Review

Procalcitonin: A New Biomarker for Medullary Thyroid Cancer? A Systematic Review

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Abstract. *Medullary thyroid cancer (MTC) is a rare but aggressive thyroid malignancy. The gold-standard biomarker for its diagnosis and follow-up is calcitonin (CT); however, it has a variable half-life dependent on its circadian variability. It has been suggested that a more stable hormone, procalcitonin (PCT), may overcome these problems and its introduction to routine practice may give more accurate results in the diagnosis and follow-up of MTC. We systematically reviewed Pubmed, Scopus, Biosis Previews and Embase databases up to March 2016. A total of 15 out of 184 articles were retrieved and analyzed. Of these 15 studies, 3 were case reports. In these 15 studies, the values of CT and PCT were assessed in both patients with MTC and patients that were either healthy volunteers or with benign/malignant thyroid nodular disease or with bacterial infection. Our search suggests that PCT seems to be a useful biomarker for the diagnosis and follow-up of MTC when used in conjunction with CT, particularly in a small proportion of tumors that are CT-negative or secrete low levels of CT. So far, there has not been enough data to suggest a specific threshold for normal PCT. However, most studies indicate a value of 0.1 ng/ml as an acceptable cut-off in everyday clinical practice. At present, CT should continue to be the primary biomarker in MTC with the addition of PCT in some patient groups. Nevertheless, larger patient series need to be conducted in order to provide safer and more accurate results.*

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Medullary thyroid carcinoma (MTC) is a relatively rare malignancy, accounting for 2-5% of all thyroid cancers (1). It originates from thyroid neuroendocrine cells (C-cells) that secrete calcitonin (CT), currently, the gold standard biomarker used in the diagnosis, evaluation and follow-up of MTC (2, 3).

Calcitonin is a 32-amino-acid polypeptide hormone that is formed by the splitting of a larger protein precursor, which is a product of the *CALC1* gene (4, 5). In healthy individuals, CT is involved in calcium homeostasis and its release is stimulated by increased levels of serum calcium and by the hormones gastrin and pentagastrin (PG) (5-7). In disease, apart from MTC, an elevated CT may be seen in C-cell hyperplasia, non-thyroidal small cell or other malignancies, acute and chronic renal failure, hypercalcemia or hypergastrinemia of any cause and gastrointestinal and pulmonary disease (8).

Procalcitonin (PCT) is a peptide precursor of CT (9). It is also encoded by the *CALC1* gene and produced by thyroid C-cells and other neuroendocrine cells in the lung and bowel. In disease, PCT is produced in response to inflammatory stimuli, predominantly by the cells in the lung and bowel and, therefore, plays an important role in the diagnosis and prognosis of sepsis (10).

Compared with CT, PCT has more thermal stability and less circadian variability. It has an *in vivo* half-life of approximately 24 h, unlike CT, which follows a biphasic pattern (11-13). These advantages of PCT are stirring interest among academics and there is growing evidence about the feasibility and usefulness of introducing PCT assays to routine practice as a prognostic marker for MTC.

This is a systematic review and analysis of the recent available evidence to evaluate the accuracy and efficacy of measuring PCT compared to CT for the diagnosis and follow-up of patients with MTC.

Literature Search

A search was conducted of all the available literature up to March 2016 using PubMed, Scopus, Embase and Biosis Previews databases. The following search terms were used: "(procalcitonin) AND (medullary OR medullary thyroid carcinoma OR MTC)". Only articles published in English, French or Greek were evaluated. There was no limit placed on the year of publication. A systematic review was then performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Study Selection

Any original article, poster or case report presenting data on the use of PCT in patients with histologically proven MTC was evaluated. Material evaluating PCT in other thyroid diseases was also included.

Data Extraction

The demographic data collected for each study included the author's name, year of publication, study design, country of origin and the number of patients involved. Any data comparing CT to PCT was also collected; this included predictive values, sensitivities and specificities.

Results

Our search revealed 184 articles (44 from Pubmed, 56 from Scopus, 28 from Biosis Previews and 56 from Embase). After applying the inclusion criteria (Figure 1), 15 studies remained and were included in this review (14-28). Of these, 3 were case reports (26-28), 5 were prospective (15, 16, 18, 22, 24) and 2 retrospective cohort studies (14, 19). For the remaining articles, a study design could not be identified (17, 20, 21, 23, 25). There were no randomized controlled trials.

Serum CT was measured using different assays; radioimmunological assays were used in 3 studies (20-22), chemiluminescent ones in 7 (15, 16, 18, 19, 23, 25, 27) one study (14) used both radioimmunological and chemiluminescent assays and a further study (17) used 3 separate assays (fully automated CT assays (Immulite (IL) and Liaison (LIA)) and 1 non-automated CT assay (IRMA, Medipan)). Unfortunately, the remaining 3 studies (24, 26, 28) did not report a method for measuring CT. PCT measurements were made using Kryptor assays in 7 studies (14, 15, 17, 19, 22, 23, 25), chemiluminescent assays in 4 studies (16, 18, 21, 27) and immunochromatographic in one study (20). The remaining 3 articles did not report on the method used for measuring PCT (24, 26, 28). What were considered 'normal levels' for CT and PCT varied with each study and were dependent on the particular method used to measure the hormones. Five of the studies used a pentagastrin-stimulation test, where a 0.5µg/kg intravenous bolus of pentagastrin was administered and CT and PCT levels were measured at 2- and 5-min intervals (15, 17, 21, 23, 27). PCT:CT ratios were also calculated in one study (18).

A total of 485 patients with MTC were included in this systematic review and were compared with 1,035 patients, who were either healthy volunteers, had benign or malignant nodular thyroid disease or a bacterial infection. Only one study included patients with thyroid diseases other than MTC (25), while another study did not present any histological data (22).

Case Reports

The characteristics of the included case reports are described in Table I. The first case report described a 39-year-old woman presenting with a left thyroid nodule, visualized with magnetic resonance imaging (MRI) (26). Fine-needle aspiration revealed malignant cells and MTC was a possibility. Serum CT tested negative (<2 pg/ml), while PCT was raised at 0.21 ng/ml. The patient had a thyroidectomy, which demonstrated a tumor measuring 2.6×2.0×1.2 cm. MTC was confirmed with no lymph node or distal metastases and serum PCT became negative.

The second case report described a 55-year-old male with histologically proven MTC measuring up to 5.2cm (27). Post-operatively, the pre- and post-pentagastrin stimulation CT levels were <10 pg/ml. After a 4-year interval, the patient was readmitted with a left thyroid nodule, lymphadenopathy and a suspicious lesion in the liver. The serum CT and PCT levels were both raised; measuring 50 pg/ml and 10.3 ng/ml, respectively.

Another case report described a 74-year-old woman presenting with fever, retrosternal pain and anemia (28). Investigations revealed a right thyroid nodule and a high PCT level. A source of infection could not be identified; therefore, the patient's symptoms were thought to be paraneoplastic. Subsequent fine needle aspiration confirmed MTC.

Clinical Studies

The characteristics of the included studies are described in Table II. The first study was a retrospective analysis of 457 patients with untreated MTC, admitted to a German hospital over 20 years (14). In 112 patients, preoperative CT and PCT levels were elevated. A strong correlation was found between PCT and CT levels (r=0.88) and also between PCT and CT levels and primary tumor diameter (r=0.80 and r=0.82, respectively) and the number of lymph node metastases (0.70 and 0.65, respectively). A weaker correlation with primary tumor diameter and the number of lymph node metastases was
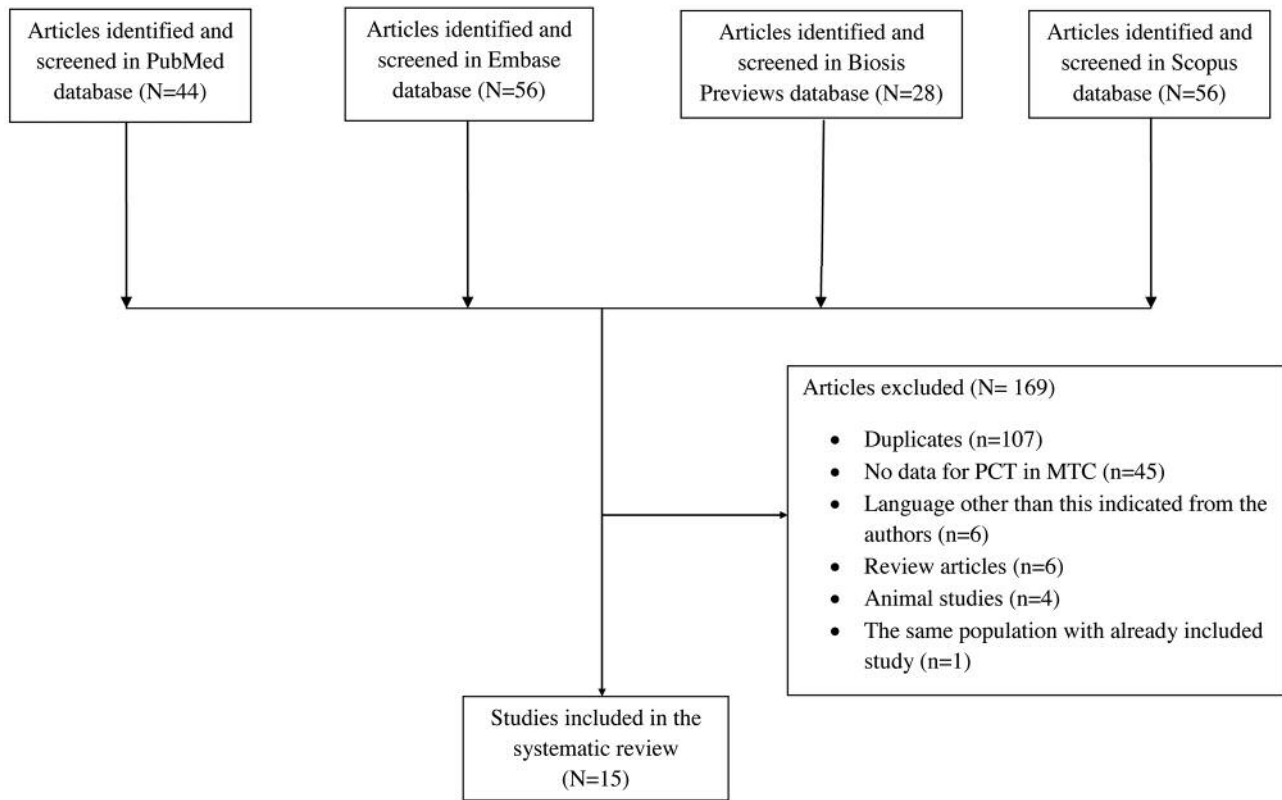
Figure 1. *Flow diagram of the systematic search and process of study selection.*

Table I. *Summary of case reports with medullary thyroid cancer reporting calcitonin and procalcitonin levels.*

Author, year	Clinical characteristics	Diagnosis	CT	PCT	Comments
Brutsaert 2015 (26)	39-year-old woman 2 cm left-sided thyroid nodule No palpable cervical lymphadenopathy	Histology: T2N0Mx, 2.6*2*1.2 cm Positive immunochemistry for CT CEA (3.1 ng/ml) Chromogranin A (6.2 ng/ml)	<2 pg/ml (<0.6 pg/ml)	0.21 ng/ml (<0.1 ng/ml)	Follow-up: CT undetectable CEA and PCT in the reference range
Bugalho 2014 (27)	55-year-old man Multinodular goiter with a 5.2 cm dominant solid nodule in the left lobe and coarse calcification No lymphadenopathy	Histology: bilateral MTC T3N1aMx Preoperative: CT was not measured Postoperative basal and after pentagastrin CT <10 pg/ml	4 years later: 50 pg/ml (<10 pg/ml)	4 years later: 10.3 ng/ml (<0.5 ng/ml)	4 years later: Chromogranin A: 240 ng/ml (<100 ng/ml) CEA: 54 ng/ml (<3 ng/ml) Recurrence in the left thyroid bed Lymphadenopathy and liver lesions
Canale 2011 (28)	74-year-old woman Right thyroid nodule	Ultrasound and elevated CT	Elevated	Remarkably elevated	Paraneoplastic signs on examination (fever)

Pts, Patients; CT, calcitonin; CEA, carcinoembryonic antigen; PCT, procalcitonin.

demonstrated using the PCT to CT ratio (r=0.19). It was also shown that patients with a higher PCT level (>1 ng/ml) were more likely to have metastases at more distant sites, like the contralateral neck and upper mediastinum, compared to patients with a lower PCT (<1 ng/ml), which were more likely to only have metastases in the ipsilateral neck. Lower PCT

Table II. *Summary of studies with medullary thyroid cancer reporting calcitonin and procalcitonin levels.*

First author, Year	Study design; study period; country	Patients number, Clinical information	CT	PCT	Comments
Machens 2014 (14)	Retrospective; 1994-2014; Germany	N=457 Untreated MTC PCT measured in 112 CT measured in 345	Strong correlation with primary tumor diameter (r=0.82) and lymph node metastases (r=0.65)	Strong correlation with primary tumor diameter (r=0.8) and lymph node metastases (r=0.7)	Strong correlation between PCT and CT levels (r=0.88)
Lim 2014 (22)	Prospective; NR; France	N=476 Serum samples		Based on CT cut-off of 20 pg/ml: NPV 99.1% for PCT 0.05 ng/ml, 98.3% for 0.1 ng/ml and 97.2% for 0.15 ng/ml Based on CT cut-off of 100 pg/ml: NPV 100% for every PCT cut-off	Good correlation of PCT with CT (r=0.754) for CT >10 pg/ml, *p*<0.0001 No MTC with PCT <0.1 ng/ml, using a CT threshold of 20 pg/ml
Giovanella 2013 (15)	Prospective; 2008-2010; Switzerland	N=14 with a high CT level underwent a PCT calculation and PG stimulation test (among 1236 pts with nodular thyroid disease)	For basal CT value >10 pg/ml, sensitivity and PPV of detecting MTC: 100% and 14% For basal CT value >100 pg/ml, sensitivity and specificity: 100%	For basal PCT >0.1 ng/ml, the sensitivity, specificity, NPV and PPV were 100%	For PG-stimulated CT >100 pg/ml: sensitivity 100%, specificity 66%, PPV 50%, NPV 83% For PG-stimulated PCT > 0.1 ng/ml: sensitivity, specificity, NPV and PPV 100%
Kazcka 2012 (16)	Prospective; NR; Poland	N=70 (4 groups) 1 (n=6): active MTC 2 (n=23): MTC in remission 3 (n=11): NTNG 4 (n=30): bacterial infection	1 elevated in all 6 2 elevated in 8/23 3 elevated in 1/11 4 elevated in 3/30	1 elevated in all 6 2 elevated in 3/23 3 elevated in 1/11 4 elevated in 20/30	Good correlation between PCT and CT levels in MTC: 1: r=0.95, *p*=0.004 2: r=0.60, *p*=0.002 3: r=0.77, *p*=0.02 4: r=0.002, *p*=0.99
Kratzsch 2011 (17)	NR; NR; Germany	N=10 Postoperative recurrent MTC	Elevated in all (18.2-1511 pg/ml)	Elevated in all (0.226-11.6 ng/ml)	For a PCT level of >0.25 ng/ml, sensitivity for MTC: 100%
Walter 2010 (18)	Prospective; NR; Switzerland and the Netherlands	N=165 69 proven MTC 96 controls (3 groups) 1: carriers of MEN-related *RET* mutations (no MTC) 2: post-thyroidectomy for differentiated cancer, goiter or Grave's 3: euthyroid	Levels >20 pg/ml MTC: 62/69 1: 16/16 2: 0/26 3: 6/56 MTC *vs.* Controls (levels >20 pg/ml) Sensitivity: 89.9% Specificity 98.8% Diagnostic accuracy: 94.7% MTC *vs.* C-cell hyperplasia (levels >100 pg/ml) Sensitivity: 60.7% Specificity: 100% Diagnostic accuracy: 67.9%	Levels >0.16 ng/ml MTC: 67/69 1: 16/16 2: 24/26 3: 53/56 MTC *vs.* Controls (levels >0.5 ng/ml) Sensitivity: 84.1% Specificity: 84% Diagnostic accuracy: 84% MTC *vs.* C cell hyperplasia (levels >0.16 ng/ml) Sensitivity: 9.4% Specificity: 100% Diagnostic accuracy: 66.7%	Good correlation of PCT:CT ratio with clinical outcome High ratio in metastasized MTC PCT:CT >2.4 is optimal for predicting progressive disease: Sensitivity: 72.2% Specificity: 73.5% Diagnostic accuracy: 73.2%
Azevedo 2010 (23)	NR; NR; Portugal	N=57 41 MTC 16 Controls (FTC and benign thyroid disease)	Elevated in 15/41 (24-31745 pg/ml) 0/16	Elevated in 12/41 (0.9-134 ng/ml) 0/16	Good correlation of CT with PCT (r=0.9, *p*<0.001) 3 pts with borderline CT (24.1-36.6 pg/ml) had PCT <0.5 ng/ml and no residual thyroid tissue

Table II. *Continued*

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First author, Year	Study design; study period; country	Patients number, Clinical information	CT	PCT	Comments
Kowalska 2010 (24)	Prospective; NR; Poland	N=41 MTC	Elevated in 8/41	Elevated in 8/41	Complete correlation of CT with PCT levels
Giovanella 2010 (25)	NR; NR; Switzerland	N=168 107 proven benign nodules 61 metastatic DTC	Elevated in 5/168 (4 nodular lymphatic thyroiditis and 1 hyperplastic goiter)	Elevated in 1/168 (1 nodular lymphatic thyroiditis)	All healthy pts or with DTC had normal CT or PCT A negative PCT excluded 80% with a positive CT PCT more specific in non-MTC
Algeciras-Schimnich 2009 (19)	Retrospective; NR; USA	N=835 1 (n=197) controls 2 (n=91) active MTC 3 (n=42) cured MTC 4 (n=225) NET 5 (n=48) mastocytosis 6 (n=120) cured FTC 7 (n=55) resistant/ recurrent FTC 8 (n=57) benign thyroid disease	Levels >16 pg/ml in males and >8 pg/ml in females 1: 0/197 2: 90/91 3:1/42 4: 8/225 5: 2/48 6: 0/120 7: 0/55 8: 0/57 Active MTC *vs.* Controls Sensitivity: 99% Specificity: 100%	Levels >0.15 ng/ml 1: 1/197 2: 83/91 3: 0/42 4: 22/225 5: 2/48 6: 0/120 7: 3/55 8: 1/57 Active MTC *vs.* Controls Sensitivity: 91% Specificity 99.5%	Good correlation between CT and PCT levels (*p*<0.0001) Active MTC *vs.* other thyroid diseases PCT: sensitivity 98%, specificity 100% Active MTC *vs.* all other cases PCT: sensitivity 96%, specificity 99%
Bolko 2003 (20)	NR; NR; Poland	N=24 Proven MTC Distant metastases (2) Regional recurrence (8) Residual thyroid tissue (14)	Normal levels: 8/24 Levels <100 pg/ml: 6/24 Levels >100 pg/ml 10/24	Out of 8 CT-normals, 2/8 had an elevated PCT Out of 6 CT-positive <100 pg/ml, 4/6 had a raised PCT Out of 10 CT-positive >100 pg/ml 10/10 had increased PCT	Good correlation between CT and PCT levels (r=0.84, *p*<0.0001) Good correlation between CT levels and disease stage
Bihan 2003 (21)	NR; 1988-2001; France	N=21 Proven MTC (except for 2 diagnosed using *RET* mutation and abnormal CT)	57.1% normal	CTpr detectable in all cases (20-233.16 pg/ml)	Good correlation CTpr with CT levels (r=0.61, *p*<0.001)

pts, Patients; NR, not reported; CT, calcitonin; PCT, procalcitonin; MTC, medullary thyroid cancer; PG, pentagastrin; PPV, positive predictive value; NPV, negative predictive value; NTNG, non- toxic nodular goiter; MEN, multiple endocrine neoplasia; NET, neuroendocrine tumors; FTC, follicular thyroid cancer; CTpr, calcitonin precursor; DTC, differentiating thyroid carcinoma; r, correlation coefficient.

levels also correlated well with postoperative biochemical cure; complete biochemical cure was observed in all patients with a serum PCT<0.15 ng/ml. The biochemical cure rate significantly worsened with increasing PCT levels; it was 71% for 1 ng/ml, 36% for 5 ng/ml, 23% for 10 ng/ml and only a mere 10% if the PCT level was 50 ng/ml.

The second study was a 2-year prospective analysis of 1,236 patients with nodular thyroid disease (15). PCT and CT levels were measured and a pentagastrin stimulation test was performed on those patients with a high CT (14 patients). High levels of CT (>10 pg/ml) were detected in 1.1% of patients. Of these, 4 had malignancies, 2 of which were histologically proven MTC, 1 had C-cell hyperplasia and 9 were shown to have benign thyroid disease. If an even higher CT threshold was used (100 pg/ml), only the 2 patients with MTC would have been detected. After stimulation with pentagastrin, however, 2 additional patients had CT levels >100 pg/ml. On the other hand, when considering PCT, its basal and stimulated levels were increased only in the 2 MTC patients (basal 1.1 ng/ml and 0.75 ng/ml and stimulated 3.7 ng/ml and 1.5 ng/ml). Therefore, with a basal PCT cut-off level of 0.1 ng/ml, the sensitivity, specificity, positive and

negative predictive values were 100%, while with a CT cut-off of 10 pg/ml, although the sensitivity was 100%, the positive predictive value was 14%.

The third study (16) included 70 patients divided into 4 groups: active MTC (n=6), MTC in remission (n=23), non-toxic nodular goiters (NTNG) (n=11) and bacterial infections (n=30). In the first group, both markers were elevated. The mean levels of PCT and CT were 3.5 ng/ml and 973 pg/ml, respectively, for group 1, while for group 2 they were 0.06 ng/ml and 3.12 pg/ml, respectively. Among patients with MTC in remission, only 3 had positive, but a low PCT level. Regarding CT, this was positive in 8 patients. There was good correlation between CT and PCT levels in patients with MTC (r=0.95, p=0.004 in group 1 and r=0.60, p=0.002 in group 2). Notably, there was no correlation in the group of the patients with bacterial infections (r=0.002).

In a fourth study Kratzsch et al. (17), estimated CT and PCT postoperatively in 10 patients with MTC. These two biomarkers were measured in patients with chronic kidney disease, thyroiditis and bacterial infections. CT (calculated using 3 different assays) and PCT were both positive in cases of recurrent MTC. It follows that, like CT, a PCT level greater than 0.25 ng/ml can help confirm MTC.

A fifth study (18) analyzed 69 patients with histologically proven MTC and compared them with 96 controls; these included carriers of multiple endocrine neoplasia (MEN)-related RET mutations without MTC, patients post-thyroidectomy for differentiated cancer, patients diagnosed with a goiter or Grave's disease and euthyroid healthy volunteers. A CT level of 10 pg/ml and PCT level of 0.6 ng/ml were used as thresholds. CT was elevated (10.2-18.2 pg/ml) in 6/56 of the healthy volunteers, none (0/56) of the post-thyroidectomy patients, all (16/16) of the patients with MEN syndrome (40.7-95.5 pg/ml) and 62/69 patients with MTC (20.7-20,710 pg/ml). PCT was elevated in 53/56 of the healthy volunteers (0.6-28 ng/ml), 24/26 of the post-thyroidectomy patients (0.7-6 ng/ml), all (16/16) of the patients with MEN syndrome (0.6-15.6 ng/ml) and 67/69 patients with MTC (0.6-2478 ng/ml). It follows that the optimal cut-off for differentiating MTC from healthy controls was a CT level of 20 pg/ml and a PCT level of 0.5 ng/ml, while, differentiating MTC from C-cell hyperplasia, a CT level of 100 pg/ml and PCT level of 0.16 ng/ml were required. Also, it was shown that the PCT to CT ratio correlated well with clinical outcome; a threshold of 2.4 predicted progressive disease with 84.1% sensitivity, 84% specificity and a diagnostic accuracy of 73.2%. The ratio was also predictive for the presence of metastases but not for local recurrence.

Similar results were found in another study (19), that was a retrospective analysis of 835 patients, including 197 healthy volunteers. CT levels in the healthy subjects were <16 pg/ml in males and <8 pg/ml in females, while the cut-off used for PCT was 0.15 ng/ml. Ninety-one patients with

active MTC were evaluated; CT was elevated in all (8/8) of those newly diagnosed with MTC (mean=1,336 pg/ml), most (42/43) of the patients with recurrent MTC (20,447.9 pg/ml) and all (40/40) of the patients with stable disease (334.7 pg/ml). Regarding PCT, it was elevated in all (8/8) patients newly diagnosed with MTC (13.8 ng/ml), most (42/43) of those with recurrent MTC (241.7 ng/ml) and a significant number (33/40) of those with stable disease (3.3 ng/ml). A subgroup of 42 patients with cured MTC showed only one with elevated CT levels and none with elevated PCT levels. There was a good correlation between CT and PCT levels in MTC patients (p<0.0001). This correlation persisted after surgery as well with a similar decrease in both their levels seen. However, in those with residual metastatic disease, both markers remained high and, in those with distant metastases, there was an increase in levels during follow-up (over a year). Other subgroups were also analyzed; raised CT levels were observed in 8/225 patients with neuroendocrine tumors (mean=CT 16.2 pg/ml) and 2/48 with mastocytosis (6.1 pg/ml). Raised PCT levels were found in 22/225 patients with neuroendocrine tumors (0.17 ng/ml) and 2/48 patients with mastocytosis (<0.1 ng/ml). Although an elevated CT was not demonstrated in patients with cured or recurrent follicular thyroid cancer (FTC) or those with benign thyroid disease, PCT was elevated in 3 patients with metastatic FTC and one with hyperthyroidism.

A different study (20) examined 24 patients post-thyroidectomy for MTC and also observed a positive correlation between CT and PCT (p<0.0001) levels. Sixteen patients had PCT concentrations of 0.5 ng/ml or more and CT concentrations more than 60 pg/ml (measured by immunochromatographic and radioimmune assays). These values were considered cut-offs. Patients with distant metastases or regional recurrence showed large increases in both hormone levels. Of the 14 patients with residual thyroid tissue, CT was undetectable in 8 patients; however, 2 of them had measurable PCT levels. The remaining 6 had an elevated CT (<100 pg/ml) with 4 of them also having an increased PCT. Bihan et al. (21), estimated CT precursors (PCT and its component peptides) in 21 patients with MTC and showed that the values of CT precursors correlated well with CT levels (p<0.001). PCT levels were not measured.

Another study (22) looked at 476 samples referred to a laboratory; no histological data were collected and CT concentrations greater than 20 pg/ml were used to indicate MTC. PCT levels were <0.05 ng/ml in 45%, <0.1 ng/ml in 75% and <0.15 ng/ml in 82% of the samples. None of the patients with a PCT level <0.1 ng/ml had MTC. The negative predictive value for a serum PCT of 0.1 ng/ml was 98.3% for a 20 pg/ml CT cut-off and 100% for a 100 pg/ml CT cut-off. In another study (23), in 41 patients with MTC, high CT and PCT levels were detected in 15/41 and 12/41 patients, respectively. The 3 patients who were not detected using

PCT (<0.5 ng/ml) had borderline CT levels (24.1-36.6 pg/ml) and no residual thyroid tissue. Once again, there was good correlation between the 2 biomarkers.

A smaller study (24) observed 41 patients after surgery for MTC where CT, PCT and pentagastrin stimulation were performed. There was complete correlation between CT and PCT levels with 33 patients returning normal values for both markers. The remaining 8 patients showed high baseline and post-stimulation levels of CT and PCT that ranged from 0.11-3.19 ng/ml at time 0 and 0.13-15.74 ng/ml after 3 or 5 min.

The last study (25) included 168 patients, 107 of them with benign thyroid nodules and 61 with metastatic differentiated thyroid carcinoma. Although CT was elevated in 5 patients (9.2-19.2 pg/ml), PCT was only high in one (0.2 ng/ml).

Discussion

MTC is a rare but aggressive thyroid malignancy. The gold-standard biomarker for its diagnosis and follow-up is calcitonin; however, it has a variable half-life dependent on its differing levels throughout the day (29). Also, each laboratory may evaluate different isoforms of calcitonin making it difficult to establish a widely accepted 'normal' range. CT is also unstable at room temperature and this may give false-negative results (30). It has been suggested that a more stable hormone, PCT, may overcome these problems and, if used together with CT or on its own, could give more accurate results (19).

Existing data on the role of PCT as a predictive marker and in the diagnosis of MTC is promising and suggest that PCT could be a useful marker together with CT (31). Particularly, in a small proportion of MTC tumors that are CT-negative or secrete low levels of CT (32). PCT may be a helpful adjunct in establishing the diagnosis of MTC (as shown in 2 out of 3 case reports) (26, 27). In a particular patient with metastatic MTC, disease recurrence was better demonstrated using PCT compared with CT, further adding to the prognostic value of this marker. These findings suggest that PCT could be used together with CT not only for the diagnosis but also for the follow-up of MTC, especially for CT-negative or low CT-secreting tumors; a small but important patient group.

In Machens *et al*., the diagnosis of MTC and rates of disease recurrence correlated with both CT and PCT levels (14). PCT also correlated with the size of the primary tumor, the presence of malignant lymphadenopathy, as well as distant metastases. Also, both markers correlated well with biochemical cure. Giovanella *et al*. found that 14 out of 1,236 patients had a markedly raised CT (>10 pg/ml); however, only 2 of these patients had a histologically proven MTC (15). Interestingly, baseline and after PG stimulation PCT levels were raised in only these 2 patients, therefore, showing 100% sensitivity and specificity. Positive and negative prognostic values were also 100% using cut-off levels of

0.1 ng/ml for basal and PG-stimulated PCT. This, together with a drop in both PCT and CT levels post-thyroidectomy further emphasizes the usefulness of PCT as a possible tool for the follow-up of more *lege artis* cases of MTC.

Findings from other studies were consistent; the best diagnostic accuracy for PCT compared to CT was shown by Algeciras-Schimnich *et al*. (19), while Bolko *et al*. (20), demonstrated a correlation between serum CT levels and the stage of disease. Complete correlation between the 2 biomarkers was demonstrated in Kowalska *et al*.'s study (24). It follows that assessment using both CT and PCT together appears to improve overall accuracy compared with using CT alone in the management of MTC (15).

Two studies showed that PCT has a better negative prognostic value compared to CT. Giovanella *et al*. (25) showed that none of the healthy volunteers or patients with a differentiated thyroid malignancy had elevated CT or PCT levels and that a negative PCT excluded 80% of CT-positive patients. Azevedo *et al*. confirmed the above findings in non-MTC conditions, also showing that PCT levels are more specific than CT in these patients (23).

The studies included in this review demonstrate a good correlation of clinical outcome with the PCT:CT ratio. In Walter *et al*. (18), a low PCT:CT was associated with thyroid gland hyperplasia, while a high ratio was associated with metastatic MTC. An increased prognostic accuracy for differentiating progressive from stable MTC was also seen, particularly for CT values <4,000 pg/ml with the optimal PCT:CT cut-off for predicting progressive disease being 2.4 (sensitivity 72.2%, specificity 73.5%). Similar results were presented in Bihan *et al*. (21) where a positive correlation between PCT and CT levels was again seen.

The few limitations of PCT are that it is not widely available and, currently, only indicated in the context of sepsis. Also, in most studies, symptoms that were considered to represent systemic infections, such as pyrexia, were excluded before PCT measurements were taken. This could limit its use in a hospital setting where infections are common, as well as make the interpretation of PCT levels more difficult. A further limitation of PCT is that there is no current consensus on 'normal' ranges or 'target' values, particularly in the context of malignancy, where it is not routinely used. In the studies reviewed, the majority adopted a cut-off value of 0.1 ng/ml for MTC, also the threshold used by the majority in everyday clinical practice.

Conclusion

PCT is a useful biomarker for the diagnosis and follow-up of patients with MTC, especially when used in conjunction with CT. Unfortunately, there is not enough data to suggest a particular threshold; however, 0.1ng/ml appears to be the most acceptable in everyday clinical practice. Further

prospective studies with larger patient cohorts are still required to support the promising preliminary data presented here. At present, CT should continue to be the primary biomarker in MTC. The addition of PTC may be beneficial in some patient groups and may be considered an adjunct to CT in the management of patients with MTC.

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