

RESEARCH

Free triiodothyronine/free thyroxine ratio in children with congenital hypothyroidism

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Abstract

Thyroid-stimulating hormone is generally regarded as a standard parameter for the evaluation of thyroid function. However, relying on this hormone alone can be misleading. Therefore, thyroxine/free-thyroxine levels are used in patients with levothyroxine substitution for the adjustment of therapy. Even with normal values for free thyroxine, decreased values for the free-triiodothyronine/free-thyroxine ratio have already been described in adults. In this study, the free-triiodothyronine/free-thyroxine ratio of 25 children with congenital hypothyroidism was compared with 470 healthy children seen for other reasons and then for thyroid dysfunction. Mean free thyroxine in congenital hypothyroidism was just below the upper limit of normal and significantly higher than in control group. Mean values for free triiodothyronine showed no significant difference between the two groups. The mean value for the free triiodothyronine/free-thyroxine ratio in control group was 3.23. Significantly lower ratios were found in the congenital hypothyroidism group with a mean value of 2.5, due to higher values for free thyroxine compared to free triiodothyronine. Furthermore, an increased free triiodothyronine/free-thyroxine ratio was found at higher thyroid-stimulating hormone values due to lower values for free thyroxine. In this study, we demonstrate that the free triiodothyronine/free-thyroxine ratio was significantly lower in children with congenital hypothyroidism compared to the control group. This is most likely due to the higher values for free thyroxine in this group compared to similar values for free triiodothyronine in both groups. Further studies with differentiated thyroid hormone therapy are needed in order to understand the role of peripheral euthyroidism.

Key Words

- ▶ congenital hypothyroidism
- ▶ free triiodothyronine
- ▶ free thyroxine
- ▶ levothyroxine

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Introduction

Thyroid-stimulating hormone (TSH) is generally regarded as a standard parameter for the evaluation of thyroid function. However, in several conditions relying on TSH levels alone can be misleading, for instance in central hypothyroidism. Therefore, thyroxine/free thyroxine (T₄/fT₄) levels are used as an additional parameter for therapy adjustment in patients treated with levothyroxine (LT₄).

However, peripheral euthyroidism cannot be reliably assessed even with both parameters, as triiodothyronine/free triiodothyronine (T₃/fT₃) levels may be low (1, 2). In

healthy individuals, fT₃ levels can be stable over a wide range of corresponding TSH levels (3). The regulation of thyroid hormones is reflected in an adjusting fT₃/fT₄ ratio (4, 5). A significant proportion of adult patients receiving LT₄ therapy for hypothyroidism nevertheless report physical and mental fatigue (6, 7, 8, 9). Even adequate substitution with LT₄ and resulting fT₄ levels at the upper limit of normal do not always ensure normal serum fT₃ levels (1, 4, 5, 10, 11, 12, 13, 14). Two hypotheses could be put forward for this. First, it could

be related to altered activity of peripheral deiodinase (11, 15). Secondly, at least in thyroid patients, 20% of fT3, which is physiologically produced by the thyroid gland itself, would have to be replaced by additional conversion from substituted LT4 (5, 16).

Thus, not only do normal values for thyroid hormones reflect euthyroidism but also the ratio of fT3 to fT4 (5, 17). In children, fT3 levels correlate with body fat mass and onset of puberty but not fT4 or TSH levels. This could be due to the different functions of circulating fT3 and fT4 (18). Combination therapy with LT4 and LT3 has already been investigated in numerous studies with adult patients (5, 19, 20). However, meta-analyses could not demonstrate any benefit of such therapy forms (20, 21, 22). Mono-treatment with LT4 is still the standard therapy for hypothyroidism (17). In this context, there is an ongoing discussion on optimal thyroid hormone levels and the best parameter for laboratory surveillance of treatment.

Considering the crucial influence of thyroid hormones on cognitive functions and the overall development of the child, the most optimal adjustment of therapy in children with congenital hypothyroidism (cH) seems to be even more important than in adults. There are only a few studies to date that have investigated fT3 levels or the fT3/fT4 ratio in healthy children or children with cH (24).

In the present retrospective analysis, we aimed to compare pediatric values for fT3/fT4 ratio in children with cH receiving LT4 substitution and healthy controls.

Materials and methods

Patients

We conducted a retrospective study of pediatric patients (age, 0–17 years) with cH between December 2016 and December 2018 who were monitored for TSH, fT3 and fT4 levels in a long-term follow-up. All patients were seen at the Division for Pediatric Endocrinology at Dr von Hauner Children's Hospital based at the University Hospital Munich (LMU). The cohort comprises 25 patients (13 males and 12 females). The control group shows a higher age on a mean, but the reference values between the age groups are only minimally different according to the manufacturer of the test.

All blood samples were collected in the morning before the intake of medication (levothyroxine). The diagnoses were distributed as follows: 12 patients with thyroid hypoplasia/ dysgenesis, 9 patients with congenital athyreosis and 4 patients with normal thyroid sonography.

Overall, we could include 307 datasets (with 3–27 datasets per patient).

The control group (cG) comprises 470 patients (age, 0–19 years, 217 males and 253 females) who were seen at the Division for Pediatric Endocrinology for other reasons than thyroid dysfunction (e.g. evaluation of growth and pubertal development, congenital adrenal hyperplasia or diabetes type 1). Thus, we excluded the patients from the analysis with the following medical conditions: thyroid dysfunction, treatment with iodine, treatment with levothyroxine, positive thyroid autoantibodies, confirmed genetic diseases or syndromes and children with acute illness. However, we could include 707 datasets from the control cohort (with 2–7 datasets per patient).

Biochemical investigations

Thyroid hormone concentrations in serum were determined by a commercially available electrochemiluminescence immunoassay (ECLIA) for Roche Elecsys® according to the manufacturer's instructions. The thyroid hormone levels are expressed in the following units: TSH in $\mu\text{U/mL}$, fT4 in ng/dL and fT3 in pg/mL . The normal values (nv) for fT4 are 0.8–1.8 ng/dL and for fT3 2.6–5.0 pg/mL .

Statistical analysis

Statistical analysis was calculated using SPSS software for Windows version 15.0. Results are presented as mean in normal or median in non-normally distributed values, as applicable ($\pm\text{s.d.}$). Correlations between variables were determined by Spearman's method ($r_s = \text{Spearman's correlation coefficient}$). Throughout, the level of significance for each test was $P < 0.05$. For between-group comparisons, we used the Student's *t*-test or single-factor variance analysis (univariate ANOVA) and in case of non-normally distributed variables, the non-parametric Mann-Whitney *U*-test. Free triiodothyronine to free thyroxine ratio (fT3/fT4) was calculated by division without converting to the same unit.

Results

Mean values, median values, standard deviation scores (SDS) and ranges for age, TSH, fT4, fT3 and fT3/fT4 ratio for both groups are shown in Table 1. There was no sexual dimorphism (data not shown). In cH, the mean TSH value was significantly higher than in cG ($P < 0.001$) and single

Table 1 Mean values, SDS and range for age, fT4, fT3 and fT3/fT4 ratio in both groups and medians for TSH due to non-normally distribution of TSH.

		Age (years)	TSH ^a (μU/mL)	fT4 (ng/dL)	fT3 (pg/mL)	fT3/fT4 (ratio)
cH <i>n</i> = 25 (data sets: 308)	Mean	6.19	2.86	1.57	3.84	2.50
	SDS	4.14	5.38	0.26	0.56	0.48
	Minimum	1.00	0.02	0.75	2.00	1.40
	Maximum	17.00	31.30	2.60	6.60	4.35
cG <i>n</i> = 470 (data sets: 707)	Mean	11.30	2.1	1.23	3.91	3.23
	SDS	3.89	0.89	0.16	0.57	0.56
	Minimum	1.00	0.52	0.80	2.10	1.75
	Maximum	19.00	5.38	1.80	5.90	5.25

^aTSH values are shown as medians due to non-parametric distribution.

values showed high dispersion (Fig. 1 and Table 1). The value for TSH is not normally distributed so that a non-parametrical calculation of the difference using the Mann-Whitney *U*-test was carried out. This showed a significant difference in TSH (Fig. 1 between the two groups (*P* < 0.001). All other parameters shown had a normal distribution.

Mean fT4 in cH was just below the upper limit of normal (1.57 ± 0.26 ng/dL) and significantly higher than in cG (1.23 ± 0.16 ng/dL). Elevated values for fT4 up to 2.5 ng/dL were seen in 16.9% (the percentage always refers to the data sets) of the datasets in cH. In this subgroup, a decreased value for TSH was found only in 26.9%. In 4.7%, paradoxically even an increased value for TSH was found.

In cG, the values for fT4 showed a very narrow range in most patients (this is also evident from the very low standard deviation score of ± 0.16 ng/dL) and only minor deviations from the normal range with values from 0.8 to 0.9 ng/dL in 2.97% and from 1.7 to 1.8 ng/dL in 0.84% of the data sets.

Mean values for fT3 showed no significant difference between the two groups. In cH, the mean value was 3.84 pg/mL (±0.56), while in cG, the mean value was 3.91 pg/mL (±0.57).

For cG, the mean value for fT3/ fT4 ratio was 3.23 (±0.56). Significantly lower ratios were found in the cH with a mean value of 2.5 (±0.48), due to higher values for fT4 compared to fT3. There was no overlap of mean values

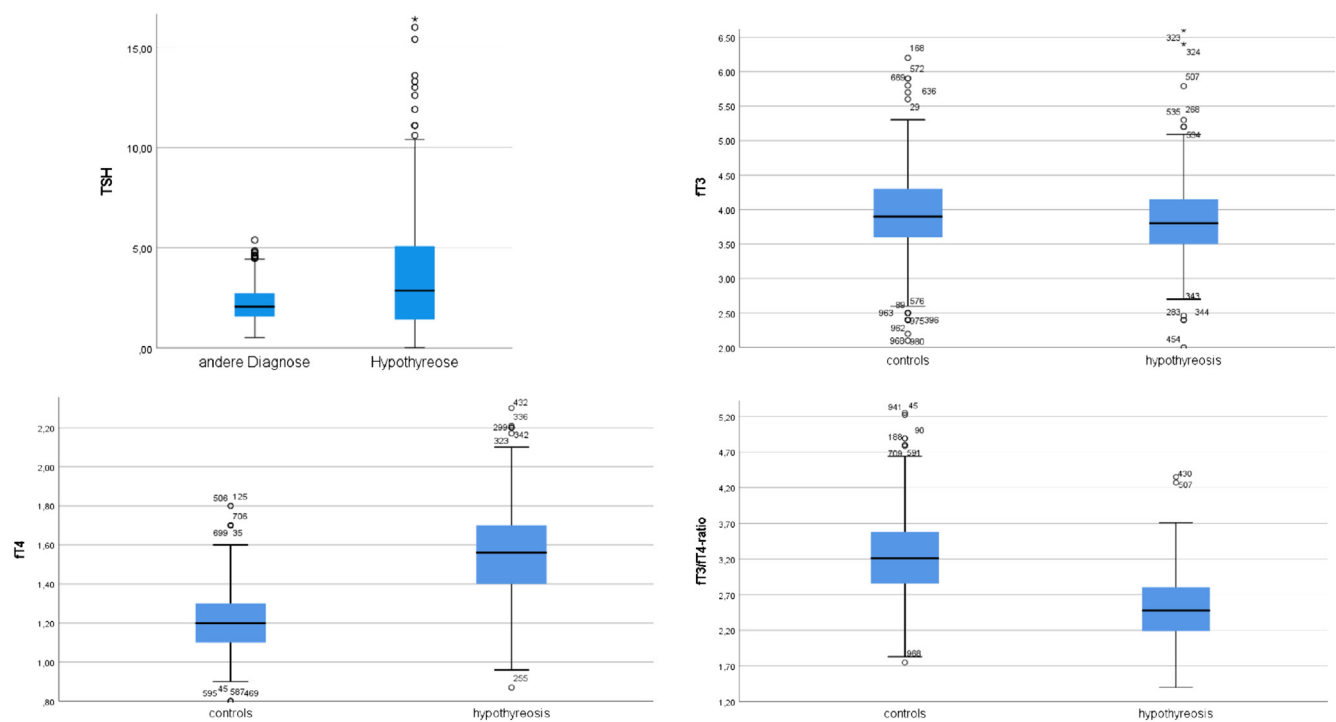


Figure 1

Mean values and SDS for fT4, fT3 and fT3/fT4 ratio in both groups and medians for TSH due to non-normal distribution of TSH.

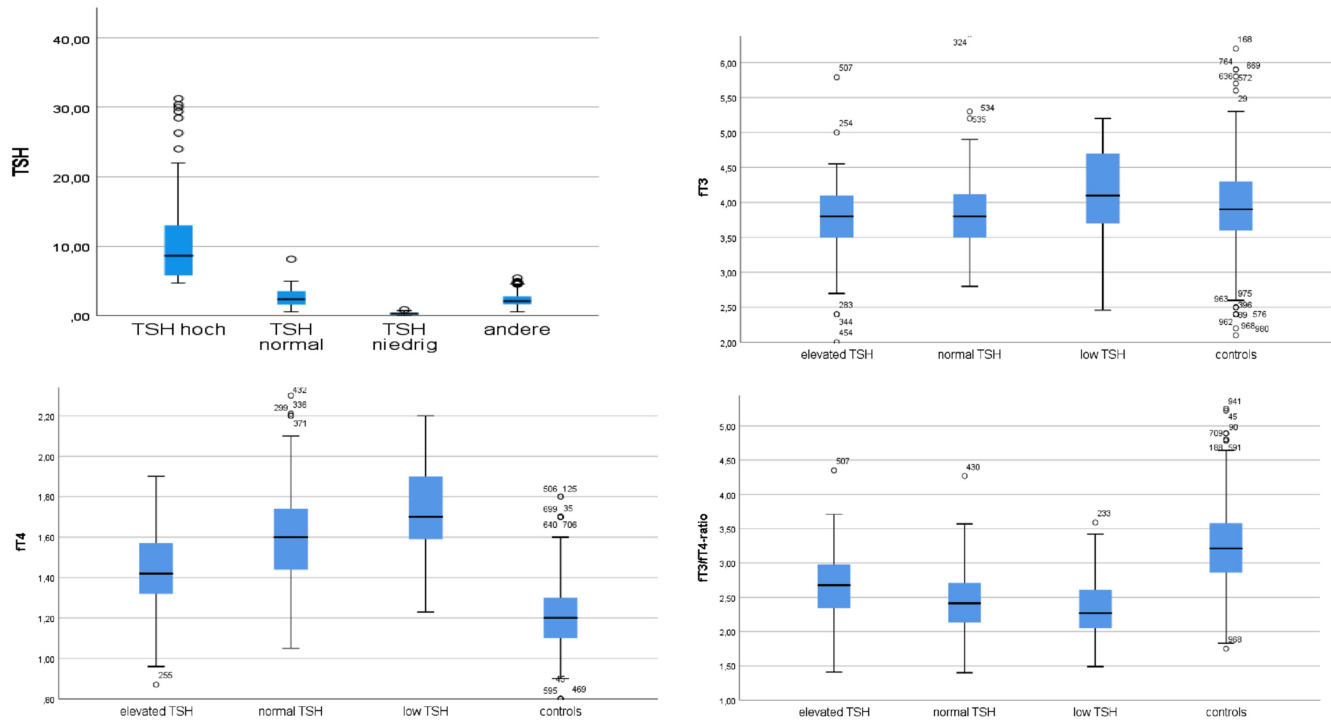


Figure 2

Mean values and SDS for ft_4 , ft_3 and ft_3/ft_4 ratio in elevated, normal, low TSH subgroups and control group and medians for TSH due to non-normal distribution of TSH.

in the comparison of ft_3/ft_4 ratios in the two groups. In only 18.5% in cH, the ft_3/ft_4 ratio showed values within the mean values for ft_3/ft_4 ratio ± 1 SDS of the cG.

These higher values for the ft_3/ft_4 ratio in cG can be explained by higher values for ft_3 and normal values for ft_4 , respectively.

Additionally, we analyzed subgroups with high (>4.0 $\mu\text{U/mL}$), normal ($0.5\text{--}4.0$ $\mu\text{U/mL}$) and low (<0.5 $\mu\text{U/mL}$) levels of TSH separately to exclude the influence of altered TSH levels on ft_3/ft_4 ratio (Fig. 2 and Table 2). Furthermore, it is evident that the value for ft_4 was lower and the ft_3/ft_4 ratio was higher with an

increasing TSH value in cH. For the ft_3 value, the difference in the subgroups was not statistically significant. However, in the subgroup of cH with normal TSH values, the mean ft_3 value was closest to the mean ft_3 value of cG: 3.84 and 3.92 pg/mL , respectively. The differences for the ft_3/ft_4 ratio between all TSH subgroups and the control group were statistically significant ($P < 0.001$).

Additionally, we divided the cH group into two subgroups with an ft_4 value below and above 1.5 pg/mL , respectively. We did this in order to investigate the influence of an elevated ft_4 value on the level of ft_3 (Table 3). This showed that 64.1% of the cH had an ft_4

Table 2 Subgroup analysis of high, normal and low TSH levels.

		Age (years)	TSH ^a ($\mu\text{U/mL}$)	ft_4 (ng/dL)	ft_3 (pg/mL)	ft_3/ft_4 (ratio)
cH	Elevated TSH	Mean	5.59	8.53	1.42	3.73
		SDS	4.07	6.97	0.19	0.59
	<i>n</i> = 82					
cH	Normal TSH	Mean	6.53	2.28	1.61	3.84
		SDS	4.26	1.2	0.26	0.5
	<i>n</i> = 193					
cH	Low TSH	Mean	5.64	0.18	1.74	4.15
		SDS	3.44	0.19	0.28	0.75
	<i>n</i> = 33					
cG	All	Mean	11.30	2.06	1.23	3.92
		SDS	3.89	0.89	0.16	0.57

¹Significant difference between ft_3/ft_4 ratio for 'elevated TSH' and 'all' ($P < 0.001$); ²Significant difference between ft_3/ft_4 ratio for 'normal TSH' and 'all' ($P < 0.001$); ³Significant difference between ft_3/ft_4 ratio for 'low TSH' and 'all' ($P < 0.001$); ^aTSH values are shown as medians due to non-parametric distribution.

value in the upper normal range. In comparison, only 8.3% of the cG had fT4 values in the upper normal range. TSH levels in the higher fT4 subgroup were similar compared to cG (2.26 μ U/mL compared to 2.20 μ U/mL).

In the subgroup of cH with higher values for fT4, the values for fT3 were also very similar to those of cG: 3.90 and 3.92 pg/mL, respectively. In the subgroup of cH with lower values for fT4, the values for fT3 were also lower compared to those of cG: 3.75 and 3.92 pg/mL, respectively. This difference was statistically significant ($P < 0.004$).

As a result, the fT3 /fT4 ratio was significantly lower in the subgroup with higher values for fT4 compared to the subgroup with lower values for fT4. However, the fT3/ fT4 ratio was significantly lower in both subgroups compared to cG.

Discussion

The values for TSH and fT4 are generally seen as the most important parameters for the therapy adjustment of patients with hypothyroidism. However, the role of fT3 is increasingly becoming the focus of attention. Treatment with LT4 results in higher levels of fT4. This in turn decreases the activity of the type 2 iodothyronine deiodinase (D2), which is responsible for the D2-catalyzed thyroid hormone production in peripheral tissue. This effect seems to be less pronounced in the hypothalamus/pituitary region (10,12,13). Thus, a decreased ratio of fT3/ fT4 may be a consequence of normalized values for TSH (under therapy with LT4) in combination with decreased values for fT3 in peripheral tissue.

To answer this question, we compared the levels of fT3, fT4, TSH and the fT3/fT4 ratio of children with cH under LT4 treatment and healthy children.

Here, we found significantly lower fT3/ fT4 ratios in children with cH as a consequence of significantly higher values for fT4 in this group. Values for fT3 were similar in both groups. However, even with low values for fT4, a near to normal fT3/ fT4 ratio cannot be achieved. Thus, our substitution therapy may be too unspecific (4, 5, 20, 24).

It can be suggested that, among other factors, the activity of deiodinases must differ in healthy children and children with cH and plays a role in thyroid hormone homeostasis. Furthermore, our data show that adjusting therapy according to TSH levels alone does not necessarily affect fT3 and fT4 values as targeted. It follows that adjustment of therapy by TSH values alone is not sufficient.

Higher target values for fT4 are often recommended under therapy with LT4 to achieve euthyroidism, which is often defined by normal values for fT3 (1, 4, 5, 10, 11, 12, 13, 14). This explains the relatively high values for fT4 in our cohort, which are oriented to the upper reference norm. This in turn could explain why we and other research groups found almost no values for fT3 below the reference range (5, 24). On the other hand, difficulties in restoring normal fT3 values in patients with hypothyroidism under LT4 treatment have been reported (1, 3, 4, 9, 11, 12, 14). In this context, it seems interesting that the values of fT3 differed only slightly in both groups despite the high variability of TSH values in cH.

A conceivable explanation for this could be the supposedly altered sensitivity of deiodinases in patients with cH and the consequent altered fT3 production (3, 4, 11, 15). However, it is also possible that the TSH value correlates with the required value for fT3 in the peripheral tissue and thus with the activity of the deiodinases. Deiodinase activity is thought to be decreased in patients with cH because normal levels of fT3 are difficult to achieve. In addition, the amount of fT3 (equivalent to approximately 20%) that is normally produced by the thyroid gland itself must be substituted via LT4 in patients with hypothyroidism (5). In this context, the limiting factor would be the activity of deiodinases or the amount of substituted LT4. As a result, fT4 gets to be the parameter steering the production of TSH in cH. From our point of view, this could explain why we have seen a correlation between TSH and fT3 (but not between TSH and fT4) in healthy children and a correlation between TSH and fT4 (but not between TSH and fT3) in children with cH.

Table 3 Subgroup analysis of fT4 levels above and below 1.5 pg/mL.

		Age (years)	TSH ^a (μ U/mL)	fT4 (ng/dL)	fT3 (pg/mL)	fT3/fT4 (ratio)
cH	fT4 < 1.5	Mean	6.01	4.00	3.75 ¹	2.85
	<i>n</i> = 111	SDS	4.24	6.70	0.51	0.44
	fT4 \geq 1.5	Mean	6.28	2.26	1.71	2.30
	<i>n</i> = 197	SDS	4.09	4.1	0.21	0.36
cG	All	Mean	11.30	2.20	3.92 ¹	3.23
	<i>n</i> = 707	SDS	3.89	0.89	0.16	0.56

¹Significant difference between fT3 values for 'fT4 < 1.5' and 'all' ($P < 0.004$); ^aTSH values are shown as medians due to non-parametric distribution.

In summary, the low values for the fT3/fT4 ratio in patients with cH are most likely explained by the increased value of fT4 under the LT4 treatment. Thus, the question arises of whether additional substitution with LT3 is necessary for this group of patients.

Our study had a few limitations. First, the data set in children older than 14 years was smaller than in the other age groups. A possible bias in the control group cannot be excluded, especially since some blood samples were not drawn in the morning. Important strengths of the study include its uncentered approach and longitudinal data analysis.

Conclusion

In this study, we demonstrated that the fT3/fT4 ratio was significantly lower in children with cH compared to the healthy control group. This is most likely due to the higher values for fT4 in this group compared to similar values for fT3 in both groups. The subgroup of patients with cH whose value for fT3 was closest to the control group was the group with normal TSH values, while the values for fT3 in the subgroups with lower or higher values for TSH were approximately the same distance from the mean value of the control group. The subgroup with fT3/fT4 ratio closest to the control group was the group with elevated TSH values. However, this does not provide a rationale for tolerating elevated TSH values, as no conclusions can be drawn about the associated (long-term) consequences.

The fT3/fT4 ratio in patients with cH who are substituted with LT4 could provide important complementary evidence regarding euthyroidism. This is of great importance in children with still-developing neuronal tissue. In this context, the fT3/fT4 ratio as a treatment parameter for LT4 therapy and the role of supplementary LT3 therapy should also be further investigated.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Statement of ethics

The authors have no ethical conflicts to disclose. This study protocol was reviewed and approved by Ethikkommission bei der Medizinischen

Fakultaet der LMU Muenchen, approval number 21-0958. According to the decision and due to the complete and irreversible anonymization of the data, it was not necessary to obtain written personal consent forms.

Data availability statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Author contribution statement

C Sydlik and I Dubinski contributed equally to the manuscript and share the first authorship. C Sydlik and I Dubinski analyzed the data and wrote the manuscript. H Schmidt and S Bechtold Dalla-Pozza contributed to study concept and data analysis. H Schmidt provided the patients' clinical data. All of the authors have significantly contributed to this study by providing intellectual input to the manuscript. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

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