Measurement of Basal Serum Calcitonin for the Diagnosis of Medullary Thyroid Cancer

Authors
Stephanie Allelein[1][*], Margret Ehlers[1][*], Corinna Morneau[1], Katharina Schwartz[2], Peter E. Goretzki[2], Thomas Seppel[3], Joachim Feldkamp[4], Andreas Krieg[5], Wolfram Trudo Knoefel[5], Anne Kuebart[1], Matthias Haase[1], Till Dringenberg[1], Christine Schmid[1], Matthias Schott[1]

Affiliations
1 Division for Specific Endocrinology, Medical Faculty, University Hospital Duesseldorf, Duesseldorf, Germany
2 Department of Surgery, Lukas Hospital, Neuss, Germany
3 Outpatient Clinic for Endocrinology, Moenchengladbach, Germany
4 Department for Endocrinology and Diabetes, Municipal Hospital Bielefeld, Bielefeld, Germany
5 Department of General, Visceral and Pediatric Surgery, Medical Faculty, University Hospital Duesseldorf, Duesseldorf, Germany

Correspondence
Dr. Stephanie Allelein, MD, PhD
Division for Specific Endocrinology, Medical Faculty
University of Duesseldorf
Moorenstr. 5
40225 Duesseldorf
Germany
Tel.: +49/211/81 04860, Fax: +49/211/81 16443
Stephanie.Allelein@med.uni-duesseldorf.de

ABSTRACT

Calcitonin (CT), a tumor marker for medullary thyroid cancer (MTC), can be stimulated with pentagastrin or calcium. Because of the unavailability of pentagastrin, basal CT measurement is frequently used for the preoperative diagnosis of MTC. The aim of the study was to define basal serum calcitonin (bCT) cut-off thresholds for diagnosing MTC. Within a retrospective analysis, 114 patients (51 males) were included fulfilling the criteria of an increased preoperative bCT level (>10 pg/ml) and the criteria of an available postoperative histology analysis. Based on a ROC plot analysis, the cut-off values for the diagnosis of MTC vs. non-malignancy (C cell hyperplasia and goiter) were identified. The most precise bCT thresholds for the identification of MTC were ≥46 pg/ml for males (sensitivity: 93.6%, specificity: 95.0%, PPV: 97%, NPV: 90%) and ≥35 pg/ml for females (sensitivity: 87.3%, specificity: 87.5%, PPV: 98%, NPV: 50%). Using these cut-offs, only 6% of male patients were not identified of having MTC, whereas 5% were false positive (having instead C cell hyperplasia). In females, the discrepancy was higher since 13% of female MTC patients were false negative by using the cut-off of ≥35 pg/ml, and 13% had false positive results (suffering from C cell hyperplasia). Gender-specific bCT cut-offs for the identification of MTC vs. C cell hyperplasia and non-malignancy were defined, which can be used in clinical routine. In female patients, however, the accuracy is much lower compared to males.

Introduction

Calcitonin (CT), a polypeptide hormone consisting of 32 amino acids, is the major tumor marker for medullary thyroid carcinoma (MTC). CT is mainly produced and rapidly secreted into the blood not only by the thyroidal calcium-sensitive parafollicular C cells but also by the C cell-derived MTC [1–3]. MTC itself may either occur sporadically (75% of the cases) or as part of a familial syndrome named multiple endocrine neoplasia (MEN 2) due to an activating mutation in the RET oncogene [4, 5]. MTC represents an aggressive malignancy with a 10-year survival rate of 40–50% [6, 7]. Once distant disease occurs, treatment options are limited, and conventional cancer treatments such as cytotoxic chemotherapy are of minimal benefit [8].

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[*] Both authors contributed equally to this work

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Basal serum CT (bCT) is commonly used to diagnose and to follow-up MTC patients as its serum concentration is directly related to the C cell mass [9, 10]. It can be measured by different commercially available assays [11, 12]. bCT's doubling time – together with carcinoembryonic antigen (CEA) doubling time – is currently considered to represent a strong prognostic indicator for MTC recurrence and death [13]. Additionally, bCT is used as a biochemical screening tool for MTC in relatives with RET mutations, including those where prophylactic and therapeutic thyroidectomy is considered [14]. Furthermore, the American Thyroid Association recommends the measurement of CT levels in the washout of fine-needle aspiration (FNA) biopsies for thyroid nodules with (i) histologically inconclusive results or (ii) features suggestive of MTC [9, 15].

Depending on the assay used, 56–88 % of subjects without thyroid disease usually show a CT level below the functional sensitivity, while 3–10 % have CT levels greater than 10 pg/ml [14, 16]. A CT stimulation test using pentagastrin or calcium should be performed (i) to differentiate MTC from C cell hyperplasia (CCH) to avoid unnecessary thyroidectomies; (ii) for patients with normal or slightly elevated basal CT findings and clinically suspected MTC; and (iii) possibly for screening for MTC in RET mutation-carrying relatives. The benefit of the pentagastrin-stimulation test is its higher sensitivity to detect C-cell disease compared to measurement of bCT [17]. Nevertheless, pentagastrin is not available any longer. An alternative method represents the calcium stimulation test, being described as sensitive as well, however, also having side effects [18, 19]. Nevertheless, due to the (partly life-threatening) adverse effects [20–22] of this stimulation test and due to the not yet well defined cut-offs for the calcium stimulation test [20, 23, 24], bCT levels are gaining in importance.

Therefore, the aim of the present work was to determine by analyzing a large series of patients cut-off values of basal (non-stimulated) bCT to diagnose MTC and to distinguish it from non-malignancies.

Patients and Methods

Patients

Within this retrospective analysis in total, 114 patients with bCT levels > 10 pg/ml were identified at four different endocrine centers in Germany between January 2008 and April 2016. All patients underwent surgery; postoperative histology results were available. We included patients with bCT levels above 10 pg/ml even though a higher limit of 15 pg/ml was discussed in another study to reduce false-positive cases [25]. By using this cut-off the chance of missing patients with very small MTCs could have been minimized [26, 27].

Sixty-three patients were females (age 63 ± 15 years) and 51 were males (age 64 ± 12 years). 86 patients had MTCs (n = 31 men), 23 patients had CCH (n = 15 men) and 5 male patients had goiter without additional malignancy. Patients with genetically identified familial MTC or MEN 2, respectively, including those who received prophylactic thyroidectomy were excluded from the analysis. In all patients, total thyroidectomy was performed and a professional examination of the removed tissue was done by experienced pathologists. According to previously published criteria CCH was de-fined as 50 or more cytologically bland intrafollicular calcitonin positive cells in at least one low power field (1OOX) [28]. The study has been approved by the Local Ethical Committee of the Heinrich-Heine-University Duesseldorf (No. 5625).

Calcitonin measurement

Altogether, four different assays based on three assay types were used for calcitonin measurement. Each assay has its specific gender-dependent cut-off value for positivity. The following assays were used (cut-off value for positivity for women and men): Calcitonin ELISA, IBL International (≥ 13 pg/ml; ≥ 30 pg/ml); Calcitonin IRMA, Euroimmune (≥ 8 pg/ml; ≥ 21 pg/ml); SELco Calcitonin IRMA, MEDIPAN (≥ 10 pg/ml; ≥ 15 pg/ml); Calcitonin chemiluminescence assay, Siemens (≥ 11.5 pg/ml; ≥ 18.2 pg/ml).

Statistical analyses

The CT levels are reported as single values. In order to obtain the optimal decision threshold level for positivity, receiver-operating characteristic (ROC) analysis was performed [29]. Sensitivity/Specificity pairs were calculated by varying the decision threshold levels over the entire range of CT values. Sensitivity (the true positive results) was calculated from patients with MTC. Specificity (the true negative results) was calculated from patients without malignancy and CCH.

The positive predictive value (PPV) was calculated as follows: PPV = number of test true positive MTC patients as a fraction of the total number of test positive subjects (true and false positive subjects). The negative predictive value (NPV) was calculated as follows: NPV = number of true test negative non-MTC patients as a fraction of the total number of test negative subjects (true and false negative subjects). Comparison was done by Kruskal–Wallis test and Dunn's multiple comparison test (not normally distributed data) and calculated using Prism computer software (GraphPad Software Inc., San Diego, CA). A p-value less than 0.05 was considered statistically significant.

Results

Serum calcitonin levels in patients with MTC, CCH, and non-malignancy

Serum CT levels are given in ▶ **Fig. 1**. As expected, in males as well as in females, significantly higher bCT levels were seen in MTC patients in comparison to CCH patients (male: 2173 ± 5352 pg/ml vs. 25.0 ± 11.0 pg/ml, p < 0.0001; female: 1574 ± 5826 pg/ml vs. 34.8 ± 52.0 pg/ml). Male MTC patients also showed significantly higher bCT levels in comparison to goiter patients without malignancy and CCH (22 ± 12.8 pg/ml, p < 0.0001).

Gender-specific significant differences were neither seen for CCH nor for MTC patients (comparing the mean values). Of note, however, detailed analyses of moderately increased CT levels revealed gender-dependent differences: Investigating non-MTC patients with bCT levels below 34 pg/ml significant differences could be identified (men: 20.6 ± 7.0 and women: 13.6 ± 3.4 pg/ml, p = 0.023). A similar picture was seen for bCT levels ≤ 200 pg/ml. Here, significantly higher CT levels were seen for male patients compared to females (men: 108.1 ± 61.5 and women:

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67.5 ± 47.3 pg/ml, p = 0.046). This data, as well as the fact that men thyroids harbor twice more C-cells than women's [30], indicate the necessity to consider male and female CT levels individually.

### Cut-off definition for the diagnosis of medullary thyroid cancer

In order to calculate gender-specific CT thresholds, ROC plot analyses were performed (▶ **Fig. 2**). Sensitivity and specificity were calculated in order to differentiate non-MTC (control and CCH) from MTC in men as well as in women. The areas under the curve (AUC) were as follows: 0.9661 (95 % CI: 0.9175–1.015), p < 0.0001 for men; and 0.9364 (95 % CI: 0.8473–1.025), p < 0.0001 for women (▶ **Fig. 2**). In male patients, optimal sensitivity (93.6 %) and specificity (95.0 %) were seen at a cut-off of ≥ 46 pg/ml to distinguish the non-MTC group from the MTC group. The corresponding PPV was 97 %, whereas the NPV was estimated to be 90 % (▶ **Fig. 2**). In females, optimal sensitivity (87.3 %) and specificity (87.5 %), with a PPV of 98 % and a NPV of 50 %, were seen at a cut-off level of ≥ 35 pg/ml (▶ **Fig. 2**).

In addition, we also analyzed CT levels, which were under the defined cut-offs. Here, in the group of male patients with CT levels below 30 pg/ml 2 patients had MTC (2/31; 6 %) resulting in a sensitivity of 93.6 % and a specificity of 75.0 %. The corresponding PPV and NPV were 85 % and 88 %. Below 20 pg/ml only 1 patient suffered from MTC (1/31; 3 %). Using this cut-off, a sensitivity of 96.8 %, a specificity of 40.0 %, a PPV of 71 %, and a NPV of 89 % were reached. Similarly, in the group of female patients with CT levels below 30 pg/ml 5 patients had MTC (5/55; 9 %; sensitivity: 90.9 %; specificity: 75.0 %; PPV: 96 %; NPV: 55 %). Below a threshold of 20 pg/ml 2 patients suffered from MTC (2/55; 4 %; Sens: 96.4 %; Spez.: 75.0 %; PPV 96 %, NPV 75 %).

Discussion

The aim of the present study was to identify the most accurate basal CT (bCT) cut-off for the preoperative identification of patients with medullary thyroid cancer (MTC). Based on ROC curve analyses we identified cut-offs to distinguish non-MTC patients (including goiter patients without signs of malignancy and C cell hyperplasia, respectively) from MTC patients. In females, a cut-off of ≥ 35 pg/ml was identified whereas in males the cut-off was ≥ 46 pg/ml for diagnosing MTC. According to previous data, we also saw a significant correlation of bCT with tumor size for men and women (data not shown) as well as an association of bCT level and lymph node metastasis (data not shown) [31, 32].

Due to the gender dependent differences in lower bCT levels and due to the fact man having a larger C-cell mass than women [30], we calculated ROC analysis for male and female patients separately. In our analysis, only 2 female patients and 1 male patient with bCT ≥ 35 pg/ml or ≥ 46 pg/ml, respectively, did not have MTC. In these patients, however, a CCH was detected. Therefore, patients with bCT levels above the defined gender-restricted cut-offs have to be informed about the rare chance of not having a MTC (female: 13 %; male: 6 %). On the other hand, there were 7 female MTC patients and 2 male MTC patients who would have been missed by using the defined thresholds. Therefore, patients with CT levels below the calculated cut-off have to be informed about a 25 %
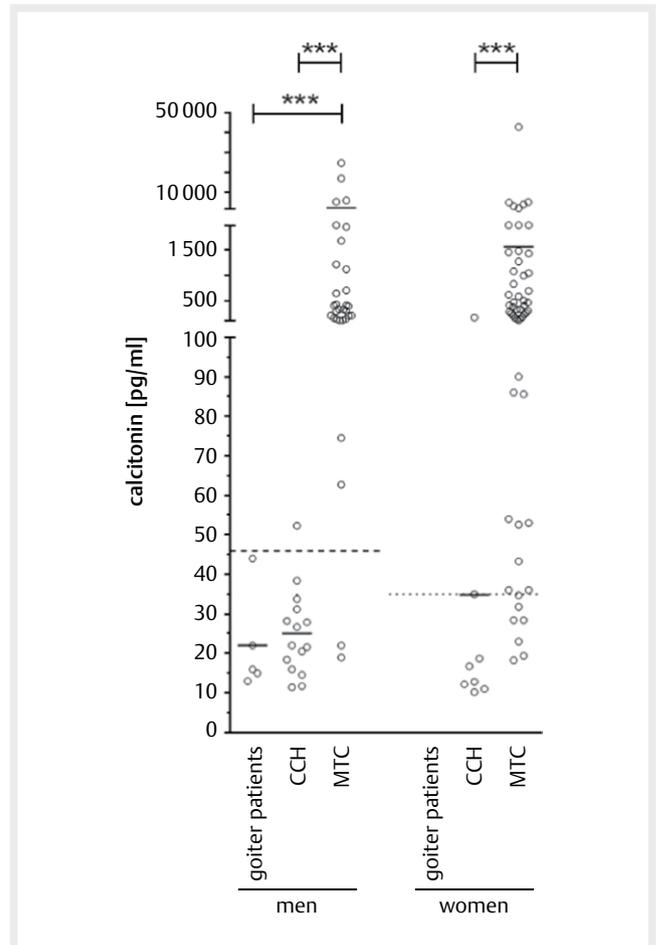
▶ **Fig. 1** Distribution of CT in male and female goiter, CCH, and MTC subjects; CT levels of male and female patients suffering from goiter, C cell hyperplasia (CCH), and medullary thyroid cancer (MTC): The gender-specific distribution of serum CT levels of goiter patients, CCH patients, and MTC patients is shown. The calculated cut-offs (men: 46 pg/ml; women: 35 pg/ml) are indicated (dashed lines). One male non-MTC patient was above and two male MTC patients were below the calculated cut-off. For females, two non-MTC patients showed CT levels above and 7 MTC patients showed CT levels below the calculated cut-off.

chance in females and 5 % chance in males, respectively, of having MTCs, as well. Of note, taking the lowest CT-level being measured in MTC would result in very low specificities (men: 40 % and women: 62.5 %), leading – at least for male patients – to a multitude of unneeded surgical interventions (men: 23.5 % and women: 4.8 % of all patients).

Irrespectively, one has to keep in mind, that falsely negative of positive bCT values, respectively, can be obtained due to influencing factors such as heterophilic antibodies, drugs, hook effect etc. [33, 34] as well as disease related pathological conditions, for example, renal failure, neuroendocrine tumors of the lung or gastrointestinal tract, or sepsis [27, 35, 36]. In order to reduce the impact of genetic factors we excluded genetically identified familial MTC or MEN 2, respectively, and patients with additional tumor diseases. It has also to be mentioned that cut-off calculations in our study was based on single CT measurements. Therefore, we cannot ex-
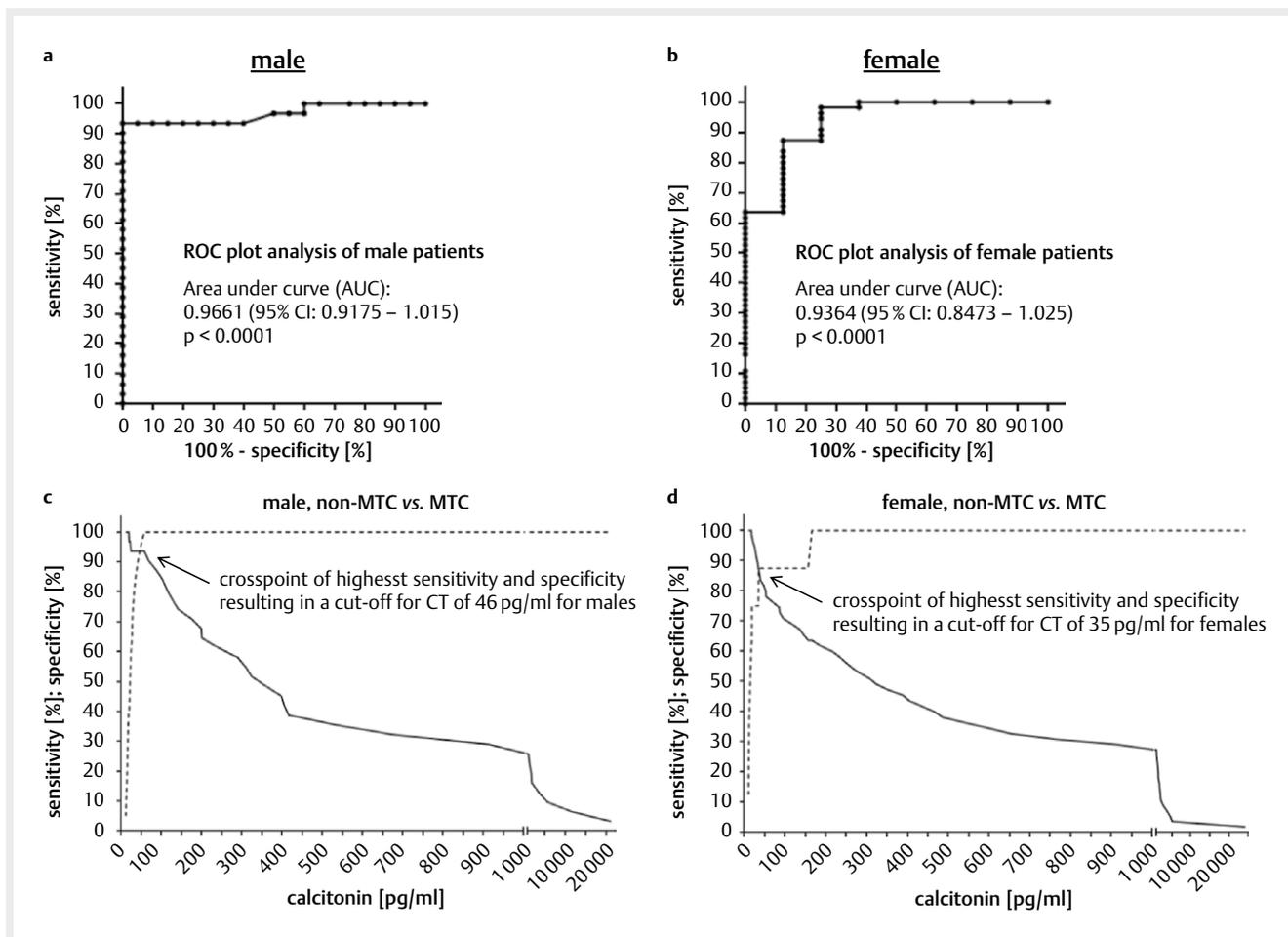
▶ Fig. 2   Cut-offs for serum CT levels (non-MTC vs. MTC); ROC plot analysis and determination of CT cut-off for male and female patients: ROC plot analysis including the data of patients with MTC for sensitivity and non-MTC subjects including goiter patients without malignancy and patients suffering from CCH for specificity is shown for males **a** and females **c**. Based on these data the calculated sensitivity (solid line) and specificity (dashed line) is shown for males **b** and females **d**. The cross-point of both lines represents the calculated cut-off for CT with highest sensitivity and specificity.

clude that additional CT measurements might have led to slightly different results.

Most data in the past have shown that the positive predictive value of measuring basal CT for the diagnosis of MTC is lower than for stimulated CT [19]. In contrast, Mian et al. [23] indicated that bCT values are at least as good predictors for MTC as stimulated CT values and suggested that bCT assays with improved functional sensitivity may avoid the stimulation test in several conditions. Our data with a larger cohort of patients revealed almost identical results for the diagnosis of MTC compared to previously published data with less patient numbers [23] even though in our study the specificity was not as high as previously published (of note, the AUC were similar). Another study by Chambon et al. reported the detection of i) MTCs in 26 % of patients and ii) CCH in 76 % of patients with bCT levels >10 pg/ml [26]. Within this study – with only 43 patients with elevated CT levels – no threshold for the detection of MTC was, however, calculated as we did. Taken together, the possibility of relying only on bCT would definitely increase the cost-effectiveness of the measurement of CT and the practicability in diagnosing MTC.

Our study also has some limitations. One drawback is the use of different assays. Within our retrospective analysis, altogether four different calcitonin assays have been used for testing. Each of these assays have gender-specific cut-offs for positivity ranging from 8 to 13 ng/ml for females and 15 to 30 ng/ml for males. In the past, however, it has already been demonstrated that interassay variabilities of these assays are quite low (<10 % for CT concentrations higher than 10 pg/ml) [16]. Although the definition of an assay-independent cut-off being questionable [12] our thresholds for bCT (≥46 ng/ml for males and ≥35 ng/ml for females) are comparable to those found in other assay-dependent reports (males: ≥68 ng/ml and ≥32.8 ng/ml; females ≥26 ng/ml, 18.7 ng/ml, and ≥14.6 ng/ml) [20, 23] indicating an advantage of our data: our results can be applied to different assay types for CT determination, at least for the assays used in our study.

Further limitations of our study are the missing data regarding the use of for instance proton pump inhibitors (PPIs) that have been described to increase CT concentrations [12, 37]. Besides, no data were available regarding the handling of the sample (from the time point of blood sampling till CT measurement), the age and weight

of patient or cigarette smoking. Although all these factors (including the use of a single test optimally) were not taken into account, the calculated cut-offs were – as mentioned above – similar to previous studies [16, 23].

A further drawback of our study is the absence of female goiter patients. The relatively low number of female CCH subjects (with one female having an extremely high bCT level) and the missing female controls might explain the relatively high cut-off (≥ 35 ng/ml, in comparison to ≥ 26 or ≥ 18.7 ng/ml as previously reported) [20, 23] and the poor specificity for females in our study.

In summary, we have identified gender-specific thresholds for the preoperative diagnosis of MTC, which can be used in clinical routine with reliable sensitivities and specificities. The data are comparable with previously published data. Additional studies are certainly required in order to confirm our data. These studies should also include double calcitonin measurements and a postoperative follow-up analyses. Still, until data with larger patient cohorts are available, we recommend the identified cut-offs for preoperative diagnostics and the indication of surgery.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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