


# Transition from gynaecomastia to lipomastia in pubertal boys

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## Funding information

This study received grant support from Ferring for this study. However, the hypothesis development, analysis, interpretation and conclusions contained in this study are those of the authors' alone.

## Abstract

**Objective:** Gynaecomastia is frequent in pubertal boys and is regarded as a self-limiting abnormality. However, longitudinal studies proving this hypothesis are scarce.

**Design:** Longitudinal follow-up study (median 2.4, range 1.0–4.8 years).

**Methods:** The regression of breast diameter was analysed in 31 pubertal boys aged 11.7–16.1 (median 13.2) years with gynaecomastia. Furthermore, weight changes (as BMI-SDS) and pubertal stage, oestradiol [E2], oestriol, oestrone, androstenedione, testosterone [T], dihydrotestosterone, gonadotropins, IGF-1, and IGFBP-3 serum concentrations determined at first clinical presentation were related to breast diameter regression determined by palpation and disappearance of breast glandular tissue in ultrasound in follow-up to identify possible predictors of breast regression.

**Results:** During the observation period, the breast diameter decreased (in median –1 (interquartile range [IQR] –5 to +1) cm). At follow-up, 6% of boys had no breast enlargement any more, and 65% developed lipomastia. Gynaecomastia was still present in 29%. None of the analysed hormones was related significantly to breast diameter regression or disappearance of breast glandular tissue. In multiple linear regression analyses adjusted for observational period, as well as age and BMI-SDS at first presentation, changes in BMI-SDS ( $\beta$ -coefficient  $6.0 \pm 2.3$ ,  $p = .015$ ) but not the E2/T ratio or any other hormone determined at baseline was related to changes in breast diameter.

**Conclusions:** Breast diameter regression seems not to be predictable by a hormone profile in pubertal boys with gynaecomastia. In pubertal boys presenting with gynaecomastia, conversion to lipomastia of smaller volume is common. The reduction of weight status was the best predictor of breast diameter regression.

## KEYWORDS

androgens, dihydrotestosterone, gynaecomastia, IGF-1, IGFBP-3, oestradiol, oestrogens, pseudogynaecomastia, testosterone

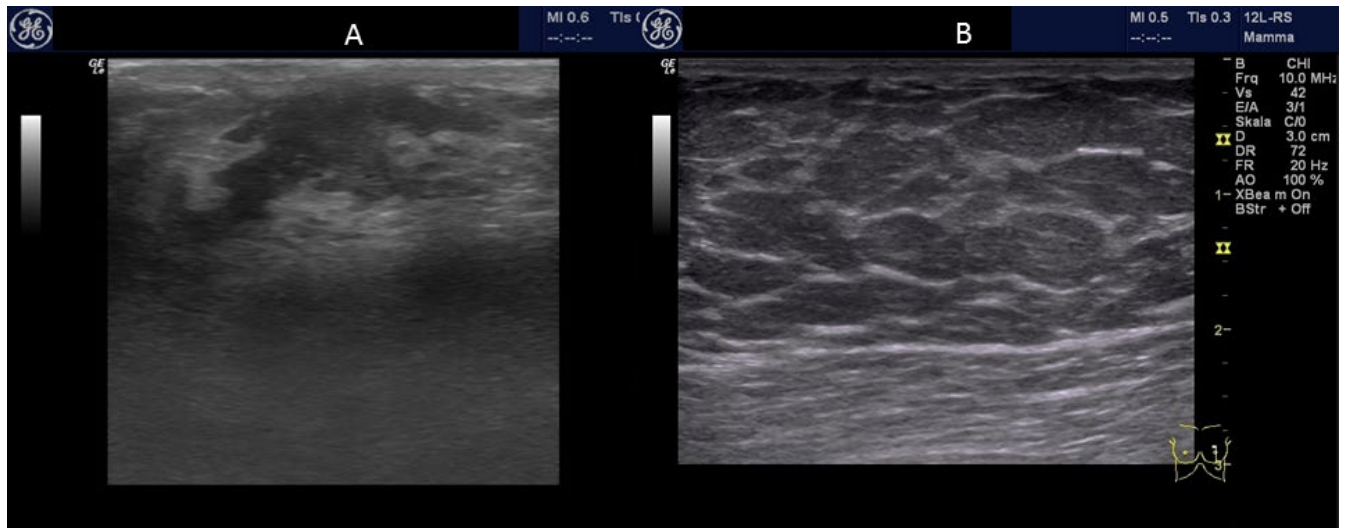
## 1 | INTRODUCTION

Gynaecomastia is defined as a benign glandular proliferation in the male breast and has to be differentiated from lipomastia (a

proliferation of adipose rather than glandular tissue), which is commonly seen in obese males.<sup>1</sup> The two forms can be differentiated by palpation but more accurately by ultrasound.<sup>2</sup> We have previously demonstrated that an imbalance between testosterone and

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**FIGURE 1** Ultrasound of the breast in a 11.8-year-old boys with gynaecomastia (breast diameter 10 cm on each side, height 149.0 cm, weight 46.0 kg, BMI-SDS 0.90) at baseline (A) and lipomastia (B) at follow-up 3.7 years later (breast diameter 4 cm on each side, height 173.5 cm, weight 67.0 kg, BMI-SDS 0.74) [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

oestradiol concentrations is the most striking finding in pubertal boys with gynaecomastia compared to pubertal boys with lipomastia.<sup>3</sup>

Physiological gynaecomastia in pubertal boys is regarded as a self-limiting condition.<sup>1,4-10</sup> However, longitudinal data are scarce and only three studies have analysed boys with gynaecomastia longitudinally.<sup>7,8,10</sup> Importantly, it is unclear, which factors predict a regression of gynaecomastia. Such predictors would be helpful to advise the affected patients for example if surgery of gynaecomastia is requested. It is well known that pubertal gynaecomastia has a negative impact on the self-esteem of adolescent boys. It can lead to depression as well as decreased participation in various social activities.<sup>11</sup>

The aim of this longitudinal study was to identify predictors of breast diameter regression in pubertal boys with gynaecomastia based on the diagnostic work-up at first presentation in our clinic consisting of ultrasound of breast, gonadotropins, IGF-1, IGFBP-3, and a comprehensive serum profile of sex steroid hormones and their precursors,<sup>3</sup> using a liquid chromatography-tandem mass spectrometry (LC-MS/MS) steroid profiling method.<sup>12</sup>

## 2 | METHODS

The study was approved by the local ethics committee of the Vestische Kinder- und Jugendklinik, University of Witten/Herdecke in Germany. Written informed consent was obtained from all boys and parents of the participants.

All pubertal boys presenting with gynaecomastia at the Vestische Kinder- und Jugendklinik Datteln, University of Witten Herdecke in the time period between 1.10.2013 and 2.5.2019 and recruited for our previous study<sup>3</sup> were contacted for this follow-up examination. This cohort consisted of 86 boys with gynaecomastia. All boys who agreed to participate and with a follow-up interval of at

least one year after baseline and having achieved a voice break (as indirect parameter for achieving the end of puberty) were included in this study. Boys with surgery of their breast were excluded from this study. Boys with pseudogynaecomastia (including lipomastia) at baseline or gynaecomastia due to syndromes (eg Klinefelter syndromes) or disorders of sexual development or taking any medication were also excluded from the study. For details of the initial study recruitment see.<sup>3</sup>

### 2.1 | Measurements

We analysed height, weight and breast diameter determined by palpation on each side at baseline and follow-up examination. Breast diameter was measured by a flexible measuring tape to the nearest cm. Furthermore, an ultrasound examination of the breast was performed at baseline and follow-up.

Height was measured to the nearest millimetre using a wall-mounted stadiometer. Weight was measured in underwear to the nearest 0.1 kg using a calibrated balance scale. BMI was calculated as weight in kilograms (kg) divided by the square of height in meters (m<sup>2</sup>). The degree of overweight was quantified using Cole's least mean square method, which normalized the BMI skewed distribution and expressed BMI as a standard deviation score (BMI-SDS).<sup>13</sup> Reference data for German boys were used.<sup>14</sup>

Ultrasound measurements were performed by one well-trained investigator using a transportable Siemens Logic E ultrasound system with a 12 MHz linear transducer. Adipose tissue is characterized in the ultrasound as hypoechoic or anechoic, while ultrasound signs of breast tissues are retroareolar ovoid hyperechoic tissue and branched duct development flame-shaped with finger-like extensions into the surrounding tissue presenting as central hypoechoic star-shaped areas encircled by hyperechoic peripheral rim.<sup>2,15-17</sup> If

any sign of breast tissue was detected by ultrasound the boy was classified as having gynaecomastia even if there were also hints of adipose tissue. An example of gynaecomastia in ultrasound which converted to lipomastia in the follow-up examination is presented in Figure 1.

Available data from the first presentation at our clinic were pubertal stage (Tanner stage P as well as testis volumes), height, weight, breast diameter on each side, serum gonadotropins (LH, FSH), IGF-1, IGFBP-3, and serum sex steroid hormones (oestradiol [E2], oestriol [E3], oestrone [E1], androstenedione [A], testosterone [T], dihydrotestosterone [DHT]) determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS, for details see<sup>3</sup>). In order to interpret the relationship between E2 and T we calculate the E2 to T ratio.

## 2.2 | Statistics

Statistical analyses were performed using the Winstat<sup>®</sup> software package (R. Fitch Software, Bad Krozingen, Germany). For descriptive analysis, data were presented as median, interquartile range (IQR) and range.

To compare baseline variables, Fisher exact test, Student's *t*-test for unpaired observations, and Mann-Whitney *U*-test were used as appropriate. Normal distribution was tested by the Kolmogorov-Smirnov test. Associations were calculated by Spearman rank correlation.

Changes during the observation period were calculated as value at follow-up minus baseline value. To statistically assess these changes, Fisher exact test, Student's *t*-test for paired observations, and Wilcoxon test were used as appropriate.

We performed a multiple linear backwards regression analysis with the dependent variable 'change of breast diameter' (sum of the changes of left and right breast diameter in cm) and the independent variables observation period, age at baseline, BMI-SDS and E2/T ratio at first presentation as well as all baseline hormone values related to breast diameter regression in univariate analyses with a *p*-value <.10.

A *p*-value  $p < .05$  was considered as significant in the multiple linear regression analysis. In univariate tests and Spearman rank correlations, a *p*-value <.005 was assigned as significant to account for multiple comparisons.

## 3 | RESULTS

One boy with gynaecomastia received surgery of the breasts and was excluded from this longitudinal analysis. A total of 31 boys with gynaecomastia agreed to participate in this longitudinal study and were included in the analyses (baseline characteristics see Table 1). They were re-examined 2.4 (median, IQR 1.3-2.9, range 1.0-4.8) years after the first presentation. These 31 boys did not differ significantly from the 55 boys with gynaecomastia not included in this

TABLE 1 Baseline characteristics of the study cohort

Number	31
Age [years]	13.2 (11.8-14.2) [11.7-16.1]
BMI-SDS	0.69 (0.18-1.76) [-1.15-2.96]
Breast diameter left [cm]	8 (4-11) [3-28]
Breast diameter right [cm]	8 (3-11) [0-28]
Testis volume right [ml]	6 (5-11) [4-20]
Testis volume left [ml]	6 (5-11) [4-20]
Tanner stage P	3 (2-4) [1-5]
Duration of breast swelling [months]	12 (6-24) [2-36]

Note: Data as median, interquartile range in () and range in []

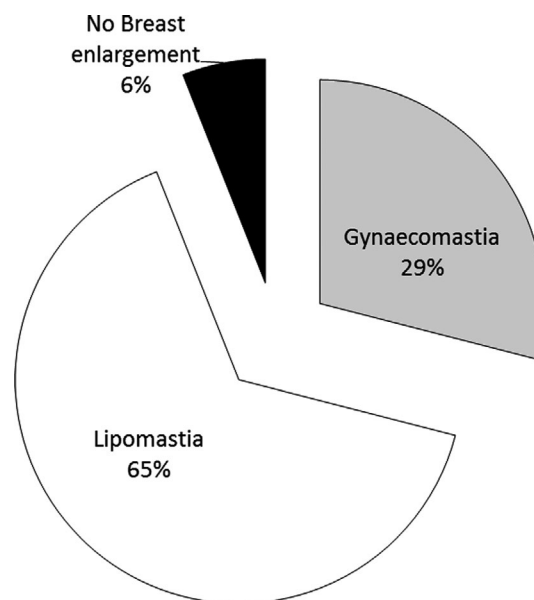


FIGURE 2 Findings at 2.4-year follow-up in 31 pubertal boys with gynaecomastia at initial presentation

longitudinal study in respect to diameter of breast enlargement, age, testis volume, Tanner stage, gonadotropins, sex steroid hormones, and gonadotropins concentrations at baseline. The reasons for lack of follow-up were missing contact ( $n = 18$ ) or refusal of re-presentation for follow-up ( $n = 37$ ).

During follow-up, the weight status did not change significantly ( $\Delta$ BMI-SDS in median + 0.20 (IQR -0.30-0.41, range -1.76-1.46,  $p = .367$ ). At re-evaluation, most boys converted to lipomastia (see Figure 2).

The two boys with complete remission of their gynaecomastia had a breast enlargement of 8 respective 7 cm on each side at baseline. One of these boys reduced his BMI-SDS (-1.45), the other boy had stable BMI-SDS in the observation period (-0.02).

At baseline, eight (88.9%) of the nine boys with remaining gynaecomastia in the follow-up had a breast enlargement >4 cm on each side. At follow-up, six (66.6%) of these boys had a breast enlargement >4 cm on each side. At baseline, the breast diameters were 8 (median, IQR 4-11, range 3-21) cm on the left size and 8 (median, IQR 4-12, range 0-21) cm on the right size. At follow-up, the breast diameters were 9

(median, IQR 4–16, range 4–22) cm on the left side and 10 (median, IQR 3–16, range 0–22) cm on the right side. The changes of the breast diameter were on the left side –1 (median, IQR –1–5, range –2–10) cm and on the right side –1 (median, IQR –1–5, range –2–5) cm. The boys with persistent gynaecomastia had a slight increase of their BMI-SDS during follow-up (median + 0.09, IQR –0.41–0.46, range –1.76–0.82).

At baseline, ten (45.4%) of the 20 boys converting to lipomastia in follow-up had a breast enlargement >4 cm on each side. At follow-up, seven (31.2%) of these boys had a breast enlargement >4 cm on each side. At baseline, the breast diameters were 8 (median, IQR 3–11, range 3–28) cm on the left size and 7 (median, IQR 3–11, range 0–28) cm on the right size. At follow-up, the breast diameters were 4 (median, IQR 2–9, range 1–32) cm on the left side and 4 (median, IQR 1–11, range 0–32) cm on the right side. The changes of the breast diameter were on the left side –1 (median, IQR –6–1, range –8–8) cm and on the right side –1 (median, IQR –5–1, range –8–10) cm. The boys converting to lipomastia demonstrated an increase of their BMI-SDS during follow-up (+0.21, IQR 0.10–0.41, range –0.65–1.46).

### 3.1 | Predictors of breast size regression

The associations between baseline parameters, changes in BMI-SDS, duration of observation period, and changes in breast diameter are presented in Table 2. Except changes in BMI-SDS no other parameter was significantly related to changes in breast diameter (see also Figure 3). The 14 boys without an increase of their BMI-SDS during the follow-up period, reduced their breast diameter significantly (left: –2 (median, IQR –6 to –1, range –8–1) cm,  $p = .003$ ; right: –3 (median, IQR –6 to –3, range –8–0) cm,  $p = .002$ ). The 17 boys, who increased their BMI-SDS during the follow-up period, demonstrated no change of their breast diameter (left: 0 (median, IQR –2–5, range –8–10) cm,  $p = .362$ ; right: 0 (median, IQR –2–5, range –8–10) cm,  $p = .346$ ).

In multiple linear regression analysis the following independent variables were assessed: observation period, as well as age, BMI-SDS, E2, E3, FSH and E2/T ratio at first presentation. In contrast, the other parameters in Table 2 were excluded since their  $p$ -values in univariate regression was  $\geq 0.10$ . The regression model, using backwards parameter selection, revealed that only the change in BMI-SDS (follow-up measurement minus baseline) was significantly related to the reduction in breast diameter. The regression coefficient for delta BMI-SDS was 6.0 (95% confidence interval 1.3–10.7,  $p = .015$ ). This model resulted in a  $r^2$  of .19, indicating that 19% of between-subject variability was explained by the change in BMI-SDS during the observation period.

### 3.2 | Predictors of persistence of breast glandular tissue in ultrasound

The comparison between boys with persistence of breast glandular tissue and boys with complete disappearance of breast glandular tissue in ultrasound is presented in Table 3. None of the hormones

**TABLE 2** Associations ( $r$ ) between baseline variables, changes in BMI-SDS, duration of breast swelling, and duration of observation period with changes in breast diameters in the observation period of in mean 2.4 years in 31 boys with breast enlargement

	$\Delta$ left breast diameter $r$	$\Delta$ right breast diameter $r$
Age	–.09	–.11
Duration of breast swelling before first presentation	–.01	.03
BMI-SDS	.17	.15
Breast diameter	–.04	–.06
Testes volume right	.03	.05
Testes volume left	–.06	–.03
Tanner stage P	.06	.09
LH	–.16	–.10
FSH	–.30	–.30
E1	.19	.06
E2	.23	.28
E3	–.25	.26
E2/T	.26	.25
T	–.12	–.07
DHT	–.15	–.15
A	–.18	–.18
SDS-IGF-1	–.06	–.02
SDS-IGFBP-3	.04	.05
Duration of observation period	.11	.14
Changes in BMI-SDS	<b>.54</b>	<b>.53</b>

Note: Significant associations ( $p < .005$ ) are plotted in bold, Spearman rank correlation.

analysed at the first presentation in our clinic differed significantly between the boys with persistence or disappearance of breast glandular tissue in ultrasound.

## 4 | DISCUSSION

This longitudinal study analysed the breast regression in pubertal boys with gynaecomastia differentiating between breast glandular tissue and adipose tissue using ultrasound. In line with the assumption that gynaecomastia in pubertal boys is reversible in most cases,<sup>1,4–10</sup> breast glandular tissue disappeared in the ultrasound examination in two thirds of our patients. However, a remarkable number of our patients converted from gynaecomastia to lipomastia at the follow-up examination.

Our findings of regression of breast diameters in boys with gynaecomastia but with a remaining breast swelling (which seems to be adipose tissue) is contrary to expert opinions stating that only 10% of boys at the age of 17 years have persistent breast enlargement.<sup>1,5</sup> However, all longitudinal studies are in line with our findings: The three-year longitudinal study of Biro et al in 377 boys

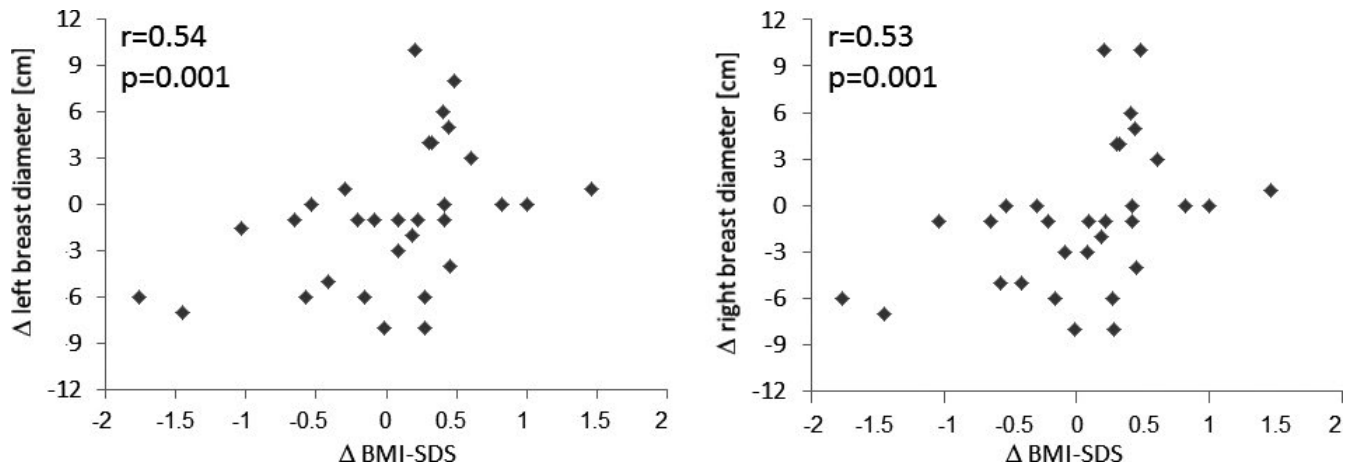


FIGURE 3 Changes of breast diameter related to changes in weight status as BMI-SDS during 2.4 years of follow-up (Spearman rank correlation) in 31 pubertal boys with gynaecomastia at initial presentation

TABLE 3 Comparison of boys with and without disappearance of breast glandular tissue in ultrasound

	Disappearance of breast glandular tissue	Persistence of breast glandular tissue	p-value
Number	21	10	
At baseline			
Age [years]	13.1 (11.7–14.1) [11.7–16.1]	13.9 (12.8–15.4) [11.8–16.1]	.204
BMI-SDS	0.90 (0.20–1.68) [–1.15–2.96]	0.53 (0.06–2.03) [–0.94–2.50]	.658
Duration of breast swelling before presentation [months]	6 (3–12) [2–30]	24 (12–30) [12–36]	.011
Breast diameter left [cm]	8 (4–11) [3–28]	8 (5–11) [4–21]	.774
Breast diameter right [cm]	7 (3–11) [0–28]	8 (4–12) [0–21]	.768
Testis volume right [ml]	6 (5–9) [4–15]	10 (5–13) [4–20]	.047
Testis volume left [ml]	6 (5–8) [4–15]	10 (5–14) [4–20]	.045
Tanner stage P	2 (2–3) [1–5]	4 (3–5) [2–5]	.005
LH [mU/ml]	2.1 (0.8–2.9) [0.1–3.5]	2.8 (2.3–3.5) [0.1–4.4]	.182
FSH [mU/ml]	2.2 (1.3–3.4) [0.2–7.0]	2.8 (1.6–5.1) [0.5–7.1]	.590
E1 [pM/L]	19 (11–49) [11–112]	25 (17–42) [11–109]	.536
E2 [pM/L]	29 (11–48) [10–151]	61 (44–79) [28–123]	.001
E3 [pM/L]	10 (10–13) [10–58]	10 (10–10) [10–49]	.822
E2/T	28 (8–73) [2–138]	15 (7–64) [4–131]	.567
DHT [nM/L]	0.2 (0.1–0.4) [0.1–4.1]	0.3 (0.1–0.4) [0.1–0.7]	.352
A [nM/L]	1.0 (0.6–1.9) [0.2–46.7]	1.0 (0.8–1.5) [0.8–2.2]	.368
T [nM/L]	1.0 (0.5–2.4) [0.2–5.6]	2.2 (1.3–7.6) [0.8–16.0]	.013
IGF-1-SDS	–0.4 (–1.1–0.3) [–1.6–1.4]	–0.1 (–0.6–0.4) [–1.3–0.9]	.500
IGFBP-3-SDS	–0.2 (–0.7–0.4) [–1.29–1.3]	–0.1 (–0.4–0.6) [–1.11–0.94]	.385
At follow-up			
Observation period [Years]	2.7 (1.4–3.4) [1.0–4.8]	1.9 (1.3–2.5) [1.3–4.6]	.660
Change in BMI-SDS	–0.09 (–0.47–0.45) [–1.76–1.46]	0.21 (0.01–0.40) [–0.65–0.82]	.642

Note: Data as median, interquartile range in ( ) and range in [ ]; p-values derived from U-test (not normally distributed variables) or from unpaired t-test (normally distributed variables).

aged 10–15 years reported that approximately half of adolescent boys with gynaecomastia have persistent breast swelling. Mieritz et al reported in a nine-year longitudinal study that 19 (37%) of

52 boys with gynaecomastia still had breast development at the end of the study.<sup>7</sup> These two studies did not differentiate between lipomastia and gynaecomastia by ultrasound. Therefore, it is not

ruled out that there was a transformation from gynaecomastia to lipomastia according to our study in those cases with persistent breast swelling. One might speculate that this transformation is the result of distension of the skin through breast tissue during the period of gynaecomastia which -when breast tissue disappeared- did not normalize completely. The feature in ultrasound at follow-up seems to represent at least in part the subcutaneous adipose tissue.

The only significant predictor for a decrease of breast swelling in our pubertal boys with gynaecomastia was the reduction in BMI-SDS during the observation period, while all hormones at baseline were not related to breast regression in our study. Since many boys converted from gynaecomastia to lipomastia during follow-up and lipomastia is related to weight status<sup>3</sup> it seems not surprising that changes of BMI-SDS were a predictor of breast regression. However, the likelihood that glandular tissue remained in our cohort was independent from change of BMI-SDS or any hormone determined at baseline. The lack of an impact of sex hormones on the breast regression or disappearance of breast glandular tissue in ultrasound in our study maybe explained with the hypothesis that hormonal changes (oestrogen/androgen imbalance) precede the enlargement of breast tissue and are not detectable at presentation.<sup>10</sup> However, we have reported previously an E2/T imbalance in pubertal boys with gynaecomastia in contrast to pubertal boys with pseudogynaecomastia or without breast enlargement.<sup>3</sup>

Apart from sex hormones a role of the growth hormone (GH) / IGF-1 axis on the pathogenesis of gynaecomastia has been speculated,<sup>7</sup> since enlargement of mammary glands following exogenous GH administration has been observed.<sup>18,19</sup> A significant positive association between breast enlargement and IGF-1 levels in pubertal boys has been reported in two studies from the same research group,<sup>7,9</sup> while confirmatory studies are missing. In our study IGF-1 concentrations at baseline were not a predictor of breast regression or disappearance of breast glandular tissue in ultrasound.

#### 4.1 | Strengths and limitations of the study

The strengths of this study are analysing a cohort of pubertal boys with manifestation of gynaecomastia at a typical age around 13 years of age,<sup>1,6,7,20,21</sup> analyses of a comprehensive profile of sex hormones and their precursors by a state-of-the-art LC-MS/MS multisteroid profiling method<sup>12</sup> and the differentiation between lipomastia and gynaecomastia by ultrasound. The latter is of importance since many other studies reported that boys with breast enlargement are frequently obese.<sup>1,6,22</sup> Our findings suggest that boys with lipomastia were likely included in most previous studies of adolescent gynaecomastia making previous studies difficult to interpret.

However, our study presents some potential limitations. First, only one third of the initial study population agreed to participate in this follow-up examination probably leading to a selection bias. Therefore, we cannot exclude that the number of boys with complete regression of their breast enlargement is higher than in our

cohort. Therefore, we cannot give an exact number of boys with gynaecomastia who will convert to lipomastia. Assuming that all 55 boys with gynaecomastia who did not agree to participate in this longitudinal study had a complete breast regression, the portion of boys converting from gynaecomastia to lipomastia would still be 31%. Second, we cannot exclude the possibility that other androgens and oestrogens or sex hormone binding globulins not measured in this study might influence the development of physiological gynaecomastia. For example, 11-ketotestosterone is very abundant in pubertal children and active at the androgen receptor.<sup>23,24</sup> and the desulfation of E1 sulphate to E1 might play also a role.<sup>25</sup> Third, we have not measured pubertal stages, sex hormones or IGF-1 during or at the end of the follow-up period. We decided to avoid blood drawing and to avoid displeasing examinations to have the highest number as possible of boys with available follow-up. Fourth, serum samples do not necessarily reflect the intra-tissue conditions in the breast. For example, subcutaneous skin seems to contribute significantly in the biosynthesis of steroidogenesis including sex hormones.<sup>26</sup> Fifth, the differentiation between adipose and breast glandular tissue has not been proven by histological biopsies due to ethical reasons. Sixth, the follow-up period might be too short for detecting complete regression of the breast enlargement. However, previous longitudinal studies have reported that gynaecomastia lasts usually between <1-2 years.<sup>7,8</sup> Therefore, our observation period of in mean > 2 years seems not to be too short. Furthermore, in the majority of the boys gynaecomastia was not detectable in ultrasound even when a (smaller) breast enlargement exists. The finding of remarkable adipose tissue in ultrasound at follow-up points against a complete regression of breast enlargement in longer follow-up. Seventh, our multiple linear regression model explains only 19% of variance of the breast regression suggesting further important contributors. Finally, due to the moderate study sample our study is rather hypothesis generating and does not allow final conclusions.

In summary, we were not able to identify in pubertal boys with gynaecomastia a special hormone profile predicting breast regression or disappearance of breast glandular tissue in ultrasound. We found a remarkable portion of boys converting from gynaecomastia to lipomastia at the follow-up examination. An important factor for the regression of breast enlargement seems to be the change of weight status in pubertal boys. Therefore, boys with gynaecomastia should be advised not to increase their weight status to avoid lipomastia. Future larger longitudinal studies with lower drop-out rates are necessary to estimate the number of pubertal boys with gynaecomastia converting to lipomastia and to confirm our observation that change of weight status is related to breast regression.

#### ACKNOWLEDGMENTS

We thank the participating boys.

#### CONFLICT OF INTEREST

TR and PH received grant support from Ferring for this study. However, the hypothesis development, analysis, interpretation and



conclusions contained in this study are those of the authors' alone. AB and JA have nothing to declare.

## AUTHOR CONTRIBUTION

Thomas Reinehr and Paul Martin Holterhus developed the study design, Thomas Reinehr and Andre Barth performed the anthropometrical measurements. Jonas Ackermann performed the ultrasound measurements. Alexandra Kulle performed the laboratory measurements. Reinhard Holl supervised the statistical analyses. All authors discussed the findings and participated in writing of the paper. Thomas Reinehr wrote the first draft of the manuscript. He and Paul Martin Holterhus were the leading writers of the paper.

## DATA AVAILABILITY STATEMENT

Restrictions apply to the availability of data generated and analysed during this study to preserve patient confidentiality. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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**How to cite this article:** Reinehr T, Kulle A, Barth A, Ackermann J, Holl RW, Holterhus P-M. Transition from gynaecomastia to lipomastia in pubertal boys. *Clin Endocrinol (Oxf)*. 2021;94:583-589. <https://doi.org/10.1111/cen.14403>