

## CLINICAL STUDY

# Thyroid morphology in lethal non-thyroidal illness: a post-mortem study

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## Abstract

**Objective:** Non-thyroidal illness (NTI) is associated with alterations in thyroid hormone metabolism. Whether morphological changes of the thyroid gland accompany NTI is unknown. The aim of the present study was to describe thyroid morphology in patients with lethal non-thyroidal disease.

**Design:** In an autopsy study 267 cases have been examined.

**Methods:** Clinical data were obtained from medical records. Subjects were patients with chronic disease (group A), intensive care patients (group B) or persons who had died suddenly without pre-existing illnesses (group C). Patients ( $n = 93$ ) who did not fit into one of these categories and subjects with pre-existing thyroid disorders were excluded. Thyroid histology was assessed semi-quantitatively: grade I <25%, grade II 25–50% or grade III >75% occupation of the thyroid gland by follicles with a diameter <200  $\mu\text{m}$ .

**Results:** Mean thyroid weight was 19.9 g in group A ( $n = 75$ , age 19–96 (median 75) years, 48 males); 25.7 g in group B ( $n = 64$ , age 24–93 (median 69) years, 43 males); and 26.0 g in group C ( $n = 35$ , age 31–89 (median 69) years, 22 males) ( $P < 0.0005$ , A vs B/C). Grade I thyroid histology was present in 6 out of 75 patients with chronic illness, in 3 out of 64 intensive care patients and in 33 out of 35 sudden-death subjects. Grade III thyroid histology occurred in 30 out of 75 chronically ill patients, in 17 out of 64 intensive care patients and in 0 out of 35 sudden-death subjects ( $P < 0.0005$ , C vs A/B).

**Conclusions:** NTI is associated with reduced thyroid follicular size that is accompanied by lower thyroid weight in chronically ill patients but not significantly in intensive care patients.

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## Introduction

During non-thyroidal disease or starvation several changes of thyroid function occur. The so-called non-thyroidal illness syndrome (NTI) is characterized by multiple alterations in thyroid hormone metabolism including disturbance of transmembrane transport of thyroid hormone, impaired extrathyroidal conversion of thyroxine ( $T_4$ ) to triiodothyronine ( $T_3$ ), decreased binding of  $T_4$  to  $T_4$ -binding globulin, blunted thyrotropin (TSH) response to TSH-releasing hormone, reduction in frequency and amplitude of TSH pulses, and disappearance of nocturnal surges in TSH (1–7). NTI is not a rare phenomenon; it is estimated that about 70% of hospitalized patients meet the criteria for NTI (2, 8). Already within 1–24 h after onset of severe non-thyroidal disease, serum  $T_3$  concentration falls rapidly and progressively with a concomitant rise in serum reverse  $T_3$  concentration;

with ongoing disease the serum  $T_4$  level will also decrease (1, 2, 4). Low serum  $T_3$  and  $T_4$  concentrations are associated with poor outcome (1, 3, 4, 9–11). Despite these low  $T_3$  and  $T_4$  concentrations the serum TSH concentration can decrease below normal values too; this 'low TSH syndrome' is associated with substantial mortality (1, 5, 12). Although NTI is usually regarded as a protective adaptation of the body during severe disease or starvation, there is some evidence that a state of functional hypothyroidism may be present (5, 13–17).

In contrast to the extensive data that have been published on biochemical and metabolic features hardly any data on thyroid morphology in NTI are present. In a post-mortem study we have examined macroscopic and microscopic features of the thyroid gland in patients who had died in the course of severe non-thyroidal disease in comparison to suddenly deceased previously healthy subjects.

## Subjects and methods

All autopsies that were performed at the Department of Pathology, St Franciscus Gasthuis, Rotterdam, The Netherlands in the period 1993–1995 were evaluated. Autopsy cases concerning subjects aged less than 18 years (mainly stillborn fetuses) were excluded. From the remaining 267 subjects the clinical history was obtained by examination of the medical records. Subjects were divided into three groups. Patients who had died after severe and ultimately fatal chronic disease with a duration of at least 3 months were included in group A. Group B consisted of patients with acute or subacute disease who had died after at least 48 h of treatment in the intensive care unit. Finally, persons who had died suddenly without manifest pre-existing illness were assigned to group C.

At autopsy the thyroid gland was excised with care and weighed on a digital balance. Next, both lobes of the gland were cut in the frontal plane in three slices. Then all portions were examined by palpation and visually with a magnifying glass for irregularities such as fibrotic areas, nodules, hemorrhages, calcifications or cysts. Only the homogeneous glands were included in the study. Subsequently, two standard pieces from the middle slice of each lobe were excised and fixed in 4% neutral buffered formaldehyde solution. After 48–72 h of fixation these thin pieces were embedded in paraffin. Routine sections (5  $\mu\text{m}$ ) were stained with hematoxylin and eosin (HE). We refrained from staining all sections immunohistochemically for thyroglobulin after we learned that this staining did not further substantiate the observations based on the study of the HE sections in any of the three groups of patients. Reticulin staining was only used for photographic clarity. Microscopic examination was carried out by one experienced pathologist (A C J) without knowledge of the medical history or the weight of the thyroid gland. During microscopic examination thyroid follicles were divided into approximately normal-sized follicles with a diameter of at least 200  $\mu\text{m}$  and so-called microfollicles measuring less than 200  $\mu\text{m}$  as determined by means of a calibrated ocular micrometer. This classification was chosen for its clarity and concurs with data in general, as mentioned in the literature (18). The presence of microfollicles was graded in a semi-quantitative manner. In grade I less than 25% of the parenchyma consisted of microfollicles, in grade II 25–75% and in grade III more than 75% of the surface was occupied by microfollicles. Only glands with homogeneously developed parenchyma and without inflammatory infiltrate were included in the study; this was established at the microscopic level by examining the tissue at three levels by means of step sections. A possible influence of autolysis on thyroid follicular size was excluded by the examination of sections from five surgical excisions that were

fixed 1, 3, 6, 12, 24, 36 and 48 h after surgical resection; no significant change in follicular diameter was found.

Ninety-three of the 267 subjects (44 men and 49 women aged 22–97 with a median of 77 years) were excluded from the analysis. Fifty-three patients did not fit any of the defined patient groups and 40 had pre-existing thyroid disorders. The 174 subjects who met the inclusion criteria of the study were 75 chronically ill patients (group A), 64 intensive care patients (group B) and 35 persons who had suddenly died without manifest pre-existing illness (group C). Group A consisted of 48 men and 27 women with a mean age of 72 (range 19–96) years. Of these 75 chronically ill patients, 51 had malignant diseases (41 solid, 10 hematological neoplasms). The remaining 24 subjects had a variety of ultimately lethal non-malignant diseases (chronic obstructive pulmonary disease, interstitial pulmonary disease, heart failure, chronic renal failure, liver cirrhosis, autoimmune disorders). Median duration of illness was 6 months (3–84, mean 12, standard deviation 16 months). Group B consisted of 43 men and 21 women aged 24 to 93 with a mean of 66 years. Forty-three of these 64 intensive care patients had a diagnosis of sepsis and/or multiple organ dysfunction syndrome; other conditions included respiratory failure caused by pneumonia, chronic obstructive or interstitial pulmonary disease, cardiac failure, neurological catastrophes and complications after major surgery. Duration of illness varied between 2 days and 2 years with a median of 4 weeks; median duration of admission to the intensive care unit was 10 days (2–90, mean 16, standard deviation 17 days). Finally, group C consisted of 22 men and 13 women aged 31 to 89 (mean 68) years. In this group the causes of death were acute myocardial infarction ( $n = 17$ ), fatal arrhythmia without myocardial infarction ( $n = 3$ ), acute dissection of the thoracic aorta ( $n = 3$ ), aortic stenosis ( $n = 1$ ), ruptured aneurysm of the abdominal aorta ( $n = 4$ ), pulmonary embolism ( $n = 4$ ) and cerebrovascular accident ( $n = 3$ ).

For statistical analysis we used ANOVA. Unpaired Student's *t*-tests were applied for comparison of continuous variables (age, thyroid weight) and chi-square tests for comparison of non-continuous variables (sex, histological grade).

## Results

Table 1 shows patient characteristics as well as the main results of our study. Thyroid weight ranged from 10 to 36 g in group A (chronic illness), from 13 to 52 g in group B (intensive care) and from 16 to 40 g in group C (sudden death). Group A patients had a mean thyroid weight of 19.9 g with a standard deviation of 5.3 g and 95% confidence limits of 18.7–21.1 g. In group B, mean thyroid weight was  $25.7 \pm 8.2$  g with a 95% confidence interval of 23.7–27.7 g. Mean thyroid

**Table 1** Patient characteristics and main results. Group A: death from severe chronic non-thyroidal disease. Group B: death after at least 48 h of treatment in the intensive care unit. Group C: sudden death; no indication of pre-existing illness. Thyroid histology grade I: <25% of thyroid parenchyma consisting of follicles with diameter <200  $\mu\text{m}$ ; grade II: 25–50% of thyroid parenchyma consisting of follicles with diameter <200  $\mu\text{m}$ ; grade III: >75% of thyroid parenchyma consisting of follicles with diameter <200  $\mu\text{m}$ .

	Chronic illness (group A)	Intensive care (group B)	Sudden death (group C)
Number of subjects	75	64	35
Sex (male/female)*	48/27	43/21	22/13
Age (years)#			
Range	19–96	24–93	31–89
Median	75	69	69
Mean	72.7	66.4	68.1
Standard deviation	12.5	14.3	13.8
Thyroid weight (g) <sup>†</sup>			
Range	10–36	13–52	16–40
Median	19	24.5	26
Mean	19.9	25.7	26.0
Standard deviation	5.3	8.2	6.4
Thyroid histology‡			
Grade I	6	3	33
Grade II	39	44	2
Grade III	30	17	0

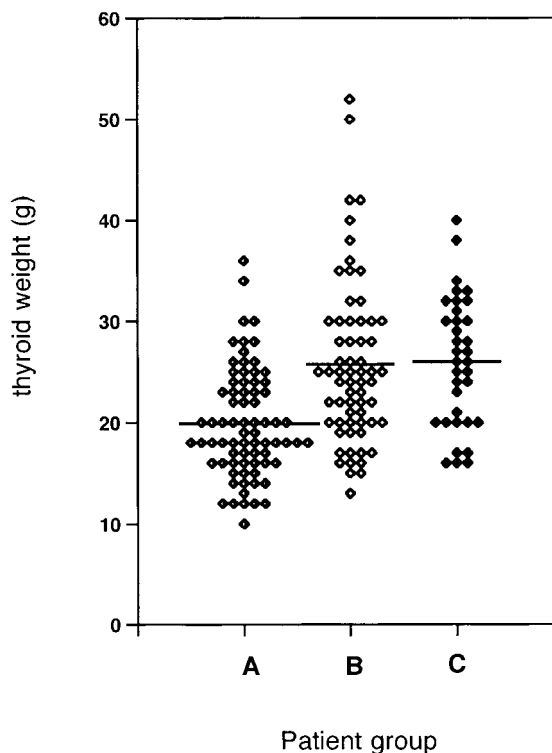
\*  $P$  values for comparison between patient groups: \* $P = 0.889$ ; # $P = 0.019$  (age higher in group A); <sup>†</sup> $P < 0.0005$  (thyroid weight lower in group A); <sup>‡</sup> $P < 0.0005$  (histological grade lower in group C).

weight in group C was  $26.0 \pm 6.4$  g (95% confidence interval 23.9–28.1 g). Thus, thyroid weight was significantly lower in group A as compared with groups B and C, which is further illustrated in Fig. 1. Groups A, B and C were completely comparable with regard to sex distribution ( $P = 0.89$ ). Age was slightly but significantly ( $P = 0.019$ ) higher in the chronically ill patients; for mean age the 95% confidence intervals were 69–75 years in group A, 62–70 years in group B and 63–72 years in group C. After correction for age, thyroid weight remained significantly lower in group A ( $P < 0.0005$ ).

Thyroid histology differed considerably between the patient groups (see Table 2, Figs 2 and 3). Grade I thyroid histology was observed in 6 out of 75 subjects of group A, in 3 out of 64 of group B and in 33 out of 35 of group C. Thus, only 9 of the 139 (6%) of the patients with the clinical condition compatible with NTI had grade I thyroid histology as compared with 33 of the 35 (94%) sudden-death and previously healthy subjects ( $P < 0.0005$ ). In contrast, the majority of patients in groups A and B had grade II or grade III histology (i.e. reduced thyroid follicular size). Grade II histology was observed in 39 out of 75 (52%) of the subjects of group A, 44 out of 64 (69%) of group B and 2 out of 35 (6%) of group C. Grade III histology occurred in 30 out of 75 (40%) subjects of group A, 17 out of 64 (27%) of group B and 0 out of 35 (0%) of group C.

## Discussion

In the literature hardly any data are available on thyroid size and histology in NTI. In a Hungarian



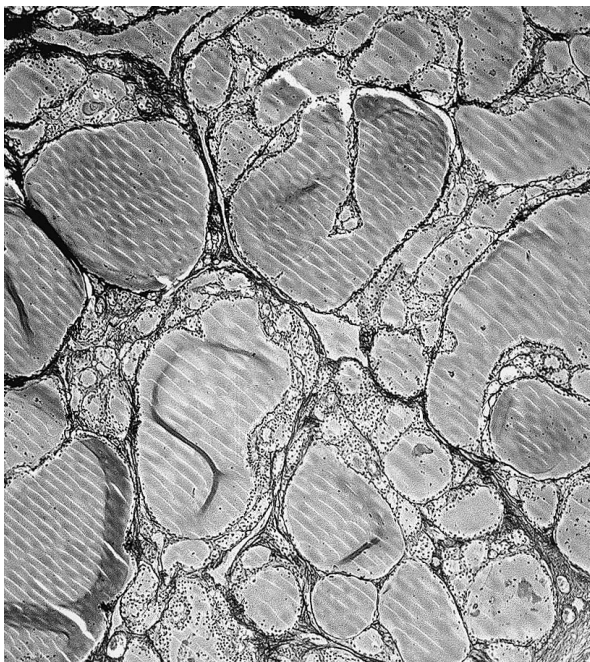
**Figure 1** Thyroid weight according to patient group. Each symbol represents one subject. Mean thyroid weight is significantly lower ( $P < 0.0005$ ) in group A (19.9 g) as compared with group B (25.7 g) and group C (26.0 g). No difference between groups B and C ( $P = 0.8$ ).

**Table 2** Thyroid histology according to patient group. Observed distribution of thyroid histology between the three patient groups. In parentheses: expected frequencies. Patient groups significantly differed with regard to thyroid histology:  $P < 0.0005$  (chi-square-test).

	Grade I histology	Grade II histology	Grade III histology
A (chronic illness)	6 (18.1)	39 (36.6)	30 (20.3)
B (intensive care)	3 (15.5)	44 (31.3)	17 (17.3)
C (sudden death)	33 (8.5)	2 (17.1)	0 (9.5)

geriatric population a significant decrease in ultrasonographically determined thyroid size was found that correlated with the severity of chronic disease (19). In earlier ultrasound studies Hegedüs had already reported that thyroid size can be influenced by NTI (20). Acute hepatic disease and chronic renal disease were associated with increases in thyroid volume, whereas chronic non-renal disease had no influence on thyroid size (20). Chronic alcoholism was associated with a decrease in thyroid volume and fibrosis of the thyroid gland probably due to a direct toxic effect of ethanol (20, 21). Apart from this alcohol-induced fibrosis of the thyroid gland we could find no data in the literature on thyroid histology in NTI.

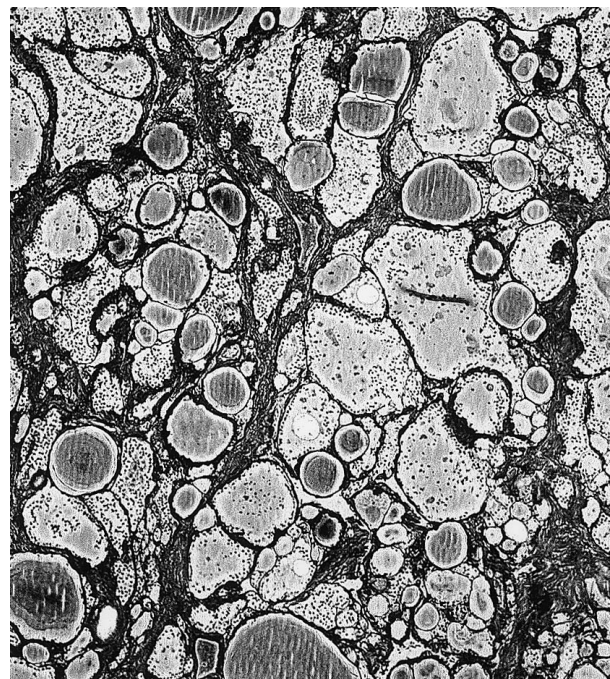
The main finding of our study is the reduction of thyroid follicular size in patients with lethal NTI as compared with apparently healthy subjects who had died suddenly. This reduction of follicular diameter is associated with depletion of colloid inside the thyroid follicles.



**Figure 2** Example of grade I thyroid histology. The follicles are essentially large with abundant colloid as is usual in normal thyroid glands. Due to the vast amount of firm, compact colloid material there is an inevitable artifact (scrubbing board appearance) caused by the vibration of the microtome knife. Paraffin section (5  $\mu\text{m}$ ); reticulin/HE stain. Original magnification  $\times 80$ .

Although all subjects were inhabitants of a non-iodine deficient area the mean thyroid weights in the three patient groups of this study are in the upper range of those reported in the literature (22, 23). However, this is not of major importance because only the comparison of mean thyroid weights between the three patient groups has been studied.

One of the shortcomings of the present study is the lack of solid information on body length and body weight since, at least in healthy individuals, thyroid volume is mainly dependent on lean body mass (24, 25). Thyroid function tests were not performed routinely due to the retrospective design of the study. Therefore, the presence and severity of NTI could not be documented for the majority of our study subjects. However, because of the severity of disease, it can be presumed that the majority of the chronically ill and of the intensive care patients in this study had NTI. In contrast to this, the subjects from group C (sudden death) had no manifest pre-existing illness. Hence, the majority of these subjects only had NTI of very short duration or no NTI at all. Therefore we consider them



**Figure 3** Example of grade III thyroid histology. The follicles are small and practically devoid of colloid. Paraffin section (5  $\mu\text{m}$ ); reticulin/HE stain. Original magnification  $\times 80$ .

as control subjects. Thirty-three of the 35 thyroid glands from the control subjects had normal light-microscope features. However, an overwhelming majority of the thyroid glands from the chronically ill and intensive care patients had abnormal histology that was characterized by the appearance of microfollicles (see Figs 2 and 3). This finding might imply that severe NTI is associated with follicular changes and depletion of colloid. To our knowledge, an association between thyroid morphology and NTI has not been described before. The pathogenetic mechanism remains to be elucidated. A possible cause could be the presence of functional central hypothyroidism in severe NTI (5, 13, 14). This could lead to understimulation of the thyroid gland resulting in involutinal changes as described above. However, before speculating about the possible cause of abnormal thyroid histology in NTI our findings should ideally be first confirmed in other studies.

As expected from the histological findings of our study, thyroid weight was lower in group A as compared with the control group C. Although similar histological findings in intensive care and chronically ill patients were found, thyroid weight in chronically ill patients was significantly lower, whereas the groups of intensive care patients and sudden-death subjects did not differ. It is postulated that this discrepancy is caused by excessive amounts of extravascular fluid in intensive care patients suffering from severe sepsis and/or multiple organ dysfunction. Unfortunately, we are not able to prove this because of the unavailability of dried thyroid weight data.

In summary, we have found that lethal NTI is associated with major morphological changes of the thyroid gland including loss of colloid substance with reduction of follicular diameter. These histological features are accompanied by a reduction of thyroid weight in chronically ill patients. In intensive care patients, the same histological findings were not associated with reduced thyroid weight, probably because of the presence of excessive amounts of extravascular fluid in a substantial number of intensive care patients. It is concluded that the demonstrated histopathological characteristics of the thyroid gland might be the morphological reflection of severe NTI.

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