

# Diagnostic Utility of Procalcitonin for Sporadic Medullary Thyroid Carcinoma in Patients with Nodular Disease and Mild or Moderate Hypercalcitoninemia

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## ABSTRACT

Many authors recommend the measurement of serum calcitonin (Ctn) to screen for sporadic medullary thyroid carcinoma (MTC) in patients with thyroid nodules. In this situation, procalcitonin (pro-Ctn) would have greater utility in patients with hypercalcitoninemia < 100 pg/ml. The aim of this study was to evaluate the utility of pro-Ctn in patients with thyroid nodules and without a suspicion of familial MTC or type 2 multiple endocrine neoplasia who had mild or moderate hypercalcitoninemia without an apparent cause. Consecutive patients with nodular thyroid disease assessed routinely by Ctn measurement were selected. Sixty patients with basal Ctn > 10 pg/ml but < 100 pg/ml were included. Nine patients (15 %) had MTC, with cytology being diagnostic in only four. Among the 51 patients without MTC, pro-Ctn was < 0.1 ng/ml in 46 (90.2 %). All patients with MTC had pro-Ctn > 0.1 ng/ml. Basal Ctn was > 24.6 pg/ml in all patients with MTC and in 42 patients (82.3 %) without MTC. It is noteworthy that among patients with basal Ctn > 24.6 pg/ml (n = 18) pro-Ctn > 0.1 ng/ml identified all patients with MTC and 64.2 % of subjects with these pro-Ctn concentrations had this tumor. In conclusion, we did not find superiority of pro-Ctn over Ctn for the diagnosis of sporadic MTC in patients with nodular disease and mild or moderate hypercalcitoninemia. However, in the case of patients with hypercalcitoninemia in the gray zone, pro-Ctn has an excellent negative predictive value while the data regarding its positive predictive value are not uniform.

## Introduction

Many authors recommend the measurement of serum calcitonin (Ctn) to screen for sporadic medullary thyroid carcinoma (MTC) in patients with thyroid nodules. Despite the pre-analytical and analytical advantages of procalcitonin (pro-Ctn) measurement, the clinical experience with the diagnosis and follow-up of MTC is greater for Ctn [1]. Thus, it does not yet seem possible to replace Ctn with pro-Ctn measurement, but the latter can complement the former [1].

In view of the very low risk of MTC, pro-Ctn measurement without cytology or a molecular test to suggest this cancer would be of

little utility in patients with no “suspicious” family or personal history who have basal Ctn < 10 ng/ml. On the other hand, MTC is very likely in patients with thyroid nodules and basal Ctn > 100 pg/ml in the absence of any other known cause (such as chronic renal failure, another secreting tumor). In addition, at these Ctn concentrations, pro-Ctn is almost always elevated [2–5]. Thus, to screen for sporadic MTC, pro-Ctn would be more useful in patients with basal Ctn > 10 pg/ml but < 100 pg/ml [1]. In this situation, stimulation tests are traditionally recommended to distinguish between patients with and without MTC. Pentagastrin, the most widely studied stimulus, is not available in many countries while few studies

have evaluated calcium stimulation specifically in patients with nodular disease and mild or moderate hypercalcitoninemia [6]. There is also no agreement regarding the best cut-off for stimulated Ctn. Finally, adverse reactions to these tests may occur, which are even contraindicated in some patients.

We previously investigated patients with thyroid nodules and without a suspicion of familial MTC or type 2 multiple endocrine neoplasia (MEN 2) who had mild or moderate basal hypercalcitoninemia without an apparent cause [6]. The aim of the present study was to evaluate the utility of pro-Ctn specifically in this situation.

## Patients and Methods

### Patients

Consecutive patients with nodular thyroid disease undergoing routine basal Ctn measurement were selected. The following subjects were excluded: (i) children and adolescents (age  $\leq$  12 years), (ii) patients with a family history of MTC or MEN 2 or with a clinical suspicion of the latter, (iii) patients previously submitted to thyroid carcinoma surgery, (iv) patients who only had hot nodules on  $^{131}\text{I}$  scintigraphy (performed if TSH  $<$  0.4 mIU/l) or purely cystic nodules, and (v) patients with known presence of kidney failure, a neuroendocrine tumor, or lung cancer. The 60 patients with basal Ctn  $>$  10 pg/ml but  $<$  100 pg/ml (20 men and 40 women, age between 16 and 78 years) were included in this study. The basal Ctn results of the first 41 patients had been published previously [6].

The local research ethics committee approved the study.

### Management

Patients with stimulated Ctn  $>$  100 pg/ml were submitted to total thyroidectomy with elective dissection of the cervical lymph nodes. All patients with non-benign cytology were operated. Only patients with stimulated Ctn  $<$  100 pg/ml and benign cytology were not submitted to thyroidectomy and were followed up by repetition of ultrasonography, Ctn measurement, and fine needle aspiration (FNA) [6].

## Sonography and FNA

Sonography was performed with a linear multifrequency transducer for morphological analysis (B-mode) and for power Doppler evaluation. FNA was guided by ultrasonography. The smears (cytology and histology) were analyzed by pathologists experienced in thyroid pathology. In these patients with basal Ctn between 10 and 100 pg/ml, a new FNA was performed to measure Ctn in the needle washout (FNA-Ctn) [6].

## Calcitonin and pro-calcitonin measurement

For Ctn and pro-Ctn measurement, the patients were asked to abstain from alcohol for at least one week and to discontinue the use of proton pump inhibitors for at least 4 weeks. None of the patients had apparent bacterial infection or hypercalcemia or used supplements containing biotin at the time of measurement. The serum samples were obtained in the morning (at about 8 AM) after an 8- to 10-hour fast and were analyzed immediately after collection.

### Assays

Calcitonin was measured by an immunochemiluminescent assay, with a sensitivity of 2 pg/ml. Procalcitonin was measured by an automated enzyme-linked fluorescent immunoassay with a functional sensitivity of 0.05 ng/ml [7].

## Results

Histology was available for 52 patients and the eight patients not submitted to surgery were considered not to have MTC [these patients initially had benign cytology, stimulated Ctn  $<$  100 pg/ml, and FNA-Ctn  $\leq$  10 pg/ml; after 18 months, cytology remained unchanged and there was no increase in basal Ctn or growth of nodules]. Nine patients (15%) had MTC, with cytology being diagnostic in only four (► **Table 1**).

Among the 51 patients without MTC, pro-Ctn was  $\leq$  0.1 ng/ml in 46 patients and ranged from 0.12 to 0.23 ng/ml in the remaining patients. All patients with MTC had pro-Ctn  $>$  0.1 ng/ml (range 0.13 to 0.55 ng/ml). MTC was not detected in any of the patients

► **Table 1** Characteristics of patients with MTC.

Sex	Age (years)	Ctn (pg/ml)	Pro-Ctn (ng/ml)	Cytology (Bethesda)	Tumor size	Stage
M	56	28	0.13	Benign (II)	12 mm	T1bN0M0
M	48	35	0.18	MTC (VI)	11 mm	T1bN0M0
F	49	43	0.23	Benign (II)	5 mm	T1aN0M0
F	53	56	0.42	Suspicious for PTC (V)	7 mm	T1aN0M0
F	56	72	0.5	MTC (VI)	16 mm	T1bN1aM0
M	63	81	0.45	Insufficient (I)	15 mm	T1bN1aM0
F	45	30	0.2	Indeterminate (IV)	7 mm	T1aN0M0
F	58	76	0.55	MTC (VI)	16 mm	T1bN1aM0
F	61	65	0.38	Suspicious for MTC (V)	13 mm	T1bN0M0

MTC: Medullary thyroid carcinoma; Ctn: Serum calcitonin; F: Female; M: Male; Pro-Ctn: Procalcitonin; PTC: Papillary thyroid cancer.

with pro-Ctn  $\leq 0.1$  ng/ml ( $n = 46$ ), while all patients with pro-Ctn  $> 0.25$  ng/ml ( $n = 5$ ) and 44.4% of patients with pro-Ctn between 0.1 and 0.25 ng/ml ( $n = 9$ ) had this tumor.

Regarding basal Ctn, none of the patients with concentrations  $< 24.6$  pg/ml ( $n = 42$ ) had MTC, while all five patients with concentrations  $> 47$  pg/ml and 30.7% of patients with concentrations between 24.6 and 47 pg/ml ( $n = 13$ ) had this tumor. In the last group (intermediate basal Ctn), although the four patients with MTC had pro-Ctn  $> 0.1$  ng/ml, 5/9 patients without this tumor also had elevated pro-Ctn. It is noteworthy that among patients with basal Ctn  $> 24.6$  pg/ml ( $n = 18$ ) pro-Ctn  $> 0.1$  ng/ml identified all cases with MTC and 64.2% of the subjects with these pro-Ctn concentrations actually had this tumor.

In this group of patients with sporadic nodular disease and mild or moderate hypercalcitoninemia without an apparent cause in which the frequency of MTC was 15%, the sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and accuracy of pro-Ctn (cut-off 0.1 ng/ml) were 100, 90.2, 100, 64.2 and 91.7%, respectively. Basal Ctn (cut-off 24.6 pg/ml) showed sensitivity, specificity, NPV, PPV and accuracy of 100, 82.3, 100, 50 and 85%, respectively.

## Discussion

Few studies have evaluated pro-Ctn specifically for the diagnosis of sporadic MTC in patients with nodular thyroid disease [5, 8, 9]. For the reasons mentioned above, pro-Ctn in this situation would be useful especially for subjects with hypercalcitoninemia  $< 100$  pg/ml [1]. A small number of patients with nodular disease and mild or moderate hypercalcitoninemia have so far been evaluated using pro-Ctn measurement [5, 8, 9].

In our series, using a cut-off of 0.1 ng/ml, pro-Ctn had 100% sensitivity and of 90% specificity. A non-inferior performance was obtained with basal Ctn, with a cut-off of 24.6 pg/ml resulting in 100% sensitivity and 82% specificity. In the first study of Giovanella et al. [8], using the cut-off proposed by the authors (0.1 ng/ml), pro-Ctn provided sensitivity and specificity of 100%; however, the same performance would be achieved with basal Ctn using a cut-off of 35 pg/ml. In another study using cut-offs with better performance, Giovanella et al. [9] obtained sensitivity of 100% and specificity of 99.7% for pro-Ctn, but basal Ctn also provided sensitivity of 100% and specificity of 98.3%. Finally, in the recent study by Censi et al. [5], the cut-off proposed for pro-Ctn (0.07 ng/ml) provided sensitivity of 85.7% (97.4% for tumors  $> 10$  mm) and specificity of 98.9%. Applying the basal Ctn cut-off of 25 pg/ml, 92% sensitivity (97.4% for tumors  $> 10$  mm) and 96.6% specificity are also obtained.

Since we had no cases of MTC with Ctn  $\leq 20$ –25 pg/ml, we do not know whether the excellent sensitivity of pro-Ctn would persist in this situation. Giovanella et al. [8, 9] reported 100% sensitivity of pro-Ctn but the patients with MTC had Ctn  $> 20$  pg/ml. In the series of Machens et al. [3], among the seven patients with MTC and calcitoninemia  $< 20$  pg/ml, pro-Ctn was  $\leq 0.1$  ng/ml in five patients and  $\leq 0.15$  ng/ml in all patients. In the study by Censi et al. [5], three of the four patients with MTC and Ctn  $\leq 20$  ng/ml also had pro-Ctn  $\leq 0.07$  ng/ml and all of them had pro-Ctn  $\leq 0.1$  ng/ml.

Finally, in another study, all five patients with active MTC and basal Ctn  $< 20$  pg/ml had pro-Ctn  $< 0.15$  ng/ml [2].

On the other hand, we did not have patients without MTC with Ctn  $\geq 50$  pg/ml and we do not know whether the specificity of pro-Ctn would also be high in these cases. In the series of Giovanella et al. [8–10] in which pro-Ctn provided specificity close to 100%, subjects without MTC had Ctn  $< 50$  pg/ml. The same was observed in the study by Censi et al. [5] in which all patients without MTC exhibited Ctn  $< 30$  ng/ml and 94.3% had  $< 20$  ng/ml.

Among patients with hypercalcitoninemia between 20 and 50 pg/ml, pro-Ctn  $> 0.1$  ng/ml identified all four patients with MTC in the present study, the two cases of the series of Giovanella et al. [9], and 7/10 patients in the series of Censi et al. [5]. In our study, 5/9 patients without MTC and with Ctn between 20 and 50 ng/ml also had pro-Ctn  $> 0.1$  ng/ml. In contrast, none of the patients without MTC with these Ctn concentrations had elevated pro-Ctn in the series of Giovanella et al. [8–10] and Censi et al. [5].

In conclusion, we did not find superiority of pro-Ctn measurement over basal Ctn for the diagnosis of sporadic MTC in patients with nodular disease and mild or moderate hypercalcitoninemia. More studies are necessary to specifically assess the sensitivity of pro-Ctn in patients with MTC and mild hypercalcitoninemia ( $\leq 20$  pg/ml) and its specificity in patients without MTC with higher Ctn concentrations ( $\geq 50$  pg/ml). In the case of patients with hypercalcitoninemia in the gray zone, pro-Ctn has an excellent NPV but the data regarding its PPV are not uniform and further studies are needed.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

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