

Absent ^{99m}Tc -MIBI Uptake in the Thyroid Gland during Early Phase of Parathyroid Scintigraphy in Patients with Primary and Secondary Hyperparathyroidism

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Abstract

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BACKGROUND: Thyroid uptake of technetium-99m methoxyisobutylisocyanide (^{99m}Tc -MIBI) during parathyroid scintigraphy can be affected by various conditions.

AIM: To evaluate the frequency of absent ^{99m}Tc -MIBI uptake by the thyroid gland in the early phase of dual-phase parathyroid scintigraphy.

METHODS: The early planar images of dual phase Tc^{99m} MIBI parathyroid scintigraphy from 217 patients performed between 2014 and 2017 were retrospectively analysed. Patients were divided into two groups. The first group included 147 patients with primary hyperparathyroidism and the second group included 70 patients with chronic renal failure. Patient records, laboratory and ultrasonographic data were analysed in all patients. Descriptive statistic was used for data analysis.

RESULTS: Out of all patients in the first group, 18 patients (12.24%) showed absent thyroid uptake. Thyroidectomy was performed in 44.4% of these patients, and the rest of them had some thyroid disease. Only one patient had no thyroid or another chronic disease. In the second group, 8 patients (11.42%) presented with absent thyroid uptake of MIBI. Among them, 5 patients had no history of thyroid disease and had been on hemodialysis programme, and 3 patients had hypothyroidism.

CONCLUSION: Absent ^{99m}Tc -MIBI uptake in the thyroid during the early phase of parathyroid scintigraphy is most frequently related to thyroid disease. A small proportion of patients with chronic renal failure can present with absent ^{99m}Tc -MIBI uptake in the thyroid as well. The mechanism for this alteration is still unclear and needs further investigation.

Introduction

Parathyroid scintigraphy is an imaging modality used in the diagnosis and preoperative localisation of parathyroid adenomas or hyperplastic parathyroid glands in patients with hyperparathyroidism. Several protocols are used for this purpose: Dual-phase single isotope imaging, single phase dual-isotope subtraction method or a combination of the two [1] [2]. Most commonly used method in clinical practice nowadays is Dual-phase technetium-99m methoxyisobutylisocyanide (^{99m}Tc -MIBI) scintigraphy because of its high specificity and simplicity, despite the low sensitivity for detection of very small adenomas.

MIBI is a lipophilic, monovalent, cationic complex. The uptake by parathyroid tumours was first published in 1989 by Coakley et al., [3]. MIBI is distributed proportionally to blood flow in the body and is sequestered intracellularly within the mitochondria by passive diffusion in cells with negative transmembrane potential. The slower MIBI washout from the parathyroid adenomas and hyperplastic glands compared with the normal thyroid and parathyroid tissue provides the possibility for the use of this radiopharmaceutical for this kind of imaging. The main pathophysiological mechanism for slower MIBI washout from the parathyroid adenomas lies within the increased number of mitochondria in hyperactive parathyroid cells [4]. Several factors can influence the normal distribution of ^{99m}Tc -MIBI in the early phase of the scanning in the thyroid and parathyroid glands. Awareness about variations in the

biodistribution of MIBI is important for the proper interpretation of the scan results. Diminished MIBI uptake in the thyroid and parathyroid adenomas is reported in several studies [5] [6]. Our study aimed to evaluate the frequency of absent ^{99m}Tc-MIBI uptake by the thyroid gland in the early phase of dual-phase parathyroid scintigraphy in patients with primary hyperparathyroidism and patients with secondary hyperparathyroidism due to chronic renal failure.

Material and Methods

Retrospective analysis of 278 parathyroid scintigraphies from 217 patients (151 females 66 males, aged 16 to 82 years, and mean age 54.7 ± 14.13) from the archive of the Institute of Pathophysiology and Nuclear Medicine at the Medical Faculty in Skopje was performed. The scintigraphies were performed under the same protocol in the period from January 2014–June 2017. Patients were divided into two groups. The first group included 147 patients, 119 females 28 males, age range 16-78 years (mean age 55.9 ± 12.75), referred for investigation of primary hyperparathyroidism and the second group included 70 patients, 32 females 38 males, age range 16-82 years (mean age 53 ± 14.58), referred with diagnosis of secondary hyperparathyroidism due to chronic renal failure. The parathyroid scintigraphy was performed after IV injection of 740 MBq ^{99m}Tc-MIBI. Early scans of the neck and the upper thorax were obtained 10 minutes after injection with a planar gamma camera in AP view (MEDISO-DHV) with low energy, general purpose collimator (LEGP) and 128 x 128 matrix. Late planar scans were obtained 2 hours after injection.

Some patients had SPECT/CT (OPTIMA NM/CT 640, GE Healthcare) performed in the delayed phase. Thirty 15-second images were taken by each head over 180-degree stepwise rotation and stored in a 128*128 matrix of a frame mode. All patients had thyroid ultrasound performed at our Institution with a high-resolution broadband linear array transducer (LN 12-3, Philips HD6) to verify the presence/ absence of parathyroid adenoma and to exclude the presence of thyroid nodules or other focal lesions in the thyroid gland.

All scans were evaluated for ^{99m}Tc-MIBI uptake in the thyroid gland in the early phase (thyroid phase) qualitatively by 2 nuclear medicine specialists blinded to patient data. The patients' groups were further subdivided according to these findings. The patients from the first group with a normal distribution of ^{99m}Tc-MIBI were classified as group 1a, and the patients with absent thyroid ^{99m}Tc-MIBI uptake as group 1b. The patients in the second group were subdivided in the same manner. Anamnestic and laboratory data from the patients' files were analysed

in all patients. The laboratory tests were not performed at our institution. The data were evaluated with the methods of descriptive statistics.

Results

Thyroid ^{99m}Tc-MIBI uptake in the early phase of parathyroid scintigraphy was absent in 26 patients from both groups. The rest of the patients, 129/147 in the first group with primary hyperparathyroidism and 62/70 from the second group with secondary hyperparathyroidism had normal thyroid uptake of ^{99m}Tc-MIBI in the early phase and complete washout of the tracer in the delayed planar images of parathyroid scintigraphy. Figure 1 presents a patient with normal uptake in the thyroid during parathyroid scintigraphy.

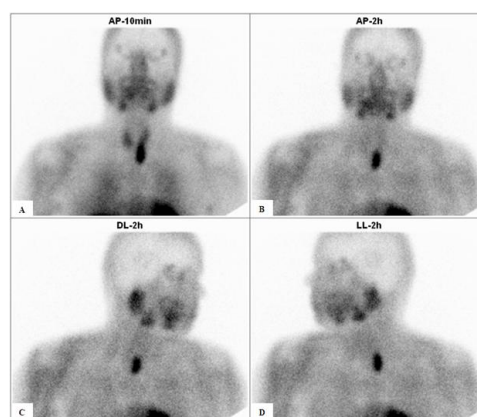


Figure 1: Early-phase (A) and delayed phase: anterior view (B), right lateral (C), left lateral (D) planar images with ^{99m}Tc-MIBI in a 42-year-old male patient referred for investigation of primary hyperparathyroidism. The PTH level was measured 890 pg/ml; plasma ionised calcium level was elevated 3.87 mmol/L. The patient had no history of thyroid disease, TSH level was within the normal range

Early-phase (A) image shows normal uptake of ^{99m}Tc-MIBI in the thyroid gland and focus of increased activity in the lower pole of the left lobe. Delayed phase images (B; C; D) show normal clearance of ^{99m}Tc-MIBI from the thyroid and persistence of the focal increased activity, a finding consistent with parathyroid adenoma.

Concomitant thyroid disease was observed in 35/129 patients (27.1%) with suspicion for primary hyperparathyroidism and 6/62 patients (9.7%) with chronic renal failure. The data regarding early thyroid ^{99m}Tc-MIBI uptake, and the frequency of thyroid disease in both patients' groups are presented in Table 1.

The most frequent thyroid disease in patients with primary hyperthyroidism and normal ^{99m}Tc-MIBI thyroid uptake (group 1a) was nodular goitre in 19 patients followed by hypothyroidism due to chronic

autoimmune thyroiditis (CAD) in 9 patients and euthyroid CAD in 5 patients.

Table 1: Number of patients with absent and normal early ⁹⁹Tc MIBI thyroid uptake in both groups with data on the presence/absence of thyroid disease

Primary hyperthyroidism 147 patients				Secondary hyperthyroidism 70 patients			
Absent thyroid uptake		Normal thyroid uptake		Absent thyroid uptake		Normal thyroid uptake	
18 (12.2%)	129 (87.8%)	8 (11.4%)	62 (88.6%)	TD	NTD	TD	NTD
17	1	35 (27.1%)	94	3	5	6	56
(94%)	(6%)	(72.9%)	(62.5)	(37.5%)	(62.5)	(9.7%)	(92.3%)

TD thyroid disease; NTD no thyroid disease

Only 2 patients had a history of Graves' disease but were in remission when scintigraphy was performed. The cause of thyroid disease in group 2a was nodular goitre in 5 patients and CAD with hypothyroidism in 1 patient. The data presenting the type of thyroid disease in all patients' groups are shown in Fig. 2.

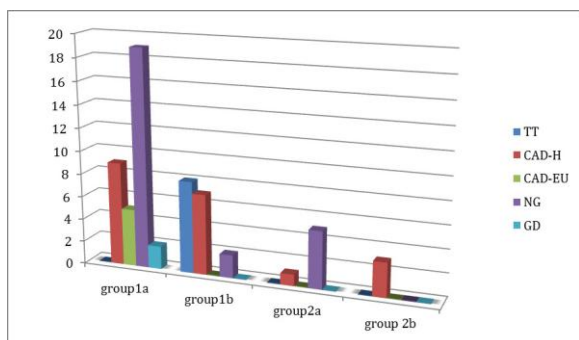


Figure 2: Thyroid diseases in all patients' groups. TT-Total thyroidectomy; CAD-H Hypothyroid chronic autoimmune disease; CAD-EU Euthyroid chronic autoimmune disease; NG Nodular goitre; GD Graves disease

The scan analysis showed that in the group of patients with primary hyperparathyroidism 18/147 patients (12.24%) showed absent thyroid uptake (group 1b). Further analysis showed that 8 out of 18 patients (44.4%) had previously performed thyroidectomy due to various reasons and their ultrasound revealed minimal to absent residual tissue in the thyroid bed. The rest of the patients except one had thyroid disease. Out of these 9 patients, 7 patients had hypothyroidism due to chronic autoimmune thyroiditis. All 7 patients were on L-thyroxine substitution therapy and had TSH level within normal range. This was the most frequently encountered thyroid disease 7/9 (77.77%), and the other patients had nodular goitre 2/7 (22.22 %). The ultrasound report in patients with autoimmune thyroiditis confirmed normal sized thyroid with non-homogenous structure in 4 patients, while 3 patients had a small atrophic thyroid gland. Only one patient presented with completely normal thyroid ultrasound, thyroid pertechnetate scan and normal values for thyroid hormones and antiperoxidase antibodies and absent thyroid uptake of MIBI. The patient didn't have a history of another chronic disease, nor was taking

any medications or nutritional supplements. The characteristics of the patients in this group are summarised in Table 2. The scintigraphy results showed parathyroid adenoma or hyperplasia in 10 out of 18 patients. The laboratory tests collected from the patients' files were not performed at the same institution and were frequently missing. Therefore, statistical analysis was not performed for these data.

Table 2: Clinical, biochemical, ultrasonographic and scintigraphic data of patients with primary hyperthyroidism with diminished thyroid uptake

Patient no.	Gender	Age (years)	iPTH (pg/ml)	Ca ⁺⁺ (mmol/L) Total Ca* (mmol/L)	Thyroid US report	TD	Scintigraphy report
1	F	38	140.1	1.43	Normal sized thyroid with the isoechoic structure	No TD	Positive
2	F	40	170.7	1.49	Normal sized thyroid with isoechoic structure and an anechoic nodule in the right lobe with dimension 21 mm	NG	Positive
3	F	60	3295	3.64*	Normal sized thyroid with isoechoic structure and a hypoechoic nodule in the right lobe with dimension 25 mm	NG	Positive
4	F	60	82.2	NA	Small sized thyroid with the hypoechoic and inhomogeneous structure	CAT-H	Positive
5	F	63	105.5	1.44	Small sized thyroid with isoechoic and inhomogeneous structure with fibrotic septae	CAT-H	Negative
6	F	66	331	2.9*	Normal sized thyroid with hypoechoic and inhomogeneous structure with fibrotic septae	CAT-H	Positive
7	F	52	183	NA	Normal sized thyroid with hypoechoic and inhomogeneous structure with fibrotic septae	CAT-H	Positive
8	F	57	520.2	1.61	Normal sized thyroid with isoechoic and inhomogeneous structure with fibrotic septae and small circumscribed hypoechoic lesions	CAT-H	Positive
9	F	33	263	1.5	Small sized thyroid with the isoechoic and inhomogeneous structure	CAT-H	Negative
10	F	72	304	2.9*	Normal sized thyroid with the isoechoic and inhomogeneous structure	CAT-H	Positive
11	F	42	140.4	1.12	Absent thyroid gland	TT	Negative
12	F	66	119	1.23	Residual thyroid parenchyma in the right thyroid bed with dimension 7 mm	TT	Negative
13	F	58	134	NA	Absent thyroid gland	TT	Negative
14	F	68	391.5	1.2	Absent thyroid gland	TT	Positive
15	F	43	NA	NA	Residual thyroid parenchyma in the right thyroid bed	TT	Negative
16	F	40	NA	NA	Absent thyroid gland	TT	Positive
17	F	62	NA	NA	Residual thyroid parenchyma in the left thyroid bed	TT	Negative
18	F	66	NA	NA	Absent thyroid gland	TT	Negative

m: male; f: female; iPTH: intact parathyroid hormone; Ca⁺⁺: plasma ionized calcium; * total plasma calcium level; NA: not available; US: ultrasound; TD: thyroid disease; NG: Nodular goiter; CAT-H: Hypothyroidism due to chronic autoimmune thyroiditis; TT: Total thyroidectomy; Scintigraphy report-Positive: presence of parathyroid adenoma/hyperplasia; Negative: absence of parathyroid adenoma/hyperplasia.

Normal ranges for laboratory results: iPTH: 12.0-65.0 pg/ml, Ca⁺⁺: 1.12-1.32 mmol/L, Total plasma Ca: 2.10-2.16 mmol/L. In the group of patients with secondary hyperparathyroidism due to chronic kidney failure, 8 patients presented with absent thyroid uptake of MIBI in the thyroid phase of the scanning (Figure 3).

From these patients (group 2b), 5 patients (7.1%) had normal thyroid ultrasound and no history of thyroid disease. The laboratory tests for thyroid function were within normal range. One of the patients had repeated scans, and both times the thyroid uptake was absent during the early phase. The other 3 patients had hypothyroidism and were on L-thyroxine substitution therapy with TSH level within normal range. All 5 patients had been on hemodialysis programme for more than 5 years (range 7-19 years, mean 12 ± 5.5), and had high levels of PTH (>1000pg/ml, mean 1889 ± 750.76). The data for

serum calcium and phosphate levels were not available in all patients. The patients' data are presented in Table 3.

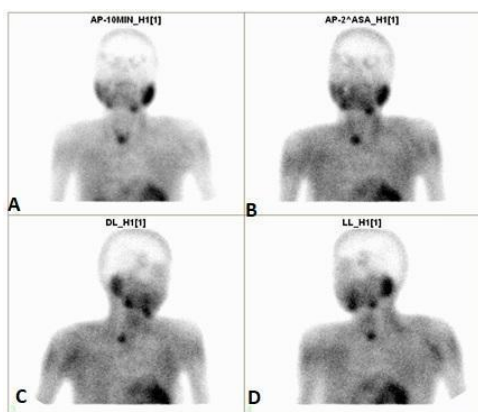


Figure 3: Early-phase (A) and delayed phase: anterior view (B); right lateral (C); left lateral (D) planar images with ^{99m}Tc-MIBI in a 45-year-old female patient with chronic renal failure who has been on hemodialysis treatment for 9 years. The PTH level was measured 2500 pg/ml, and the patient had no history of thyroid disease. In both the early and the delayed images it was not possible to see any activity in the thyroid region, only higher uptake in the lower pole of the right lobe suggestive of parathyroid adenoma

Data analysis showed that in our patients with chronic kidney failure 7.1% of patients had absent thyroid MIBI uptake in the early phase and no history of thyroid disease. The uptake on the early and late scans in the parathyroid lesions was visible in 4 patients, while in one patient there was no uptake in thyroid or parathyroid lesion. After surgery in this patient, parathyroid hyperplasia was confirmed on histopathology.

Discussion

The early uptake and washout of MIBI in the thyroid gland can be affected by several factors. The most frequently encountered reason is the pathology

of the thyroid gland. The increased uptake and slow washout in some thyroid nodules are well-established fact. This scintigraphy pattern was related with a higher probability of malignancy in several studies [7], but can also lead to difficulties in the interpretation of parathyroid scintigraphy especially in the departments where SPECT/CT is not available. Thyroid nodules can also have diminished uptake, although there are not many studies that were studying the early uptake 5-10 minutes after injection. This pattern, found in 2 patients in our study, is most probably due to degenerative changes in the nodule, although histology data was not available. The diminished thyroid uptake can also be attributed to other thyroid pathologies. There are several reports that connect the chronic thyroiditis with diminished MIBI uptake [8][9]. The study of Santos et al. was designed to estimate the thyroid MIBI uptake at a 5th minute after injection in patients with different thyroid pathologies. The thyroid MIBI uptake was correlated to euthyroid patients referred for cardiac perfusion scintigraphy. This study reports reduced thyroid MIBI uptake in patients with atrophic Hashimoto thyroiditis, but higher uptake compared with euthyroid control group in patients with hypertrophic Hashimoto disease. The authors concluded that this kind of findings is probably due to glandular destruction and fibrosis in chronic atrophic thyroiditis [9]. Our study confirmed diminished uptake in 7 patients with hypothyroidism due to chronic autoimmune thyroiditis in patients with primary hyperparathyroidism, and in 3 patients with secondary hyperparathyroidism who had been diagnosed with hypothyroidism. The ultrasound was in concordance with normal sized or atrophic thyroid with signs of diffuse changes in the parenchyma. All patients were hypothyroid, with L-thyroxine substitution therapy at the time of MIBI scintigraphy. The administration of L-thyroxine to suppress the thyroid was claimed by some authors to improve the sensitivity of parathyroid scintigraphy in primary hyperparathyroidism [10].

Table 3: Clinical, biochemical, ultrasonographic and scintigraphic data of patients with chronic kidney failure with diminished thyroid uptake in the early phase of parathyroid scintigraphy

Patient no.	Gender	Age (years)	iPTH (pg/ml)	Ca ⁺⁺ (mmol/L) Total Ca* (mmol/L)	P (mmol/L)	Thyroid US report	TD	Scintigraphy result	HD duration (years)
1	M	55	2830	NA	NA	Normal sized thyroid with the isoechoic structure	No TD	Positive	7
2	F	59	1016	2.58	1.76	Normal sized thyroid with isoechoic structure	No TD	Positive	8
3	F	45	2500	1.10 2.18*	1.26	Normal sized thyroid with isoechoic structure	No TD	Positive	9
4	M	61	1500	NA	NA	Normal sized thyroid with the isoechoic structure	No TD	Positive	19
5	M	53	1602	2.18	1.33	Normal sized thyroid with the isoechoic structure	No TD	Negative	17
6	F	65	88	2.5*	2.00	Small sized thyroid with the isoechoic and inhomogeneous structure	H	Positive	18
7	F	63	474.4	2.2	1.32	Small sized thyroid with isoechoic, inhomogeneous structure and fibrotic septae	H	Positive	6
8	F	66	1347	NA	2.2	Small sized thyroid with isoechoic, inhomogeneous structure and fibrotic septae	H	Positive	NA

Abbreviations: m: male, f: female, iPTH: intact parathyroid hormone, Ca⁺⁺: plasma ionized calcium, * total plasma calcium level, P: phosphorus, NA: not available, US: ultrasound, TD: thyroid disease, H: Hypothyroidism, HD: hemodialysis, Scintigraphy report: Positive: presence of parathyroid adenoma/hyperplasia; Negative: absence of parathyroid adenoma/hyperplasia Normal ranges for laboratory results: iPTH: 12.0-65.0 pg/ml, Ca⁺⁺: 1.12-1.32 mmol/L, Total plasma Ca: 2.10-2.16 mmol/L, P: 0.80-1.40 mmol/L.

The TSH in our patients was in normal range; therefore we concluded that the reduced thyroid uptake was due to the parenchymal destruction rather than the L-thyroxin administration. Diminished thyroid MIBI uptake is well documented in patients with amiodarone-induced hyperthyroidism type 2 [11]. The possible pathophysiological mechanism for reduced MIBI uptake in this type of thyroiditis is the presence of apoptotic or necrotic processes involving mitochondrial membrane potential collapse in these patients. However, there were no patients with this kind of thyroid disruption in our patients.

Thyroid diseases were almost the only cause of absent early thyroid MIBI uptake during parathyroid scintigraphy in our patients with primary hyperparathyroidism. Thyroid disease also caused for absent early thyroid MIBI uptake in 3 patients with secondary hyperparathyroidism. However, thyroid disease was also present in patients with normal early thyroid uptake (Table 1). The level of the damage to the thyrocytes and their mitochondrial content by thyroid disease is probably the factor that determines the ^{99m}Tc -MIBI thyroid uptake.

To the best of our knowledge, this is the first study that reports absent thyroid uptake in patients with chronic renal failure without thyroid disease during the early phase of parathyroid scintigraphy. This kind of altered MIBI distribution was reported in 7.1% of patients in this group. Few studies have aimed to evaluate MIBI uptake in the thyroid gland during dual-phase parathyroid scintigraphy in patients with chronic renal failure. The study of Kiratli et al. evaluated the ratio between the ROI over thyroid and ROI over mediastinum in patients on hemodialysis with and without calcitriol supplementation, and in patients without renal disease but with high PTH levels and calcitriol supplementation. These study groups were compared with a control group of patients without parathyroid or renal disease referred for myocardial perfusion scintigraphy. All three groups of patients demonstrated significantly lower thyroid/mediastinum ratio compared to control group of patients [5]. The authors suggested the role of calcitriol supplementation considering that vitamin D receptors and its ligands have been recognised as factors that can influence the expression of P-glycoprotein [12]. P-glycoprotein is well described cellular efflux pump for lipophilic compounds like MIBI. However, the level of P-glycoprotein in the normal thyroid of healthy individuals is not very high and is not considered a factor that influences the faster washout of MIBI from the thyroid compared with parathyroid adenomas [13]. Although it is possible that therapy with calcitriol in patients with chronic renal failure can up-regulate P-glycoprotein and induce very fast washout from the thyroid, the study of Kiratli et al., demonstrated lower MIBI thyroid uptake in hemodialysis patients that were not receiving calcitriol as well [5]. Therefore, lower thyroid MIBI uptake in this

group of patients can also be attributed to the other factors that can influence the mitochondrial and plasma membrane potentials and mitochondrial content and function in the thyroid follicular cells. Although this study reported lower early thyroid MIBI uptake, they do not report absent uptake in their patients as we did in a small proportion of our patients. The semiquantitative evaluation was not performed in our study. Therefore it is possible that thyroid uptake was lower than in healthy patients in a larger percentage of patients in our study.

However, not all studies in the literature report diminished thyroid MIBI uptake during the early phase of the parathyroid scintigraphy. Kandeel et al. report normal thyroid uptake in the early scan and appropriate wash out in their series of patients with the end-stage renal disease, although the number of patients was small and the thyroid uptake during parathyroid scintigraphy was not the aim of their research [14]. Our study found normal thyroid MIBI distribution during parathyroid scintigraphy in 88.6% of patients with chronic renal failure. Our study was retrospective and is missing a lot of information on laboratory results and therapy regimens in these patients. Therefore the mechanism underlying this altered distribution cannot be explained. Larger prospective studies might offer better insight on the biodistribution of ^{99m}Tc -MIBI in patients with secondary hyperparathyroidism due to chronic renal disease.

The most common cause of altered biodistribution of MIBI in the thyroid during parathyroid scintigraphy is thyroid disease. Thyroid surgery or chronic autoimmune thyroiditis with glandular destruction are the most common, although nodular goitre can alter the thyroid uptake of MIBI as well. The thyroid MIBI uptake can be very low in a small proportion of patients with chronic renal failure without any sign of thyroid disease. The causes for these findings in this group of patients are still unclear and need further investigation. Discovering the factors that influence the distribution of this radiopharmaceutical in the thyroid in these patients can lead to better understanding of the pathophysiology of the thyroid cell during chronic renal failure.

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