

## CLINICAL STUDY

# The association between hypoechogenicity or irregular echo pattern at thyroid ultrasonography and thyroid function in the general population

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## Abstract

**Objective:** Patients with overt hypothyroidism show decreased echogenicity of the thyroid at ultrasonography (US). The aim of this study was to investigate the association between echogenicity of the thyroid/irregular echo pattern, and thyroid function in the general population, i.e. subjects without overt thyroid disease.

**Design:** A cross-sectional investigation of 4649 randomly selected adult subjects.

**Methods:** Blood samples were analysed for serum TSH, thyroid hormones and thyroid autoantibodies. US of the thyroid was performed.

**Results:** Participants with decreased echogenicity ( $n=379$ ) had a higher mean TSH (1.65 mU/l) compared with subjects with normal echogenicity (1.21 mU/l,  $P<0.0001$ ). The association was stronger in subjects with markedly decreased echogenicity (4.20 mU/l,  $P<0.0001$ ). A similar association was seen when the subjects were divided into subgroups according to the level of TSH; more subjects with high levels of TSH had decreased echogenicity ( $P<0.0001$ ). Likewise, more subjects with high levels of TSH had an irregular echo pattern ( $P<0.0001$ ). Subjects with decreased echogenicity had a higher risk of having thyroid autoantibodies than subjects without decreased echogenicity ( $P<0.0001$ ). This association was stronger when echogenicity was markedly decreased.

**Conclusions:** We demonstrated an association between hypoechogenicity at thyroid US and higher levels of serum TSH even in subjects without overt thyroid disease, suggesting decreased echogenicity as an early sign of thyroid dysfunction. Irregular echo pattern, whether accompanied by hypoechogenicity or not, was another possible marker of thyroid failure. This indicates a possible use of thyroid US in detecting early and subclinical thyroid dysfunction.

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## Introduction

The association between decreased echogenicity of the thyroid gland when examined with ultrasonography (US) and overt hypothyroidism is well known. The change in echogenicity has also been demonstrated in subclinical (mild) hypothyroidism (1–3). Since subclinical thyroid dysfunction has a tendency to develop into overt thyroid dysfunction (4), the finding of decreased echogenicity or irregularity in echo pattern at thyroid US in these patients with the elevation of thyroid-stimulating hormone (TSH) could perhaps be seen as an early sign of thyroid failure. Most previous studies concern patients with known Hashimoto's thyroiditis (1, 3, 5–9) or patients referred to a hospital with suspicion of thyroid disease (10, 11). One study (2)

concerns apparently healthy subjects from hospital staff. To our knowledge, no studies of hypoechogenicity and thyroid function have been performed in an unselected healthy population. Not only echogenicity, but also regularity of the echo pattern in the thyroid, varies between individuals. Often, distinct nodules can be detected with diameters of a few millimetres to several centimetres; but even without nodules, irregularity of echoes is frequently found. It has not previously been published whether irregular echo pattern in itself could be a marker of thyroid function. The aim of this study was to evaluate the association between thyroid echogenicity/irregular echo pattern and thyroid function in the general population without overt thyroid dysfunction.

## Subjects and methods

### Study population

This study was based on data from the Danish investigation of iodine intake and thyroid disease. The study was designed to evaluate the distribution of goitre and thyroid dysfunction in an area with mild to moderate iodine deficiency. A cross-sectional study of 4649 persons in two regions in Denmark, Aalborg and Copenhagen, with respectively moderate (median urinary iodine excretion 45 µg/l) and mild (median urinary iodine excretion 61 µg/l) iodine deficiencies (12) was performed prior to institution of iodization of salt in 2000. The cross-section was restricted to certain age groups; women aged 18–22, 25–30, 40–45 and 60–65 years and men aged 60–65 years, and was drawn from the Civil Registration System in which all subjects living in Denmark were registered. Palpable goitre was found in 10.9% participants and 17.3% had nodules larger than 10 mm. The study and its design are more extensively described elsewhere (13). For the present study, 228 participants were excluded due to known previous thyroid dysfunction and 42 participants were excluded due to present overt biochemical hyper- or hypothyroidism. Separate analyses were made on participants with overt biochemical hyper- or hypothyroidism. Data on either US findings or biochemical thyroid status were missing in 66 participants and 4313 participants were left for the analysis. Data on thyroid peroxidase autoantibodies (TPOAb) or serum thyroglobulin autoantibodies (TgAb) were missing on a further 32 and 30 participants respectively, who were consequently left out of the analysis on antibody status.

### Data collection

The participants answered a questionnaire regarding previous thyroid disease. The questionnaire was followed by an interview and clinical examination by a medical doctor. Ultrasonographic examination of the thyroid was performed with a Sonoline Versa Pro 7.5 MHz linear transducer (Siemens, Germany), effective length 62 mm. The echogenicity was evaluated by a standardized comparison of the echogenicity of the thyroid

with the echogenicity of the adjacent muscles: m. sternohyoideus, m. sternothyroideus and m. sternocleidomastoideus, in a longitudinal scan of the thyroid lobes. Echogenicity was categorized into five groups: markedly decreased, slightly decreased, normal, slightly increased or markedly increased (compared with muscles), judged by the examiner. Echo pattern was evaluated dichotomously as regular or irregular. Two examiners, each in Aalborg and Copenhagen, performed all the ultrasound examinations. An evaluation of the inter-observer variation between the two examiners performed prior to the study showed diversity in the interpretation/estimation of echogenicity, the one being more specific and the other being more sensitive (14), making it difficult to compare between the regions. However, in this study, no inter-regional analyses were made.

### Laboratory procedures

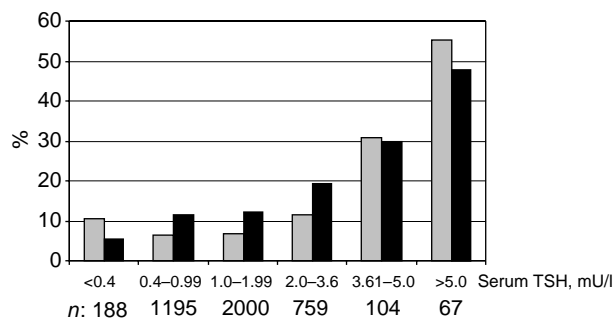
Thyroid status was evaluated from blood samples, which were drawn in connection with the US and stored at –20 °C. Subsequently, the samples were analysed in a sequence ensuring that the samples were mixed with respect to region, age, sex and season. Serum TSH, free thyroxine (fT4) and free tri-iodothyronine (fT3) concentrations were analysed with LUMItest (Brahms, Berlin, Germany). The functional sensitivity of the TSH assay was 0.01 mU/l. For the definition of normal thyroid dysfunction, a reference interval for serum TSH was defined as 0.4–3.6 mU/l, corresponding to the 2.5th and 97.5th percentiles of TSH among participants with no known thyroid disease, with TPOAb < 60 U/l (Dynotest, Brahms), with no thyroid enlargement and with no thyroid nodules at US. Level of TSH was divided into six classes: low (<0.4), low normal (0.4–0.99), normal (1.0–1.99), high normal (2.0–3.6), slightly elevated (3.61–5.0) and elevated (>5.0). Subclinical hypothyroidism was defined as serum TSH > 3.6 mU/l and absence of biochemical overt hypothyroidism, which was defined as serum TSH > 5 mU/l and fT4 < 9.8 pmol/l.

Reference intervals for fT3 and fT4 were defined as 2.5th–97.5th percentiles after the exclusion of participants with known thyroid disease or serum TSH outside

**Table 1** Mean serum thyroid-stimulating hormone (TSH) levels and risk of being thyroid peroxidase autoantibodies (TPOAb) positive (>30 U/ml) or thyroglobulin autoantibodies (TgAb) positive (>20 U/ml) in 4313 subjects from an adult Danish cohort without previous or present thyroid disease.

	N	Mean serum TSH, mU/l (CI)	TPOAb pos. (%)	Odds ratio TPOAb (CI)	TgAb pos. (%)	Odds ratio TgAb (CI)
Increased echogenicity	29	1.02 (0.80–1.31)	0	–	3.5	0.4 (0.0–2.7)
Normal echogenicity	3894	1.21 (1.19–1.24)	11.2	1 (Ref.)	11.3	1 (Ref.)
Mildly decreased echogenicity	379	1.65 (1.54–1.76)	32.1	3.5 (2.7–4.5)	27.9	2.9 (2.3–3.8)
Markedly decreased echogenicity	11	4.20 (2.82–6.27)	72.7	23.8 (6.1–93.5)	72.7	22.6 (5.8–87.8)

Participants with nodules detected at ultrasonography included. Data from linear (TSH) and logistic (TPOAb/TgAb) regression models adjusting for age, sex and region of inhabitancy. TSH used after logarithmic transformation. TPOAb data were missing for 32 individuals. TgAb data were missing for 30 individuals. CI, 95% confidence interval.



**Figure 1** The association between serum thyroid-stimulating hormone (TSH) (mU/l) in six classes and occurrence of hypoechoogenicity (grey) or irregular echo pattern (black) at thyroid ultrasonography in a, within age groups, randomly selected Danish cohort (n=4313). Subjects with overt thyroid dysfunction were excluded.

the reference interval, resulting in a reference interval of 9.8–20.4 pmol/l for fT4 and 3.6–6.9 pmol/l for fT3. Serum TPOAb was measured by RIA (DYNOfest anti-TPO; Brahms Diagnostica, Berlin). The functional sensitivity of the assay recommended by the manufacturer was 30 U/l, which has previously been confirmed in this material (15). TgAb was measured by RIA (DYNOfest anti-Tgn, Brahms Diagnostica). The functional assay sensitivity given by the manufacturer was 20 U/l, previously confirmed in this material (15).

**Statistical analysis**

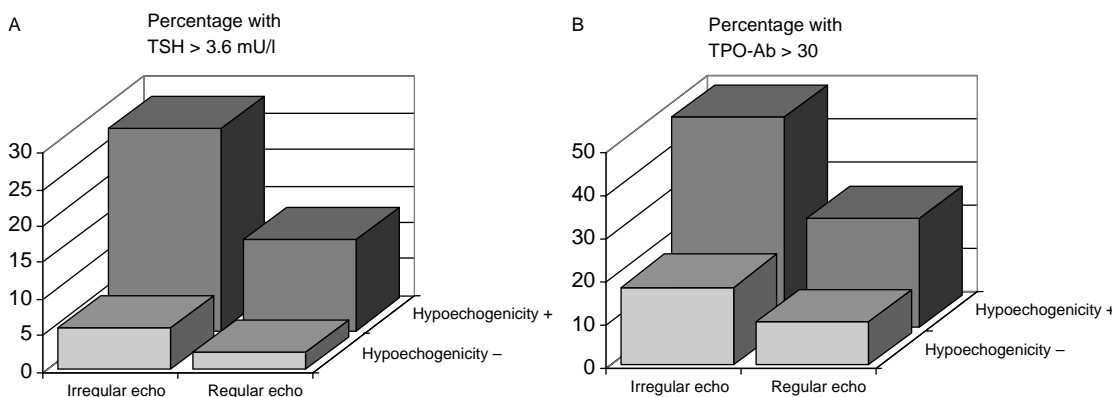
Data assessing was done with SAS version 9.1. For analysis on mean serum TSH values, linear models were used. This was done after logarithmic transformation of TSH values as these were skewed towards higher values. Adjustments were made for age, sex and region of inhabitancy. Logistic regression was used for studying occurrence of TPOAb and TgAb in relation to degree of echogenicity. Adjustments were made for age, sex and

region. Comparison between subjects at different TSH levels and between subjects with different combinations of echo pattern was done using Pearson’s  $\chi^2$ -test. The level of significance was set to 5%.

**Results**

Of the 4313 participants, 379 had mildly decreased echogenicity compared with adjacent muscles at US. These participants had a higher mean TSH (Table 1) compared with subjects with normal or increased echogenicity. The association was stronger when the subject had markedly decreased echogenicity.

A similar association was seen when the subjects were divided into subgroups according to the level of TSH; more subjects with high levels of TSH had decreased echogenicity (P<0.0001). When examined for irregular echo pattern, more subjects with high TSH levels had irregular echo pattern (P<0.0001; Fig. 1). Combining the judgement of irregular echo pattern and hypoechoogenicity was advantageous, compared with only judgement of hypoechoogenicity, in detecting subjects with subclinical hypothyroidism. When the US showed neither hypoechoogenicity nor irregular echo pattern, only a small proportion (2.2%) of subjects had subclinical hypothyroidism. These subjects were also more unlikely to be TPOAb positive than subjects with decreased echogenicity or irregular echo pattern. When participants showed both decreased echogenicity and irregular echo pattern, 48.5% were TPOAb positive (Fig. 2). Participants with decreased echogenicity had a higher risk, of being TPOAb positive and/or TgAb positive than participants without decreased echogenicity. This association was stronger when echogenicity was markedly decreased (Table 1). The association remained after excluding participants with thyroid nodules (Table 2). TPOAb showed a dose–response relationship with hypoechoogenicity, while the



**Figure 2** Percentage of subjects (n=4313) with (A) subclinical hypothyroidism, thyroid-stimulating hormone (TSH) > 3.6 mU/l or (B) thyroid peroxidase autoantibodies (TPOAb) > 30 U/ml, in relation to existence of only hypoechoogenicity (n=134), only irregular echo pattern (n=468), both (n=256) or neither (n=3455) in a, within age groups, randomly selected Danish cohort. Subjects with overt thyroid dysfunction were excluded.

**Table 2** Degree of echogenicity and risk of being thyroid peroxidase autoantibodies (TPOAb) positive (>30 U/ml) or thyroglobulin autoantibodies (TgAb) positive (>20 U/ml) among 3085 subjects from an adult Danish cohort without previous or present thyroid disease and without thyroid nodules at ultrasonography.

	N	TPOAb pos. (%)	Odds ratio TPOAb (CI)	TgAb pos. (%)	Odds ratio TgAb (CI)
Increased echogenicity	19	0	–	5.3	0.6 (0.1–4.8)
Normal echogenicity	2851	9.6	1 (Ref.)	11.0	1 (Ref.)
Mildly decreased echogenicity	206	36.3	5.0 (3.6–7.1)	31.2	3.5 (2.5–5.0)
Markedly decreased echogenicity	9	66.7	33.7 (5.5–97.9)	66.7	19.4 (4.6–81.4)

Data from a logistic regression analysis adjusting for age, sex and region of inhabitancy. Thyroid-stimulating hormone (TSH) used after logarithmic transformation. TPOAb data were missing for 22 individuals. TgAb data were missing for 20 individuals. CI, 95% confidence interval.

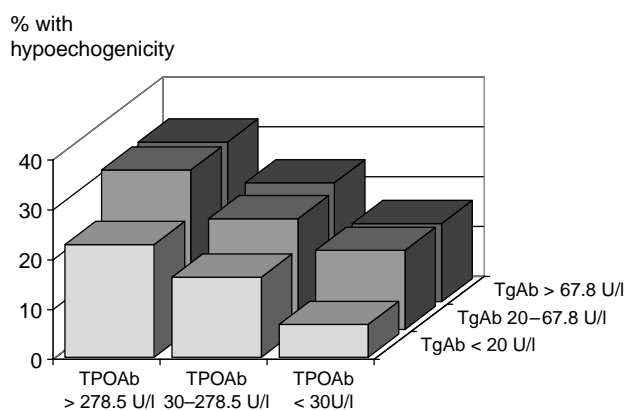
prevalence of decreased echogenicity did not differ significantly among participants with higher or lower positive levels of TgAb (Fig. 3). When studied in age groups, a stronger association between decreased echogenicity and mean TSH or TPOAb status was seen among the young participants (Table 3). There were no sexual differences. No age- or sex-related differences were found in the association between echogenicity and TgAb status. No significant differences in the level of TSH and occurrence of autoantibodies were found between the 29 participants with increased echogenicity (28 mildly increased, 1 markedly) and participants with normal echogenicity.

Participants with overt biochemical hypothyroidism ( $n=16$ ) had a high occurrence of decreased echogenicity (75%,  $P<0.05$ ). No significant association was found among participants ( $n=26$ ) with overt biochemical hyperthyroidism (34.6%,  $P=0.12$ ).

## Discussion

In this study of an unselected cross-section of the general population without prior or present overt thyroid dysfunction, we demonstrated an association between decreased echogenicity of the thyroid and high TSH, even with thyroid hormones in the serum within the reference range. Most other studies regarding echogenicity of the thyroid and its function, concern patients with known Hashimoto's disease (1, 3, 5, 7–9) or persons referred to a hospital for some kind of thyroid disease or symptoms (10, 11, 16) making a comparison difficult. All studies found an association between decreased echogenicity of the thyroid and overt hypothyroidism. In our limited subpopulation of participants with overt biochemical thyroid dysfunction, we also found an association between hypothyroidism and decreased echogenicity. A trend towards a high occurrence of decreased echogenicity among the participants with overt biochemical hyperthyroidism was found, but did not reach significance in this limited group. An association between the two has previously been demonstrated (17). One study examined apparently healthy subjects using hospital staff in a 3-year follow-up (2). They found that none of the subjects, who

developed thyroid dysfunction, had a normal echogenicity at thyroid US at inclusion. A similar result was found by Marcocci (11) in an 18-month follow-up of consecutive patients referred to a thyroid clinic. All the patients who developed hypothyroidism during follow-up had decreased echogenicity at baseline. This suggests hypoechogenicity as an early marker of hypothyroidism. Whether our study will confirm this finding remains to be seen following an expected follow-up. We found a higher occurrence of decreased echogenicity among subjects with high levels of TSH compared with subjects with average levels of TSH. This would be in agreement with the higher risk of developing thyroid disease among patients with subclinical hypothyroidism or TSH high in the reference range (4). Subclinical thyroid dysfunction may also be harmful in itself, for example, persons with subclinical thyroid dysfunction may have a higher risk of developing cardiac disease (18, 19) and have been found to have a higher mean body mass index and a higher occurrence of obesity (20). In addition to hypoechogenicity, we found that occurrence of irregular echo pattern was associated with subclinical hypothyroidism. Irregular echo pattern as another important marker of early thyroid failure has,



**Figure 3** Percentage of subjects ( $n=4313$ ) with hypoechogenicity, in relation to thyroid peroxidase autoantibodies (TPOAb) and thyroglobulin autoantibodies (TgAb) status in a, within age-specific groups, randomly selected, Danish cohort. Subjects with overt thyroid dysfunction were excluded. The antibody status was divided into three groups: negative, lower than median, and higher than median. The linearity was checked in a linear regression model.



**Table 3** Age-related relative increase of mean thyroid-stimulating hormone (TSH) with mildly decreased echogenicity ( $n=379$ ) versus normal echogenicity and age-related odds ratio for being thyroid peroxidase autoantibodies (TPOAb) positive among participants with decreased echogenicity ( $n=390$ ) compared with participants with normal or increased echogenicity.

	Relative increase in mean TSH with mildly decreased echogenicity versus normal echogenicity (CI)	Odds for being TPOAb positive. Decreased echogenicity versus not decreased echogenicity (CI)
18–22 years	1.85 (1.43–2.40)	17.3 (7.9–37.8)
25–30 years	1.81 (1.41–2.32)	16.7 (7.5–37.0)
40–45 years	1.40 (1.19–1.64)	3.4 (0.5–5.7)
60–65 years, female	1.30 (1.15–1.46)	2.3 (0.6–3.5)
60–65 years, male	1.16 (1.00–1.33)	2.2 (1.1–4.2)

Data from linear (TSH) and logistic (TPOAb) regression. TPOAb data were missing for 22 individuals. CI, confidence interval.

to our knowledge, not been described previously. The association with hypoechogenicity or irregular echo pattern was similar with or without exclusion of subjects with thyroid nodules. This indicates that irregular echo pattern is not just another expression of thyroid nodularity. When neither hypoechogenicity nor irregular echo pattern was present, only 2.2% of subjects had subclinical hypothyroidism. The specific pathological background for hypoechogenicity and irregular echo pattern is not known, but may be caused by focal or more diffuse lymphocytic infiltration of the thyroid. In our view, they both seem to be independent markers of thyroid failure. Thus, the traditional evaluation of echogenicity may be improved by inclusion of echo regularity. In agreement with previous studies (16, 21), we demonstrated a higher risk of being TPOAb positive among subjects with decreased echogenicity compared with subjects with normal echogenicity, particularly when echogenicity was markedly decreased. Other studies showed low echogenicity at grey scale histogram analysis among Hashimoto patients with high TPOAb values (3, 9). Loy *et al.* could only confirm this association among untreated hypothyroid patients, not in Hashimoto patients in general (1). We found a stronger association between decreased echogenicity and TSH or TPOAb status in the younger participants indicating a closer relationship when the changes are recent, and that other risk factors may have less impact. Only a few studies investigated the relationship between TgAb and hypoechogenicity and have found no association, which is in contradiction with our findings (3, 9). US is a subjective measure based on the experience and skills of the sonographer. As mentioned, an evaluation of the inter-observational variation between the sonographers prior to this study, showed differences in the judgement of hypoechogenicity and irregular echo pattern, one being more sensitive and the other being more specific (14). However, the finding of an association between hypoechogenicity and/or irregular echo pattern and thyroid function, as well as TPOAb status, showed the same pattern for both ultrasonographers. **In conclusion, with this unselected cross-sectional study of the general population, we demonstrated an association between**

**reduced echogenicity and/or changed echo pattern and high values of TSH even in subjects with normal thyroid function or subclinical hypothyroidism. This suggests US can be useful as a supplementary tool to biochemistry in early evaluation of thyroid status.** Further investigations with follow-up studies are needed to evaluate the usefulness of US in the prediction of progression of abnormal thyroid function.

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