and body composition (mean±standard deviation). Comparison of study population with reference population.

	Male patients (age 19–29 years: n=14; age 30–40 years: n=7)	p-Value	Female patients (age 19–29 years: n=23; age 30–40 years: n=10)	p-Value
BMD lumbar spine	1.162±0.209		1.086±0.123	
Z-score	−0.3±1.5	0.343	−0.8±1.0	<0.001[a]
T-score	−0.5±1.7		−0.7±1.1	
BMD total hip	1.042±0.214		0.929±0.132	
Z-score	−0.3±1.4	0.317	−0.7±0.9	<0.001[a]
T-score	−0.4±1.6		−0.6±1.1	
BMI, kg/m²				
Age: 19–29 years	24.8±6.6		28.8±7.2	
Age: 30–40 years	23.4±2.5		27.7±5.8	
Body fat percentage				
Age: 19–29 years	27.3±10.6		42.4±10.2	
Z-score	2.4±2.1	0.001[a]	1.8±1.3	<0.001[a]
Age: 30–40 years	24.6±10.7		38.5±10.6	
Z-score	1.0±2.4	0.309	1.1±1.3	0.028[a]

[a]Significant. For statistical analyses of BMD measurements at the total hip, the mean of the two bone mineral densities, Z-scores and T-scores were used for each patient. BMD, bone mineral density; BMI, body mass index.

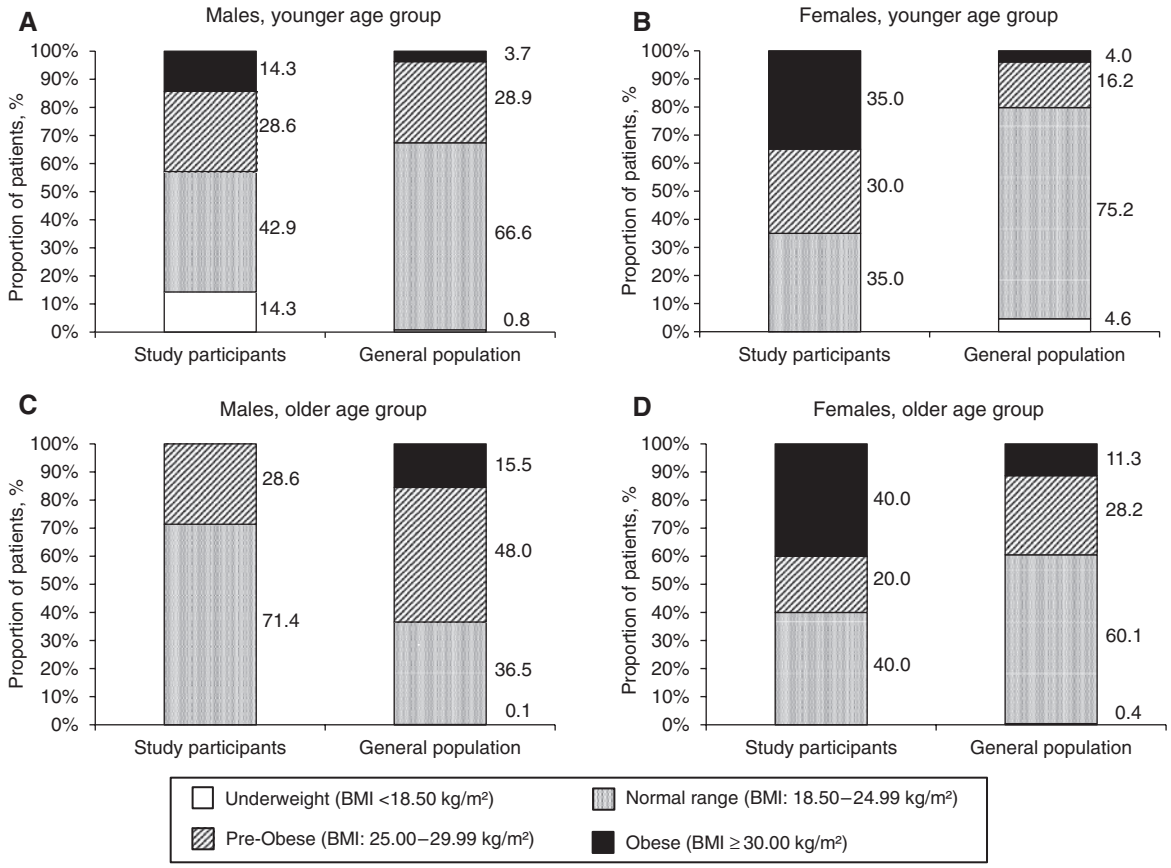

Figure 2: Weight distribution in the study population and in the German general population (13). (A) Male study population aged 19–29 years (n=14) and male general population aged 18–29 years. (B) Female study population aged 19–29 years (n=23) and female general population aged 18–29 years. (C) Male study population aged 30–40 years (n=7) and male general population aged 30–44 years. (D) Female study population aged 30–36 years (n=10) and female general population aged 30–44 years. Blank: underweight [body mass index (BMI): <18.50 kg/m²]. Dotted: normal range (BMI: 18.50–24.99 kg/m²). Hatched: pre-obese (BMI: 25.00–29.99 kg/m²). Filled: obese (BMI: ≥30.00 kg/m²).

Male patients aged 19–29 years had a higher prevalence of both underweight and obesity compared to the age-matched general male population. The increase of overweight and obesity that is observed with increasing age in the general male population was not found for our male study population.

Body fat percentage

Female study participants of both age groups, in particular the younger patients, had a significantly higher mean body fat proportion than the female reference population of the same age (Table 2). Male patients between 19 and 29 years of age also had a significantly higher body fat percentage than the age-matched reference population. The body fat in the male study participants aged 30–40 years was higher, although not significantly, than in the male reference population but lower than in the younger male study population.

Metabolic syndrome

The criteria for the diagnosis of a metabolic syndrome were met by 27% of the female and 19% of the male study participants. In comparison with the German general population (15), the prevalence of the metabolic syndrome was higher for both female and male patients of both age groups (Table 3). However, the observed differences between the study and the general population were significant only for women of the younger age group that exhibited the highest prevalence of the metabolic syndrome.

Quality of life

Thirty-two female and all 21 male study participants filled out the SF-36 questionnaire. For the summary scores,

Table 3: Prevalence of the metabolic syndrome. Comparison of study population with German general population (15).

	Study participants age: 19–29 years (male: n=14, female: n=23)	General population age: 18–29 years	p-Value	Study participants age: 30–40 years (male: n=7, female: n=10)	General population age: 30–39 years	p-Value
Males						
Metabolic syndrome, n (%)	2 (14.3%)	6.0%	0.192	2 (28.6%)	14.5%	0.290
Females						
Metabolic syndrome, n (%)	7 (30.4%)	4.2%	<0.001[a]	2 (20.0%)	8.6%	0.199

[a]Significant.

Table 4: SF-36 results (mean±standard deviation). Comparison of study population with German general population (16).

	Study participants age: 19–30 years (male: n=15, female: n=25)	General population age: 21–30 years	p-Value	Study participants age: 31–40 years (male: n=6, female: n=7)	General population age: 31–40 years	p-Value
Males						
Physical component summary score	51.72± 9.37	50.21±10.24	0.551	50.31±7.29	54.13±6.80	0.256
Mental component summary score	49.37±6.46	51.54±8.14	0.231	51.32±8.04	50.91±7.75	0.905
Physical functioning	92.00±11.15	96.21±10.19	0.011[a]	95.00±7.75	96.44±9.97	0.750
Role physical	76.67±34.68	95.82±17.56	0.027[a]	75.00±31.62	91.43±26.27	0.259
Bodily pain	87.27±25.12	88.91±21.62	0.068	85.50±24.51	89.64±20.42	0.914
General health	67.86±19.53	77.12±18.33	0.099	58.67±29.94	76.54±16.13	0.204
Vitality	57.67±13.21	67.52±18.80	0.012[a]	63.33±24.01	68.53±15.00	0.619
Social functioning	86.67±24.31	93.12±17.04	0.066	89.58±16.62	92.10±16.38	0.914
Role emotional	95.56±11.73	94.46±19.51	0.157	83.33±27.89	93.57±23.35	0.914
Mental health	71.47±19.00	76.49±16.58	0.323	79.33±15.68	77.06±16.44	0.737
Females						
Physical component summary score	55.16±7.17	50.21±10.24	0.022[a]	52.24±4.98	54.13±6.80	0.354
Mental component summary score	50.04±6.06	51.54±8.14	0.237	50.74±8.59	50.91±7.75	1.000
Physical functioning	92.92±10.83	93.95±12.89	0.001[a]	93.57±4.76	91.03±16.86	0.207
Role physical	92.00±22.50	87.75±28.57	0.066	100.00±0.00	88.99±22.45	1.000
Bodily pain	89.60±22.97	83.97±26.57	0.043[a]	85.29±20.76	84.33±21.23	0.109
General health	74.60±20.36	74.49±17.65	0.979	62.43±26.36	72.12±15.39	0.368
Vitality	60.60±18.95	62.21±17.95	0.675	64.29±16.69	63.06±15.79	0.852
Social functioning	92.00±15.68	89.14±18.34	0.026[a]	73.21±29.25	87.24±17.37	0.252
Role emotional	92.00±24.11	91.29±22.48	0.109	100.00±0.00	89.26±23.74	1.000
Mental health	69.76±14.47	71.75±16.89	0.580	78.86±17.85	71.81±14.03	0.343

[a]Significant.

male and female study participants of both age groups showed only slight differences from the general population (Table 4). However, female study participants aged 19–30 years had significantly higher mean scores for the "physical component summary score" and the domains "social functioning" and "bodily pain" but a significantly lower score in the domain "physical functioning" than the general population. Male study participants between 19 and 30 years of age had significantly lower scores than the general population in the domains "role physical", "vitality" and "physical functioning". For the older male and female study participants, no significant differences to the normal population could be observed for any of the domains.

Some of the study participants had psychiatric comorbidities that may have affected their QoL. A male study participant was treated for schizophrenia with two atypical neuroleptics and a selective serotonin reuptake inhibitor (SSRI). One patient had been receiving methylphenidate for 15 years. Two female patients were treated with an atypical neuroleptic and a SSRI, one for obsessive compulsive disorder and the other after a depressive episode

and periods of increased irritability. Another female study participant with a somatization disorder received a SSRI.

Discussion

We performed a cross-sectional study in a cohort of young adults with hypogonadism with disease-onset during adolescence assessing physical, mental and social health status, and QoL. The transition of patients with chronic illnesses from pediatric to adult medicine can be prone to obstacles that may lead to the patients dropping out of medical care (17). For example, patients with Turner syndrome are often adequately treated during childhood but do not receive satisfactory medical care in adulthood (8–10). In our study population, most patients had experienced a successful transition from pediatric to adult health care and the medical care situation of our study population was satisfactory. The majority of patients were treated by specialists with particular expertise in HRT such as endocrinologists or gynecologists. All male and most of the female patients were receiving HRT at the time of the study. Approximately 70% of the study participants had never experienced any relevant interruptions of HRT. We observed a clear gender difference in the length of HRT interruption in patients who had discontinued therapy, with male patients having far shorter interruptions than female patients. A possible explanation for this observation could be the unpleasant symptoms that male patients experienced in times of therapy discontinuation including loss of libido, increased fatigue, and depressive mood. In contrast, most female patients did not report any negative symptoms when discontinuing their treatment and some reported regular menstrual bleeding and weight gain as disadvantages of HRT.

One major result of our study is that gain in body weight could not be prevented in female patients with hypogonadism receiving HRT. In the female study population, the prevalence of obesity and the body fat percentage were considerably higher than in the general population. In women, no causal link between estrogen deficiency and increase of body fat percentage has been proven. However, there is data suggesting that a postmenopausal estrogen deficiency may be associated with an increase in body fat (18). Women with Turner syndrome have been observed to be more obese in comparison to women with normal karyotype (19). Both estrogen deficiency and the large proportion of women with Turner syndrome in our study population could be seen as possible explanations for the considerable prevalence of obesity and the high body fat percentage in our female study population.

Our male study participants exhibited a weight distribution that differed from that of the general population. In the age group 19–29 years, male patients had a higher prevalence of both obesity and underweight than the general population. The body fat percentage of the younger male patients was significantly elevated. It has been found that there is a significant inverse correlation between total testosterone blood concentration and obesity (6). In a study on men with prostate cancer undergoing androgen deprivation, a significant increase in percentage fat body mass and a significant reduction in percentage lean body mass were observed (20). Bojesen et al. found that Klinefelter patients without testosterone replacement therapy had a significantly higher body mass index and a significantly higher body fat percentage than a control group of men without Klinefelter syndrome (21). Testosterone deficiency is therefore a possible explanation for the high prevalence of obesity and increased body fat percentage in our male study participants.

In addition, we observed a much higher prevalence of the metabolic syndrome in our study population than in the German general population. This finding was statistically significant only in the group of female patients aged 19–29. However, a clinical relevance of this result for male and older patients seems likely. Low testosterone blood concentration can be considered a risk factor for metabolic syndrome in men (6). A study on 71 Klinefelter patients showed a greatly increased prevalence of the metabolic syndrome in this cohort (21). In women, it has been observed that different components of the metabolic syndrome, for example, central obesity and dyslipidemia, emerge with estrogen deficiency during menopause (7). However, the magnitude of the impact of estrogen deficiency independent of other factors, for example, aging, on these changes has not been conclusively clarified (7, 18). For both our male and female study participants, sex hormone deficiency could be a possible explanation for the highly elevated prevalence of the metabolic syndrome. In our female study population, the large proportion of patients with Turner syndrome could account for the high prevalence of the metabolic syndrome in our study population. Patients with Turner syndrome exhibit an elevated prevalence of multiple components of the metabolic syndrome (22, 23). They have a considerably increased risk of developing hypertension, impaired glucose tolerance, and type 2 diabetes mellitus (22). The increased frequency of hypertriglyceridemia in women with Turner syndrome may be a direct consequence of obesity and hyperinsulinemia (22).

Another major result of our study is the reduction of bone mineral density, especially in our female study population despite HRT. We found a significantly lower BMD in our female study population compared to the reference population. The prevalence of osteopenia as a possible preliminary stage of osteoporosis was high. Estrogen deficiency has been shown to play an important role in the development of osteoporosis as estrogen seems to have both anti-catabolic and anabolic effects on bone (24). On the general population level, women after menopause are mainly affected by osteoporosis. However, it has been shown that young women with estrogen deficiency have an increased risk for lower bone mineral density and that the period without HRT is significantly related to lower bone mineral density in these women (25). As four female patients were not receiving HRT at the time of the study and some patients had long interruptions of HRT, estrogen deficiency had likely been an important factor for the development of the observed decreased bone mineral density. It has been reported that women with Turner syndrome are at higher risk of developing osteoporosis (22). An intrinsic bone defect is probable as HRT improves but does not normalize bone mass. The reduction of bone mass is likely caused by a combination of this intrinsic bone defect and estrogen deficiency (22). Furthermore, small bone size and short height could be confounding factors in the measurement of areal bone density in women with Turner syndrome (26), possibly leading to overestimation of the bone mineral density reduction. As the majority of our female study participants were women with Turner syndrome, these factors could have contributed to the low average BMD observed in the female study population.

In the male study population, decrease of BMD was not significant. Compared to the female study population, statistical scattering of BMD was higher in the male study population, which could be explained by its higher etiological diversity. The substantial prevalence of osteopenia and osteoporosis indicates a clinical relevance of the bone mass reduction in our male patients. Hypogonadism is a common secondary cause of osteoporosis in men (4, 5). The influence of testosterone on the male skeleton is partly exerted indirectly through estrogen formed by aromatization of testosterone (4, 5). Thus, possible explanations for the decrease in BMD in our male study participants could be a testosterone deficit due to interruptions or delayed beginning of HRT as well as insufficient sex hormone levels under HRT.

Surprisingly, both female and male study participants did not show significant differences in QoL compared to the general population, as depicted in the component summary scores of the SF-36. Male patients aged 19–30 years had significantly lower QoL concerning only some domains of the questionnaire. However, female patients between 19 and 30 years of age showed even better QoL concerning certain domains such as “social functioning” than the general population. Bannink et al. found that young women with Turner syndrome after induced puberty and growth hormone therapy had a normal health-related QoL and scored higher in some of the domains of the SF-36, including “social functioning” and “bodily pain” (27). These findings are consistent with our results, considering that the majority of the female study population were women with Turner syndrome. Boman et al. also observed a normal psychological well-being and self-rated health but more self-reported social isolation in these patients (28) and other studies found poorer QoL concerning some domains of the SF-36 in women with Turner syndrome (29, 30). It is difficult to compare our results concerning the male patients to other findings because of the heterogeneity of our male study population. In an Australian study on 87 men with Klinefelter syndrome, noticeably poorer outcomes than in the general male population have been shown for all evaluated aspects of QoL including self-esteem, body image, and subjective well-being (31). Physical characteristics and difficulties in academic performance due to learning disabilities can lead to low self-esteem and withdrawal from peers in adolescents with Klinefelter syndrome (32). In a study on 25 children and adults with childhood craniopharyngeoma, patients rated their health-related QoL considerably lower than healthy controls, especially in the domains social and emotional functioning (33). In a larger prospective study, it was observed that the degree of hypothalamic surgical lesions had a negative impact on health-related QoL (34).

Our study had potential limitations. The recruitment of the patients may have led to a selection bias. Blood pressure could only be measured once for each patient due to organizational reasons. Even though the definition of the metabolic syndrome does not explicitly call for a repeated measurement, we would recommend it for a more reliable diagnosis. As our male study population in particular was heterogeneous regarding the cause of hypogonadism, comparisons of our results with previous findings may not be fully possible. Conversely, our study cohort reflects the diversity of patients referred to a pediatric endocrine outpatient clinic.

In conclusion, our study shows that patients with hypogonadism were prone to developing multiple health risks typically associated with sex hormone deficiency, even though most of the study participants had received satisfactory medical care and HRT. We found a

discrepancy between an objectively alarming health situation and a subjectively normal self-reported QoL. It seems as if the health issues found in this study have no or little influence on QoL at the relatively young age of our study participants. However, there is a high risk for substantial future health problems. Whether our findings can be generalized to all patients with early-onset hypogonadism is uncertain. Large-scale prospective studies are needed to evaluate different diagnostic and therapeutic regimens for patients with hypogonadism with onset in adolescence in order to improve long-term health.

Acknowledgments: This work was financially supported by Eli Lilly Deutschland GmbH. The authors declare that there is no conflict of interests regarding the publication of this paper.

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