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RESEARCH ARTICLE

Thyroid Function Screening among First- and Second-Degree Healthy Asymptomatic Relatives of Patients with Hashimoto's Thyroiditis

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Abstract:

Objective:

Assessment of thyroid dysfunction among relatives of patients diagnosed with Hashimoto's thyroiditis is controversial due to the lack of evidence.

Screening and prediction of thyroid dysfunction among first- and second-degree relatives (FDRs and SDRs) of patients were diagnosed with Hashimoto's thyroiditis.

Materials and Methods:

Three hundred and forty-six asymptomatic relatives of 97 patients diagnosed with Hashimoto's thyroiditis were enrolled in mixed cross-sectional and prospective assessments for thyroid dysfunction over more than two years (September 2018-December 2020).

Both FDR and SDR were evaluated by thyrotropin (TSH) and thyroid ultrasound at enrollment. Individuals with abnormal TSH were thoroughly evaluated biochemically and were subsequently classified as euthyroid, subclinical, and overt thyroid dysfunctional. The future reversion of enrolled individuals with normal and subclinical thyroid function to overt dysfunction was predicted by using the Thyroid Event Amsterdam (THEA) score.

Results:

Three-quarters of the participants were non-smoking married women. Thyroid dysfunction was diagnosed among 43% of the participants (n=150), of whom two-thirds (74%) were having overt dysfunction (n=111). Neither the demographic elements nor the initial thyroid function could predict the future thyroid function among those participants. Two out of ten (16%) were having autoimmune thyroid disease (AITD) as part of familial clustering (n=56). Four participants with subclinical hypothyroidism were treated accordingly due to their high THEA score despite the global lower THEA score (5.00±0.44).

Conclusion:

Screening of asymptomatic relatives of patients diagnosed with Hashimoto's thyroiditis could help identify the familial background of thyroid diseases in 43% of FDRs and SDRs. One-third may have an underlying autoimmune basis.

Keywords: Antithyroid antibodies, Autoimmune, Familial, Hyperthyroidism, Hypothyroidism.

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1. INTRODUCTION

The current guidelines have insufficient evidence to support the screening of asymptomatic, nonpregnant family members of patients with Hashimoto's thyroiditis, with no consensus to determine whether screening would reduce cardiovascular disease or related future mortality and morbidity [1 - 3].

The evidence-based guidelines recommended screening the thyroid function for families with a history of congenital hypothyroidism only [4, 5]. The screening of other age groups was individualized based on aggressive case findings and not in the form of universal screening [1].

The familial clustering of any disease may show shared

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pathogenic intrinsic (genetic) and extrinsic environmental factors or a combination of the two [6, 7]. The coexistence of Graves' and Hashimoto's disease within one family may suggest the genetic rule in these diseases [7].

The relatives of patients with autoimmune thyroid disease (AITD) may show the aggregation of the disease phenotype. They may show up to nine folds higher frequencies to be affected than the general population [8, 9].

The primary screening test for thyroid function is the thyroid-stimulating hormone (TSH). Still, repeating the test is needed for confirmation of the abnormal findings. The abnormal TSH may be followed by a free thyroxine (FT4) level to differentiate between subclinical and overt thyroid dysfunction [2].

The primary objective is thyroid function screening for asymptomatic healthy FDRs and SDRs of patients diagnosed with Hashimoto's thyroiditis. The secondary objective is the prediction of hypothyroid and hyperthyroid events in the next five years.

2. MATERIALS AND METHODS

2.1. Design and Setting

A mixed cross-sectional and prospective evaluation of the thyroid function of 346 asymptomatic FDRs and SDRs of patients with Hashimoto's thyroiditis was done in Faiha Specialized Diabetes Endocrine and Metabolism Center (FDEMC) in Basrah- Southern Iraq, between September 2018 and December 2020. Ninety-seven patients with previously proven Hashimoto's thyroiditis were advised to bring their asymptomatic FDRs and SDRs older than 14 years old for a voluntary thyroid function examination.

The FDRs include father, mother, siblings, sons, and daughters. The SDRs include aunts, uncles, nieces, nephews, grandchildren, grandparents, half-siblings, and double cousins [10].

The sample size was calculated according to the equation $\{\mathbf{N = P\ (1\text{-}P)\ Z^2\ /d^2}\}$ N = the minimum required size of the sample was (N = 277 cases), p = proportion of thyroid dysfunction among the population which was (18%) according to National Health and Examination Survey (NHANES), z = confidence level that will be used (z = 1.96 for 95%), d = is the desired margin of error (=0.05). The real number of cases in this study was (346) for more satisfaction and to avoid any potential sources of bias.

The number of FDRs and SDRs which were supposed to enter the study was 625 individuals. The total number of respondents who agreed to screening was 493 relatives (78.9%). Out of the 493 relatives, We enrolled 346 relatives (70.2%) only after the exclusion of 147 individuals according to the following exclusion criteria: Drug history, which interferes with thyroxin metabolism like recent steroid use, oral contraceptive pills, hormonal therapy of any kind, biotin, antiepileptics, and heparin (n=74), pregnancy at any trimester (n=18), recent hospitalization in the last four weeks (n=9), active infectious and inflammatory conditions (n=13), history of any malignancy (n=4), and patients with previously diagnosed thyroid problems (n=29).

Initially, history was obtained and relevant clinical examination was conducted. The following variables were evaluated for general characteristics like the degree of relativity, gender, ethnicity, age, body mass index (BMI), marital status, and smoking status. The initial serum TSH test was the key screening test for determining thyroid dysfunction. All participants had a baseline ultrasound examination of the thyroid gland.

All enrolled participants were planned for re-testing by TSH during follow-up within three months to confirm the diagnosis according to the United States Preventive Services Task Force (USPSTF) recommendation [2]. We scheduled further TSH testing at six, 12, and 18 months. The neck ultrasound examination was arranged at 6, 12, and 18 months.

After an initial evaluation, individuals with aberrant TSH levels were exhibited to additional evaluation for their thyroid function accordingly by the FT4 test to differentiate between overt and subclinical thyroid dysfunction.

Two types of thyroid antibodies have been measured in the study (anti-thyroid peroxidase (Anti-TPO) antibody and thyrotropin receptor antibody (TRAb), aka anti-thyroid stimulating hormone receptor (Anti-TSHR antibody). Due to the frequent unavailability of them in our center due to the cost, Anti-TPO was selectively measured for cases of subclinical hypothyroidism, while TRAb was selectively measured for cases of subclinical hyperthyroidism. Thyroid function was estimated by immunoassay analysis through electrochemiluminescence technology by COBAS e411-Roche diagnostics (Germany).

An expert radiologist did thyroid ultrasound for the enrolled individuals using either (Philips Affiniti 30. Netherlands) or (LOGIQ E9. GE Healthcare). Baseline thyroid ultrasound was performed to highlight the structure of the thyroid gland, whether nodular thyroid disease or any suggestive features of possible Hashimoto's thyroiditis, which include (diffusely enlarged heterogeneous echotexture thyroid gland, micro-nodular appearance (1-6 mm) or giraffe pattern, and the patterns of the vascular flow by color Doppler study).

After a thorough evaluation, the individuals were categorized according to their thyroid function tests to normal, subclinical, and overt thyroid dysfunction. The normal reference values at FDEMC were TSH (0.27 - 4.2 μIU/mL), FT4 (12.0 – 21.87 pmol/L), TPO antibody (<34 IU/mL), and TRAb (<1.5 IU/mL). Subclinical hypothyroidism was considered when the TSH level exceeds the upper threshold reference value but FT4 within the reference range [11]. Subclinical hyperthyroidism was considered in asymptomatic individuals with serum TSH levels below the lower threshold reference value but normal T4 and triiodothyronine (T3) levels [11]. Overt hypothyroidism criteria were elevated TSH level and a low T4 level [2]. Overt hyperthyroidism criteria were low or undetectable TSH level and an elevated T4 or T3 level [2].

Individuals were followed for 18 months to monitor the progression of their thyroid status. We used Thyroid Event Amsterdam (THEA-score) at the end of the study, which is

available at https://kresserinstitute.com/tools/thea/index.php?reset=1, for estimation of the five-year predicted future risk for 166 individuals with normal or subclinical thyroid status. THEA score may help to predict hyperthyroid and hypothyroid events in the next five years [12]. The categories of the THEA-score are four: low THEA-score (0 – 7) in which no intervention should be done; medium THEA-score (8 – 10), which necessitates annual thyroid function screening, high THEA-score (11 – 15) and very high THEA-score (16 -18) in which treatment is recommended.

The ethical committee of FDEMC provided ethical approval for the study (E2/10/2018) given in September 2018 and the Declaration of Helsinki was adequately addressed.

2.2. Statistical Analysis

The IBM Software Statistical Packages for Social Sciences (SPSS) Version 26.0 (Armonk, NY: IBM Corp.) was used to analyze the data. The study used the median±standard error (SE) to describe the continuous variables, to overcome the effect of extreme values, and the effect of being non-normally distributed data. The frequency (%) for data expression was used for categorical variables. The chi-square test was used to test the relationship between the categorical variables. A two-tailed ($p \leq 0.05$) was considered to be statistically significant.

3. RESULTS

Table **1** shows the general characteristics of the enrolled cohort. The nature of relationships between various variables to the initial thyroid status at the enrollment visit is described in Table **2**. Neither the degree of relativeness, gender, age, marital status, nor BMI had any significant association or relationship with the thyroid function status. Not all relatives had all the complementary thyroid function investigations, but only the relevant ones on a case-by-case basis.

Table 1. General characteristics of the enrolled individuals.

Variables		**Results n [%)**
Degree of relativeness	First	268 [77.46%)
	Second	78 [22.54%)
Women		277 [80.06%)
Non-black race		337 [97.40)
Married		262 [75.72%)
Non-smokers		340 [98.27)
Age	Median ± SE	34 ± 1
	Range	14 – 70
	Young 14 – 24 years	102 [29.50%)
	Adults 25 – 64 years	236 [68.20%)
	Old > 65 years	8 [2.30%)
Body mass index [kg/m^2)	Underweight BMI <18.5	14 [4.05%)
	Normal weight BMI [18.5 – 24.9)	95 [27.46%)
	Overweight BMI [25.0 – 29.9)	119 [34.39%)
	Obese BMI ≥ 30	118 [34.10%)
Thyroid-stimulating hormone [TSH) [n=346)	Median ± SE µIU/Ml	3.10 ± .92
	Range µIU/mL	0.01 – 100
	Number of individuals with abnormal TSH	158 [45.67%)
Free thyroxine [FT4) [n=220)	Median pmol/L	14.16 ± 2.96
	Range pmol/L	.77 – 167.31
	Number of individuals with Abnormal FT4	114 [51.82%)
Thyroid peroxidase antibody [TPO) [n=153)	Median ± SE IU/mL	55.20 ± 16.48
	Range IU/mL	1.10 – 981.00
	Number of individuals with High TPO	80 [52.29%)
Thyrotropin receptor antibody [TRAb) [n=60)	Median ± SE IU/mL	1.95 ± 1.14
	Range IU/mL	0.20 – 34.00
	Number of individuals with High TRAb	33 [55.00%)
Thyroid ultrasound findings	Single nodule	7 [2.02%)
	Multinodular goiter	41 [11.85%)
	Ultrasound features of Hashimoto's thyroiditis	76 [21.97%)
	Normal	222 [64.16%)

Note: The categorical variables were described as number [percentage), while the continuous variables were expressed as median ± standard error.

Table 2. Relationships of some categorical variables to the nature of thyroid function in the healthy asymptomatic relatives of patients with hashimoto's thyroiditis.

Variables		Normal TFT [n=196) n [%)	Abnormal TFT [n=150) n [%)	p
Degree of relativeness	**First [n=268)**	154	114	.571
	Second [n=78)	42	36	
Gender	**Women [n=277)**	153	124	.288
	Men [n=69)	43	26	
Age	**Young 14 – 24 years [n=102)**	64	38	.160
	Adults 25 – 64 years [n=236)	126	110	
	Old > 65 years [n=8)	6	2	
Marital status	**Married [n=262)**	146	116	.541
	Unmarried [n=84)	50	34	
Body Mass Index [kg/m^2)	**Underweight [n=14)**	8	6	.313
	Normal [n=95)	57	38	
	Overweight [n=119)	73	46	
	Obese [n=118)	58	60	
TPO [n=153)	**High TPO [n=80)**	14	66	.000055
	Normal TPO [n=73)	35	38	
TRAb [n=60)	**High TRAb [n=33)**	7	26	.668
	Normal TRAb [n=27)	7	20	

Abbreviations: TFT, Thyroid Function Tests; TPO, thyroid peroxidase; TRAb, thyrotropin receptor antibody.

We dealt with the ultimate results of TPO antibody and TRAb, which were measured in some individuals as normal and abnormal results, *i.e.*, categorical variables. There was a significant relationship between TPO antibody and thyroid function status in some enrolled asymptomatic relatives.

About 36% of the cohort (n=124) had positive findings in ultrasound examination, which did not change throughout the 18 months of the follow-up (Table **1**).

Table **3** describes the different outcomes of diagnoses of thyroid status in the enrolled relatives over the study period. Abnormal thyroid function was found in 43% of the participants (n=150), of whom 74% had overt dysfunction (n=111). The family clustering of AITD was documented in 16% of the participants (n=56), *i.e.*, the positivity of TPO antibody or TRAb. There were 16 individuals whose thyroid function had reverted from subclinical hypothyroidism to overt hypothyroidism and necessitated treatment.

Four individuals with normal thyroid function had their thyroid status changed to subclinical hypothyroidism. Four cases with subclinical hypothyroidism were reverted to normal thyroid status at the end of the study, with no change in the final numbers of normal and subclinical hypothyroidism cases.

The availability of thyroid serological tests during the study limited the testing of all patients. There 14% of the individuals (n=48) were diagnosed with Hashimoto's thyroiditis. There were only eight cases of Grave's disease. All cases of overt thyroid dysfunction received the appropriate management accordingly.

Table 3. The initial and final diagnoses of the thyroid function status for 346 healthy asymptomatic relatives for patients with Hashimoto's thyroiditis.

Findings		Enrollment Visit [n=346)	Final Number at End of Study [n=346)	TPO Antibody [positive/total) [n=153)	TRAb [positive/total) [n=60)
Normal thyroid function		196 [56.65)		14/49	7/14
Subclinical hypothyroidism		54 [15.61)	38 [10.98)	13/29	3/4
Subclinical hyperthyroidism		1 [0.29)	1 [0.29)	1/1	1/1
Overt hypothyroidism	**Hashimoto's Thyroiditis** [a]	48 [13.87)	48 [13.87)	48/69	14/33
	Non-Hashimoto's hypothyroidism	38 [10.98)	54 [15.61)		
Overt hyperthyroidism	**Grave's disease** [a]	8 [2.31)	8 [2.31)	4/5	8/8
	Non-Grave's hyperthyroidism	1 [.29)	1 [.29)		

Abbreviations: TPO, thyroid peroxidase; TRAb, thyrotropin receptor antibody.

[a] The coexistence of both Hashimoto's thyroiditis and Grave's disease was encountered in one family. Two FDRs had Hashimoto's Thyroiditis, and one FDR had Grave's disease.

Table 4. Systemic endocrine diseases which were discovered during the follow up of 346 healthy asymptomatic relatives of patients with Hashimoto's thyroiditis.

Diseases[a]	Number of Patients [n=69)
Type 1 Diabetes Mellitus	1
Type 2 Diabetes Mellitus	24
Adrenal Insufficiency	5
Celiac Disease	5
Vitiligo	2
Polycystic Ovary Syndrome	28
Primary ovarian insufficiency	1
Hypoparathyroidism	1
Hyperparathyroidism	1
Microprolactinoma	1

Note: [a] All the 69 individuals had either normal thyroid function or subclinical thyroid dysfunction.

Table 5. The use of the Thyroid Event Amsterdam [THEA) scores for 166 individuals with normal and subclinical thyroid dysfunction who are relatives to patients with Hashimoto's thyroiditis at the end of the study. The 69 individuals who were diagnosed with other autoimmune diseases were not included.

Variables		Low THEA [0-7) [n=147)	Medium THEA [8-10) [n=15)	High THEA [11-13) [n=4)	Total
Median THEA score ± standard error		3.00 ± .34	9.00 ± .10	13.00 ± .50	5.00 ± .44
Degree of relativity	**First n [%)**	140 [90.91)	11 [7.14)	3 [1.95)	154
	Second n [%)	7 [58.33)	4 [33.34)	1 [8.33)	12
Gender	**Women n [%)**	127 [87.58)	15 [10.35)	3 [2.07)	145
	Men n [%)	20 [95.24)	0	1 [4.76)	21
Thyroid function status	**Normal n [%)**	141 [95.27)	7 [4.73)	0	148
	Subclinical hypothyroidism n [%)	6 [35.29)	7 [41.18)	4 [23.53)	17
	Subclinical hyperthyroidism n [%)	0	1 [100)	0	1
More than two relatives with Grave's disease n [%)		0	0	0	0
More than two relatives with Hashimoto's disease n [%)		19 [52.78)	13 [36.11)	4 [11.11)	36

Table **4** describes the accidentally discovered systemic illnesses during the follow-up period in 69 individuals who were healthy asymptomatic FDRs and SDRs of patients diagnosed with Hashimoto's thyroiditis. These 69 individuals had either normal thyroid function or subclinical thyroid dysfunction and were managed by another endocrinology team in the center.

The final number of the cohort that had their THEA score measured was 166 individuals, *i.e*., no overt thyroid dysfunction and no diagnosis of systemic diseases. The overall median THEA score at the end of the study for these individuals was low (5.00±0.44). It represented the five-year prediction for future hypothyroid or hyperthyroid events. Further actions were planned for the management of 19 individuals with a medium and high score between (8–13) by recommending annual screening for thyroid status. No further action for the individuals with low THEA scores was planned, as shown in Table **5**.

4. DISCUSSION

Screening includes the use of a simple test for healthy, non-diseased individuals to search for a hidden disease [13]. The screening for thyroid diseases in FDRs and SDRs is a controversial issue; still, the familial autoimmune clustering of thyroid problems is frequently encountered and implicated in the pathogenesis [6, 8]. The genetic impact may affect this clustering, especially in the FDR, who show higher risk [6], up to nine-fold than the general population [9]. This study showed that 43% of the enrolled asymptomatic relatives (n=150) had subclinical or overt thyroid dysfunction. The familial clustering of AITD of different phenotypes was encountered in 19% of the cohort (n=56), of whom a vast majority had a full clinical picture of Hashimoto's thyroiditis (n=48/56) and Grave's disease (n=8/56).

There was no single variable in the study that could determine or predict the thyroid function in relatives of patients with Hashimoto's thyroiditis. A family history of AITD could increase the risk of acquiring thyroid disease [3, 7], even if the relationship lacks significance.

The finding of healthy asymptomatic individuals with either normal or subclinical thyroid status with positive thyroid autoantibodies may implicate the thyroid autoantibodies as markers for future thyroid dysfunction [3, 7]. The phenomenon was evident in 16 individuals who had their thyroid function reverted from being subclinical to overt hypothyroidism. Four individuals had normal thyroid function and were diagnosed later with subclinical hypothyroidism.

A single abnormal TSH test ca not be a satisfactory marker to decide the decision of confirmatory diagnosis, therapeutic option, and the rate of remission to euthyroid state without intervention due to the physiological diurnal secretion of TSH and its high variability it [2]. Gharib *et al*. showed a lower percentage of individuals with subclinical hypothyroidism who progress to overt dysfunction in their joint statement [14]. The reversion to a normal thyroid state from the subclinical status without treatment is more observed in old persons [15]. The current consensus emphasized the possibility of overdiagnosing asymptomatic aberrant TSH (with or without abnormal T4 levels) that may return to normal, which never results in thyroid dysfunction, even if it progresses, particularly if TSH is < 10 mIU/L. Accurate interpretation of serum TSH levels is greatly affected by measurement variability and non-thyroidal conditions on the measurement [10]. Repetition of the TSH is needed, especially if the readings lie between 0.01 and 10 mIU/L [11, 16].

Although more than 27% of the study cohort (n=95) had an overt thyroid dysfunction, they did not express any specific symptoms. The term ‘’overt” does not need the existence of symptoms and may encompass only low or high T4 levels, with or without accompanying nonspecific symptoms, to diagnose overt hypothyroidism and hyperthyroidism, respectively [2].

The coexistence of thyroid disease with other autoimmune diseases is encountered shown in Table **3**, which is like many other studies [8, 17 - 19].

There is no consensus on when to start clinical intervention for patients with thyroid dysfunction to improve the outcome. There was an agreement about optimal thyroid health if the levels were between 0.4 and 2 mIU/l [2, 20]. According to the expert opinion, TSH >10 mIU/L was accepted as a threshold because this level was associated with a higher likelihood of progressing to overt thyroid dysfunction even if the person was formerly asymptomatic [2]. The is no consensus about the reversion rate of thyroid function from subclinical to overt thyroid dysfunction or vice versa.

Strieder *et al*. tried to set the possible future road map for persons with an average or subclinical thyroid function with a positive family history of AITD to predict the five-year risk of acquiring hypothyroid or hyperthyroid status, to necessitate treatment or not [12]. This was called the Thyroid Event Amsterdam (THEA) score, which used the biochemical levels of TSH and TPO, along with the presence of a strong family history of AITD. The THEA score categorized the individuals with normal or subclinical thyroid function according to their future risk to low, medium, high, and very high scores, with the intervention to be implemented according to the score [7, 12]. The prediction of which individuals would need treatment for their advancing thyroid status, from those who will normalize their thyroid status over time is not possible [2].

Only four persons with subclinical hypothyroidism (three women and one man) had been started with a weight-adjusted dose of thyroxin therapy and were considered as an (overt) hypothyroid case.

Because we do not have any national study to determine the risk of thyroid disease in the Iraqi population, we could not determine the thyroid dysfunction risk in the relatives of patients with Hashimoto’s thyroiditis in comparison to the general population.

Performing thyroid function for relatives of Hashimoto’s thyroiditis was a useful screening tool for possible thyroid dysfunction. The screening fulfilled Wilson and Jungner’s 1968 criteria in being a common endocrinopathy with a readily available, reliable, relatively inexpensive screening and intervention tool [13]. The management intervention may halt the disease progression and may limit the complications. Overall, the agreed-upon policies and guidelines are readily available to discuss whom to treat if overt thyroid dysfunction was diagnosed during the screening of asymptomatic healthy individuals who had a positive family history of Hashimoto’s thyroiditis.

Early detection of asymptomatic individuals with biochemical thyroid dysfunction may help prevent long-term morbidity and mortality from future complications. However, screening can result in overdiagnosis and some psychological upset from labeling. All potential clinical benefits and harm should be discussed with the individuals [2].

This study had limitations. Not all the FDRs and SDRs agreed for testing, which affected the total number of enrolled individuals. Secondly, although we chose strict exclusion criteria for case selection, the ascertainment of true *versus* false-positive thyroid function followed no consensus on what constituted an average reference interval nor what level needed intervention in asymptomatic subclinical cases. Third, not all of the cohort was screened for all thyroid antibodies or iodine levels due to logistic and availability reasons, so we could not generalize the results for all FDRs and SDRs for patients with Hashimoto's thyroiditis. We could not evaluate the possible selection bias caused by the acceptance of enrollment in the study to have free medical attention. We could not monitor the psychiatric consequences of establishing the diagnosis of overt thyroid dysfunction. The study lasted 27 months only, that is why we could not follow the long-term outcome of those healthy asymptomatic individuals, especially those with AITD.

Even if we were able to have an idea about the possible risks by THEA score for the women population, we were not sure about its validated use in the men population. Another limitation of the THEA score was the five years. Many individuals may have reversion after that period, and we did not use the sequential yearly THEA score to correct that assumption due to unknown validity for frequent measurements, which needs further follow-up.

CONCLUSION

Screening of asymptomatic relatives of patients diagnosed with Hashimoto's thyroiditis could help identify the familial background of thyroid diseases in 43% of FDRs and SDRs. One-third may have an underlying autoimmune basis. Five-year risk of developing overt thyroid dysfunction can be predicted by using both thyroid function tests and THEA-score. Less than half (43%) of the high-risk relatives had an evident familial clustering of thyroid dysfunction. Longer-term longitudinal studies with a larger number of cases are

mandatory to highlight these precise results.

AUTHORS' CONTRIBUTION

SAO and MJM conceived and designed the study. SAO, MTA, and AAM conducted the primary interview and follow-up. SAO provided research statistics and collected and organized data. MJM performed the ultrasound examination. AAM supervised the study process and provided logistic support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

LIST OF ABBREVIATIONS

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ETHICS APPROVAL AND CONSENT TO PARTICIPATe

The ethical committee of FDEMC provided ethical approval for the study (E2/10/2018) was given on September 2018.

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

All the enrolled 346 individuals agreed to sign an informed consent,

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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