Innovative Journal of Pediatrics
Volume 32 · Issue 1 · e116175

OPEN PEER REVIEW

Association Between Thyroid Parenchymal Echogenicity and Thyroid Function in Pediatric Population

Edis Çolak, Behzat Özkan

SUBMITTED	REVISED	ACCEPTED	DOI
12 May 2021	3 Dec 2021	26 Dec 2021	10.5812/ijp.116175

About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

More about open peer review: brieflands.com/knowledgebase/opr

Contents

1 **Original submission** Elsayed Abdelkreem 2
2 **Revision 1** Elsayed Abdelkreem 3
Authors' reply to reviewers 4
Reviewer and editor comments 14

1 Original submission

1 comment · 18 Jun 2021

Elsayed Abdelkreem Reviewer

MAJOR REVISION 18 Jun 2021

This retrospective study evaluated the association between thyroid parenchymal echogenicity and thyroid function in the pediatric population. The findings indicate the potential role of thyroid US in predicting thyroid function in the pediatric population. The study is generally well-written, with detailed methodology and adequate discussion. However, the following points should be addressed:

• In the abstract and manuscript, the authors state that "The current study is the first to compare the homogenous and heterogeneous thyroid echo pattern with thyroid function tests in children". However, as the authors state in the introduction, Jeong et al. (2019) (ref 5 in this study) investigated the association between thyroid echogenicity and thyroid function in pediatric and adolescent Hashimoto's thyroiditis, although with a smaller sample size (n = 86). Therefore, the authors should revise their wording.

• In the methodology, "The radiologist was blinded to the results of the thyroid function tests and the clinical status of the patients". How could the authors ensure this, given the retrospective nature of the study?

• In the methodology, the authors clearly described the classification and cutoffs of thyroid laboratory tests.

• Authors are encouraged to clarify the different models of multiple stepwise linear regression analysis shown in table 2 (in the statistical analysis as well as in the table footnote).

• In the discussion, given the paucity of previous pediatric studies on the study topic, authors are encouraged to discuss the possible differences between adult and pediatric populations regarding the association between thyroid parenchymal echogenicity and thyroid functions.

• In the discussion, authors are encouraged not only to further discuss the agreement/disagreement of the current study findings with previous studies but also to explain this agreement/disagreement (particularly disagreements).

• In the discussion, authors should highlight the clinical implications of their study findings.

• Authors should further discuss study limitations besides the retrospective study design, single-center setting, and small sample size. One of the major limitations is the subjectivity of US assessment, which may largely depend on experience (operator dependent). All cases in this study were evaluated by one board-certified radiologist; it would be meaningful to compare the level of agreement in US assessment among different radiologists in future studies. Another limitation may be the variable duration between the dates of US and thyroid function testing.

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

REPLAY TO REVIEWERS

Dear Professor Gholam-Reza Walizadeh,
Dear Professor Vahid Ziaee,

Thank you for giving us the opportunity to submit a revised draft of our manuscript titled "The Association between Thyroid Parenchymal Echogenicity and Thyroid Function in Pediatric Population" in *Iranian Journal of Pediatrics.*

We agree with all the comments and we have revised the manuscript accordingly. We are already crafting a revised version of the paper that states the hypothesis and the implications of this work more clearly than before.

We respond below in detail to each of the reviewer's comments. We hope that the reviewers will find the responses to their comments satisfactory, and we are willing to finish the revised version of the manuscript including any further suggestions that the reviewers may have.

Please, find below the referees' comments repeated in italics and the point-by-point response to the reviewers' comments and concerns. To facilitate the work of the reviewers, we have highlighted the changes within the lined manuscript.

We appreciate your valuable time for editing our manuscript. We hope this revised version is suitable for publication.

Sincerely,

Author’s Response to the Reviewer’s Comment

Response to comments from Reviewer 1:

1. Reviewer Comment:

This retrospective study evaluated the association between thyroid parenchymal echogenicity and thyroid function in the pediatric population. The findings indicate the potential role of thyroid US in predicting thyroid function in the pediatric population. The study is generally well-written, with detailed methodology and adequate discussion. However, the following points should be addressed:

1. Author’s Response:

Thank you for your your positive comments and valuable time in reviewing our manuscript.

2. Reviewer Comment:

In the abstract and manuscript, the authors state that “The current study is the first to compare the homogenous and heterogeneous thyroid echo pattern with thyroid function tests in children”. However, as the authors state in the introduction, Jeong et al (2019) (ref 5 in this study) investigated the association between thyroid echogenicity and thyroid function in pediatric and adolescent Hashimoto’s thyroiditis, although on smaller sample size (n = 86).

Therefore, authors should revise their wording.

2. Author’s Response:

We apologize for the misunderstanding. As we mentioned in the Background section Jeong et al. have reported the relationship between thyroid echogenicity and thyroid function tests in 86 children with Hashimoto's thyroiditis (Jeong SH, Hong HS, Lee JY. The association between thyroid echogenicity and thyroid function in pediatric and adolescent Hashimoto's thyroiditis. Medicine (Baltimore). 2019;98:e15055.) Actually, we wanted to emphasize that the present study is the first to investigate the correlation between the thyroid gland echo pattern and the

thyroid function in a large sample of children with both normal and heterogeneous thyroid parenchyma. However, we agree with your comment that this is not the first study in this field. According to the above, we have made the recommended changes and highlighted them in the following order:

A. Abstracts - Conclusions: The previous sentence 'The current study is the first to compare the homogenous and heterogeneous thyroid echo pattern with thyroid function tests in children.' has been modified by the new sentence ' The current study compared the homogenous and heterogeneous thyroid echo pattern with thyroid function tests in children.' Please see page 2; line 1.
B. Background: The previous sentence 'However, to the authors' knowledge, no previous study has investigated the correlation between the homogenous and heterogeneous thyroid gland echo pattern with the thyroid function in children.' has been modified by the new sentence 'However, to the authors' knowledge, this is the second study that investigated the correlation between the homogenous and heterogeneous thyroid gland echo pattern with the thyroid function in children.' Please see page 3; line 12.
C. Discussion: The previous sentence ' To the best of our knowledge, this is the first study to report an association between the normal and heterogeneous thyroid gland echo pattern with thyroid function tests in children.' has been modified by the new sentence ' This study reported an association between the normal and heterogeneous thyroid gland echo pattern with thyroid function tests in a large sample of children.' Please see page 9; lines 7- 9.
D. Discussion: The previous sentence 'The current study is the first to compare the homogenous and heterogeneous thyroid echo pattern with thyroid function in pediatric population.' has been modified by the new sentence 'The current study compared the homogenous and heterogeneous thyroid echo pattern with thyroid function in a large sample of pediatric subjects.' Please see page 10; lines 9,10.
E. Discusion – Conclusions: The previous sentence 'In conclusion, the current study was the first to investigate the association of the homogenous and heterogeneous thyroid echo pattern with thyroid function in children.' has been modified by the new sentence 'In conclusion, the current study investigated the association of the

homogenous and heterogeneous thyroid echo pattern with thyroid function in a large sample of children.' Please see page 13; lines 2,3.

3. Reviewer Comment:

In the methodology, "The radiologist was blinded to the results of the thyroid function tests and the clinical status of the patients". How could the authors ensure that given the retrospective nature of the study?

3. Author's Response:

Since the study was retrospective, during the ultrasound evaluation of the children radiologist was not informed about the study aim and thyroid function tests results. We agree with your comment that the authors can not ensure this statement. The previous sentence 'The radiologist was blinded to the results of the thyroid function tests and the clinical status of the patients' in the Methods - Evaluation of the findings section has been removed. Please see page 4; lines 18,19.

4. Reviewer Comment:

In the methodology, the authors clearly described the classification and cutoffs of thyroid laboratory tests.

4. Author's Response:

Thank you for your your positive comment.

5. Reviewer Comment:

Authors are encouraged to clarify the different models of multiple stepwise linear regression analysis shown in table 2 (in the statistical analysis as well as in the table footnote).

5. Author's Response:

Thank you for your valuable input in our manuscript. We have clearly defined the 4 Models of the multiple stepwise linear regression analysis. Moreover, we have added some new values and highlighted them in order to define more clearly the implications of the four models.

The previous Table 2 has been modified. The new version of Table 2 is presented below. Please see Table 2 (page 17).

Previous

Table 2. Results of Multiple Stepwise Linear Regression Analysis

Model	R	R Square	Adjusted R Square	SEE	F Change	p value
1	0.535[a]	0.286	0.284	0.423	172.96	<0.0001
2	0.566[b]	0.321	0.318	0.413	101.74	<0.0001
3	0.598[c]	0.358	0.353	0.402	79.82	<0.0001
4	0.615[d]	0.378	0.372	0.423	65.16	<0.0001

a.Predictors: (constant), TPOAb
b.Predictors: (constant), TPOAb, Tg-Ab
c.Predictors: (constant), TPOAb, Tg-Ab, TSH
d.Predictors:(constant), TPOAb, Tg-Ab, TSH, fT4

p-value ≤0.001 was considered highly significant; *SEE*, standard error of estimate

New version

Table 2. Predictors of Thyroid Gland Echo Pattern - Results of Multiple Stepwise Linear Regression Analysis

Predictors	Unstandardized coefficients		Standardized coefficient	*t*	%95.0 CI for *β*		R	Adjusted R Square	SEE
	β	SE	*β*		Lower bound	Upper bound			
Model 1 TPOAb [F (1, 432) =172.960, p<0.0001, R2 =0.286]	*0.284*	0.022	0.535	13.15	0.242	0.326	0.535	0.284	0.423
Model 2 TPOAb Tg-Ab [F (2, 431) =101.743, p<0.0001, R2 =0.321]	0.171 0.143	0.043 0.032	0.323 0.283	5.36 4.70	0.109 0.083	0.234 0.203	0.566	0.318	0.413
Model 3 TPOAb Tg-Ab TSH [F (3, 430) =79.823, p<0.0001, R2 =0.358]	0.146 0.150 0.123	0.031 0.030 0.025	0.275 0.295 0.196	4.64 5.03 4.98	0.084 0.091 0.074	0.208 0.208 0.171	0.598	0.353	0.402
Model 4 TPOAb Tg-Ab TSH fT4 [F (4, 429) =65.156, p<0.0001, R2 =0.378]	0.143 0.152 0.108 0.220	0.031 0.029 0.025 0.059	0.269 0.300 0.172 0.144	4.60 5.20 4.37 3.74	0.082 0.095 0.059 0.104	0.204 0.210 0.156 0.336	0.615	0.372	0.396

p-value ≤0.001 was considered highly significant; SEE, standard error of estimate; SE, standard error; %95.0 CI for β, %95.0 Confidence Interval for β.

6. Reviewer Comment:

In the discussion, given the paucity of previous pediatric studies on the study topic, authors are encouraged to discuss the possible differences among adult and pediatric populations regarding the association between thyroid parenchymal echogenicity and thyroid functions.

6. Author's Response:

According to your recommendations, we added the *differences among adult and pediatric populations regarding the association between thyroid parenchymal echogenicity and thyroid functions* in the Discussion section as 'Unlike adult patients, younger patients show a weaker association between heterogeneous thyroid echo patterns and high thyroid hormone levels which might be partly attributable to the fact that children are diagnosed earlier in the euthyroid stage of autoimmune thyroiditis (5,8). Heterogeneous thyroid parenchyma on US in pediatric patients with normal thyroid hormone profiles should be regarded as an early sign of thyroid failure.' Please see page 11; lines 1-5.

7. Reviewer Comment:

In the discussion, authors are encouraged to further discuss not only the agreement/disagreement of the current study findings with previous studies but also explain this (particularly disagreements).

7. Author's Response:

According to your recommendations, we explained the both agreement and disagreement of the current study findings with previous studies in the Discussion section as

'Since the thyroid hormone levels at presentation may vary between euthyroidism and hypothyroidism or hyperthyroidism in children with thyroid disorders, thyroid antibody positivity is an important marker in the diagnosis of thyroid disorders and also matches well with the heterogeneous appearance on thyroid US. However, it does not match in nearly 40% of both

pediatric and adult patients, which is in concordance with previous studies that indicate the presence of heterogeneous thyroid echogenicity prior to the appearance of thyroid antibodies (9,10).' Please see page 10; lines 14-21.

And,

'Unlike adult patients, younger patients show a weaker association between heterogeneous thyroid echo patterns and high thyroid hormone levels which might be partly attributable to the fact that children are diagnosed earlier in the euthyroid stage of autoimmune thyroiditis (5,8). Heterogeneous thyroid parenchyma on US in pediatric patients with normal thyroid hormone profiles should be regarded as an early sign of thyroid failure.' Please see page 11; lines 1-5.

8. Reviewer Comment:

In the discussion, authors should highlight the clinical implications of their study findings.

8. Author's Response:

According to your recommendations, we added the clinical implications of our study in the Discussion section as ' These results confırm that the homogeneous echo pattern of the TG is able to predict the euthyroid pediatric subjects with a high degree of precision, however, it does not in approximately 20% of cases. This evidence may support the clinicians to consider thyroid function examination in a diagnostic work-up in children with normal thyroid US as well. On the other hand, all the thyroid function tests were within normal ranges in 14.6% of children with heterogeneous echo patterns of the TG. These findings strengthen the role of the thyroid US in the diagnosis of thyroid disorders in apparently healthy children.' Please see page 12; lines 7-13.

9. Reviewer Comment:

Authors should further discuss study limitations, besides retrospective study design, single-center, and small sample size. One of the major limitations is the subjectivity of US assessment, which may largely depend on experience (operator dependent).

9. Author's Response:

As recommended a new sentence has been added in the Limitation section 'The subjectivity of the ultrasound assessment has been seen as a limitation of our study as well.' Please see page 12; lines 19,20.

10. Reviewer Comment:

All cases in this study were evaluated by one board-certified radiologist; it would be meaningful to compare the level of agreement in US assessment among different radiologists in future studies.

10. Author's Response:

As recommended, the previous sentence in the Limitation section 'Prospective multicenter studies are recommended to confirm our findings.' has been modified as 'The ultrasound evaluations were performed by a single radiologist, thus, inter-observer variability should be taken into account in future prospective multicenter studies.' Please see page 12; lines 20,21.

11. Reviewer Comment:

Another limitation may be the variable duration between the dates of US and thyroid function testing.

11. Author's Response:

As recommended a new sentence has been added in the Limitation section 'Third, the ultrasound assessments were undertaken at a variable duration after thyroid function testing.' Please see page 12; lines 18,19.

Response to comments from Associate Editor:

Associate Editor's Comments:

Your manuscript was reviewed by our reviewers. The reviewer has raised concerns regarding the manuscript, and therefore, your paper is not acceptable for publication in this format. However since the reviewers do find some merit in the paper, I would be willing to reconsider if you wish to undertake major revisions and re-submit, addressing the referees' concerns.

Please note that resubmitting your manuscript does not guarantee acceptance, and that your resubmission will be subject to a re-review before a decision is rendered.

Author's Response:

We appreciate your valuable time for editing our manuscript. We agree with all the comments and we have revised the manuscript accordingly. We respond below in detail to each of the reviewer's comments. We hope this revised version is suitable for publication.

2 Revision 1

1 comment · 24 Dec 2021

Elsayed Abdelkreem Reviewer

ACCEPT 24 Dec 2021

The authors adequately responded to the reviewers' comments.