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ORIGINAL ARTICLE

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Calcitonin kinetics in the early postoperative period of medullary thyroid carcinoma

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Abstract *Introduction*: Calcitonin is a sensitive marker for medullary thyroid carcinoma. Normalisation of calcitonin levels following resection of medullary thyroid carcinoma has been described after a few hours; however, it may be observed more than 4 weeks after surgery. The aim of this study was to correlate the postoperative calcitonin kinetics with preoperative calcitonin levels and tumour stage. Furthermore, we wanted to test the prognostic impact of the calcitonin kinetics. Therefore, only patients with postoperative normalisation of calcitonin levels (biochemical cure) were included in this study. *Methods*: Fourteen biochemically cured patients were analysed, including measurement of postoperative basal and pentagastrin-stimulated calcitonin concentration. With respect to the time of postoperative basal calcitonin normalisation, patients were classified into two groups: (A) patients with normalisation of basal calcitonin levels within 24 h and (B) patients with normalisation of basal calcitonin levels later than 24 h postoperatively.
Results: Eight patients were found to have normalisation of basal calcitonin levels within 24 h (group A). In the remaining six patients (group B), the period to normalisation of basal calcitonin levels varied from 6 days to 14 days and longer. There were no differences between the two groups with regard to tumour size, number and pattern of lymph node metastases and tumour stage. However, preoperative basal calcitonin levels were significantly different (258 ng/ml vs 955 ng/ml, $P<0.01$). In the group with slow-decreasing calcitonin levels, no strong correlation between the preoperative level and the postoperative time to normalisation of basal calcitonin levels could be established, which may be due to the small number of patients. After a median follow-up of 21 months, no patient developed tumour recurrence. However, an increased basal calcitonin level was observed in one patient from group B. All other patients had normal basal and peak calcitonin levels.
Conclusion: Using a highly sensitive calcitonin assay, we demonstrated that normalisation of basal calcitonin levels may be delayed in patients suffering from medullary thyroid carcinoma. The lack of correlation of preoperative levels and the time to normalisation of the basal calcitonin levels, as well as the positive pentagastrin test in some of the patients, argues that this phenomenon is not simply due to prolonged biochemical calcitonin elimination. Nevertheless, a prognostic influence could not be shown in this study due to the short follow up-period. Further investigations and a longer follow-up are necessary to determine the nature and the prognostic impact of delayed normalisation of calcitonin levels.

Keywords Medullary thyroid carcinoma · Kinetics of calcitonin · Prognostic impact

Introduction

Calcitonin (CT) is encoded by the CT1 gene, which is located on chromosome 10. Three other genes with a similar structure to the CT1 gene have been described, but only the CT1 gene is active in C cells. CT is produced by the parafollicular C-cells and, in small amounts, by other neuroendocrine tissue. Its physiological role has not yet been settled [1]. CT is a well-established tumour marker in medullary thyroid carcinoma (MTC). Analysis of CT is usually performed as radioimmunoassays. Common to all assays is a detection limit for CT, in modern assays about 1–1.5 pg/ml. Detectable values of CT can be found even in highly sensitive assays in less than 50% of presumably healthy adults [2, 3, 4, 5]. In patients suffering from MTC, a postoperative cure may be reflected by decreasing CT to normal or undetectable values [6]. The postoperative normalisation of CT levels can last for several weeks. In the 1970s, only case reports about prolonged CT normalisation were published [7, 8]. The first two small series about this phenomenon were published at the beginning of the last decade [9, 10]. Fugazzola et al. examined six patients and found a normalisation of CT in four patients after 2 weeks, in one after 12 weeks and in one after 24 weeks. A pentagastrin test was not performed [9]. Girelli et al. investigated the prognostic influence of the early postoperative CT levels in 33 patients. They found CT normalisation in 15 patients within 3 postoperative days. These patients showed no relapse within the next 12 months as tested using the pentagastrin test. The other 18 patients did not achieve normalisation, and, during the follow-up, 16 of them developed recurrent disease [10]. The aim of our study was to correlate the postoperative calcitonin kinetics with preoperative calcitonin levels and tumour stage. Furthermore, we wanted to test the prognostic impact of the calcitonin kinetics. Therefore, only patients with postoperative normalisation of calcitonin levels (biochemical cure) were included in this study.

Methods

In this study, we included patients suffering from an MTC without distant metastases who consented to repetitive blood sampling on several postoperative days after complete resection of a primary or recurrent MTC. In all patients a postoperative pentagastrin stimulation test was performed. Pentagastrin (0.5 µg/kg body weight) was given intravenously, and CT serum samples were taken before administration and 5 min after injection. We established two groups of biochemically cured patients with respect to the postoperative CT serum decrease: patients with basal CT normalisation within 24 h (fast normalisation, group A) and patients with basal CT normalisation later than 24 h (slow or delayed normalisation, group B). For all the patients, the following data were recorded: preoperative CT level, tumour size, number of lymph node metastases, number of regional compartments with lymph node metastases, tumour node metastasis (TNM) classification, UICC (Union Internationale Contra la Cancrum or International Union Against Cancer) tumour stage, familial or sporadic background, concurrent disease and drug history. For CT analyses we used a commercial two-site immunoradiometric assay with a detection limit of about 1.5 pg/ml and a very high sensitivity and specificity for native human monomeric CT, which detects CT in about 40% of presumably healthy adults (ELSA-hct, CIS Bio International). Basal values of less than 10 pg/ml and pentagastrin-stimulated values less than three times the basal value are considered normal [4, 5]. Follow-up data (basal and pentagastrin-stimulated peak CT, local or systemic recurrence) were collected by the family doctor biannually. Differences were calculated using the Chi square test or the Mann-Whitney U test. A *P* value of less than 0.05 was considered significant.

Results

Fourteen patients were included in this study. In eight patients, basal CT decreased to normal values within 24 h (group A). In the remaining six patients, we found slow basal CT normalisation (group B). All surgical procedures consisted of thyroidectomy and lymphadenectomy at least of the central cervical compartment. According to the tumour extent, lymphadenectomy was expanded to the lateral cervical compartments. There were no differences in age, sex and inheritance between the groups. No patient suffered from renal or hepatic failure. There were no patients taking proton-pump inhibitors (PPIs) such as omeprazole (Table 1). Moreover, the groups did not differ in tumour size, number of lymph node metastases, number of regional compartments with lymph node metastases, TNM classification or UICC tumour stage (Table 1).

Basal calcitonin levels

Preoperative basal CT levels ranged from 46 pg/ml to 744 pg/ml in group A and from 330 pg/ml to 1557 pg/ml in group B, and the mean preoperative levels (group A 258 pg/ml, group B 955 pg/ml) differed significantly ($P<0.01$, Fig. 1). Probably due to the small number of

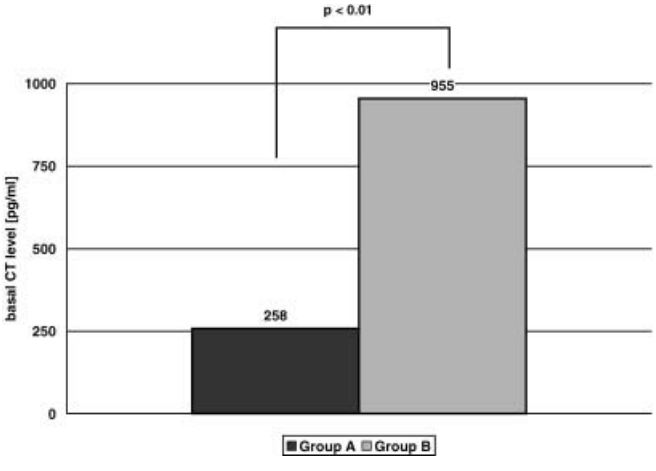

Fig. 1 Mean preoperative basal calcitonin (CT) levels

Table 1 Patient profiles. *CT* calcitonin, *MTC* medullary thyroid carcinoma, *TNM* tumour node metastasis, *n.s.* not significant, *UICC* Union Internationale Contra la Cancrum or International Union Against Cancer

	Group A (fast CT normalisation)	Group B (slow CT normalisation)	P value
Number of patients	8	6	
Mean age (years)	36	39	n.s.
Hereditary MTC	3	2	
TNM classification			
node negative (pN0)	3	4	0.28
pT1a–3a	3	3	
pT4a	0	0	
pT1b–3b	0	1	
pT4b	0	0	
node positive (pN1)	5	2	0.28
T1a–3a	3	0	
T4a	0	0	
T1b–3b	2	2	
T4b	0	0	
Number of lymph node metastases in node-positive patients (total number of dissected lymph nodes)	4 (46)	4 (31)	n.s.
Number of compartments with lymph node metastases	1	1.5	n.s.
UICC stage			
I	1	0	n.s.
II	2	4	
III	5	2	
IV	0	0	

Table 2 Preoperative basal calcitonin (CT) levels, time to CT normalisation and postoperative peak CT levels in group B

Patient	Preoperative basal CT level (pg/ml)	Time to normalisation (days)	Peak CT level (pentagastrin test, pg/ml)
1	1557	14	9, 0
2	1388	10	5, 9
3	980	14	66, 3
4	520	6	216
5[a]	330	>7	81, 3
6[a, b]	Not known/<1.5	>7	20, 5

[a] CT analysis only on the sixth postoperative day with increased values; CT normalisation at the next analysis after 16–24 weeks

[b] Male patient suffering from sporadic MTC; basal CT level after subtotal thyroidectomy <1.5 pg/ml; basal CT level after completion thyroidectomy with lymphadenectomy 12.7 pg/ml on postoperative day 6

patients in group B, we could not establish a correlation between the preoperative CT level and the postoperative time to normalisation of basal CT levels (Table 2).

In two patients (patients 1 and 2; Table 2) with preoperative CT levels of about 1500 pg/ml, normalisation of the basal CT levels occurred within 10 days and 14 days postoperatively. In patient 3 (Table 2) with a preoperative level of 980 pg/ml, we observed normalisation of basal CT levels within 14 days. In another patient (patient 5; Table 2) with a preoperative CT level of 330 pg/ml, the basal CT level on the sixth postoperative day was 41.1 pg/ml. The time to normalisation of the basal CT level is not known in this patient because he was tested only just 6 months later showing normal basal calcitonin levels. In another case, a 35-year-old man (patient 6; Table 2) who underwent subtotal thyroidectomy due to multinodular goitre, postoperative histology revealed an MTC (pT2apN0) that required completion thyroidectomy and lymphadenectomy. Unfortunately, no CT value was available before the primary operation. Before completion thyroidectomy, basal CT was undetectable (<1.5 pg/ml). On postoperative day 6, however, we found a basal CT level of 12.7 pg/ml and a stimulated peak CT level of 20 pg/ml. Four months later, basal and peak CT levels were within the normal range. The postoperative course of declining basal CT in four of the patients from group B is shown in Fig. 2.

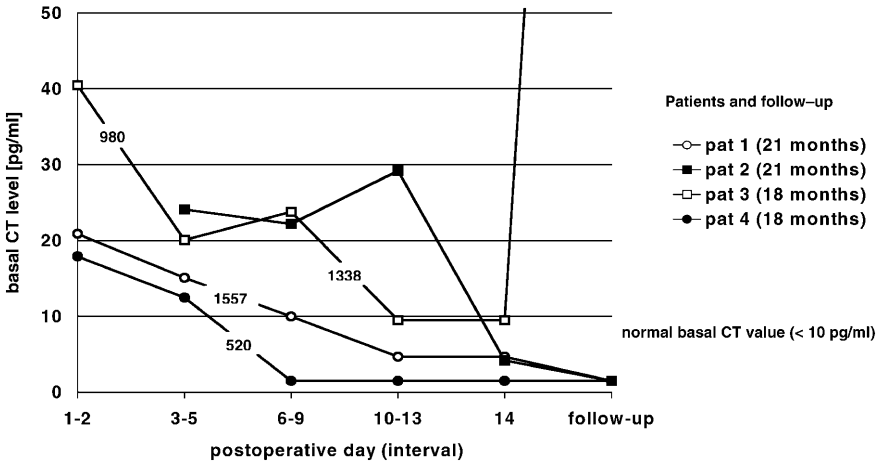

Fig. 2 Postoperative course of basal calcitonin (CT) levels and follow-up basal CT levels in group B (patients 1–4). The preoperative CT values are printed into the lines

Pentagastrin test (peak calcitonin levels)

CT stimulation by pentagastrin testing was performed in all patients. Despite fast normalisation of CT in group A, we found pathologically stimulated CT in two patients with maximums of 407 pg/ml and 74 pg/ml (Table 2). In group B, the pentagastrin test revealed pathological values in three patients with CT levels ranging from 65 pg/ml to 216 pg/ml (Table 2). Probably due to the small number of patients in group B, we could not establish a correlation between the preoperative CT level and the postoperative pentagastrin-stimulated peak CT levels (Table 2). Remarkably in the two patients with basal CT levels of about 1500 pg/ml preoperatively, pentagastrin tests were normal. However, in the patients with lower preoperative basal CT levels, peak CT levels were pathologically elevated early postoperatively.

Follow-up

After a mean follow-up of 21 months, no local or systemic relapse occurred. Only one patient (group B) developed a pathologic basal CT level after 12 months. In this female (patient 3; Table 2 and Table 3) suffering from a hereditary MTC, basal CT level increased up to 216 pg/ml after 18 months. In this patient, no pentagastrin test was performed. The remaining 13 patients had normal or undetectable CT levels (Table 3). Pentagastrin test results were available in 11 patients. Apart from the patient with increasing CT levels, all four patients with pathologic pentagastrin test early postoperatively were pentagastrin tested in the follow-up. There were no pathologic peak calcitonin levels in any of the tested patients (Table 3).

Table 3 Follow-up. *CT* calcitonin, *n.p.* not performed

Patient	Basal CT level (pg/ml)	Peak CT level (pentagastrin test, pg/ml)	Follow-up (months)
Group A			
1	<1.5	4.3	18
2	<1.5	<1.5	21
3[a]	3.2	6.0	21
4	<1.5	<1.5	24
5	<1.5	3.2	18
6[a]	2.1	5.2	21
7	4.1	8.1	21
8	<1.5	n.p.	24
Group B			
1	<1.5	4.6	21
2	<1.5	n.p.	21
3[a]	216	n.p.	18
4[a]	<1.5	5.2	18
5[a]	4.8	9	30
6	<1.5	<1.5	27

[a] Patients with pathological results in the pentagastrin test in the early postoperative period

Discussion

In this study, we confirmed that CT normalisation can be delayed in patients following surgery for MTC using a modern and highly sensitive radioimmunometric assay. Patients showing a fast basal CT normalisation within 24 h (group A) compared with patients with a delayed basal CT normalisation later than 24 h (group B) differed significantly only with regard to the preoperative CT levels. We found no difference with regard to tumour size, number of lymph node metastases and involved lymph node compartments. However, the number of dissected lymph nodes differed between the two groups (46 in group A vs 31 in group B). Hence, any difference might be masked by the so-called “down-staging phenomenon”.

In contrast to many other tumour markers, CT has a very high sensitivity and specificity for MTC. In rare instances, CT may be secreted from other neuroendocrine tissues. Persistently elevated CT levels after tumour resection almost certainly reflect residual disease [6, 11, 12]. Recently, the prognostic influence of the preoperative CT concentration has been shown by several authors [12, 13], but a clear cut-off point does not exist. In addition, other authors reported that a short doubling time of postoperatively increasing CT levels is a strong predictor for a poor prognosis [14].

The prognostic influence of early postoperative CT levels was systematically investigated by Girelli et al. using a CT assay with low sensitivity in 33 patients [10]. The authors reported a strong prognostic influence of CT normalisation within the first 72 h. All patients without a normalisation within this period had increasing CT levels at follow-up, and more than 90% of these patients suffered from tumour recurrence within 12 months after primary operation. In contrast, Wells et al. found normalisation of CT levels even after 1 week [6]. However, in single cases, CT normalisation was observed after several months [7, 8]. These data were confirmed in a small series by Fugazzola et al., who found normalisation of basal CT levels between 2 weeks and 24 weeks after surgery. In one patient, they demonstrated a rapid serum CT decrease with a half-life of 3 h followed by a slow CT decrease with a half-life of 30 h. The authors concluded that CT normalisation is not equivalent to definitive cure. Nevertheless, patients who have undetectable basal CT levels soon after surgery are those with the best prognoses [9].

In our study, we detected a delayed normalisation of basal CT levels in six patients using a very sensitive assay. The dependence of this delayed normalisation of basal CT levels on the preoperative CT level speaks in favour of a metabolic process.

Until now, only a few studies on the elimination of human CT have been published. Ardaillou et al. described in a kinetic study, using radioiodinated CT, three different half-lives of serum CT: two short half-lives of 4.5 min and 22.5 min and a long half-life of about 26 h. The authors found an increase of all half-lives in patients suffering from a renal failure in which the long half-life was mainly affected [15]. Hypercalcitonaemia was also reported in patients suffering from hepatic cirrhosis [16]. However, since in our series no patient suffered from hepatic or renal dysfunction we can exclude any influence of disturbed renal or bile excretion on the delayed basal CT normalisation kinetics.

Other authors reported only one half-life of CT of about 10–20 min based on the findings following CT stimulation by injection of either calcium or pentagastrin [1]. Either one may lead to secretion of CT vesicles but only in living C-cells. Stimulation of CT in other neuroendocrine tissues has not been reported [17, 18]. Substances other than pentagastrin that may stimulate CT secretion are gastrin and PPIs [1]. None of our patients suffered from clinical symptoms of hypergastrinaemia or took PPIs.

The nature of the different half-lives reported by Ardaillou et al. is unknown. It was assumed that secreted monomeric CT forms polymeric molecules or binds to other proteins in the peripheral blood [1, 19]. This phenomenon is one reason for the existence of high molecular-weight forms of CT in the peripheral blood of patients suffering from MTC [19]. However, whether these high molecular or bonded forms have a longer half-life due to a higher stability is not known.

Nevertheless, normalisation of CT levels later than 10 days following surgery in some patients observed in this and other studies, as well as the lack of correlation between the preoperative basal calcitonin level and the time to postoperative normalisation of CT and the postoperative peak CT levels, cannot be explained only metabolically. The delayed postoperative normalisation of CT levels and the possible stimulation of CT occurring in several patients might be an indicator for pre- or intraoperative tumour cell dissemination. Those disseminated cells might lose their hormone-producing potential or become inactive (G0) or apoptotic. However, the detection of disseminated tumour cells in MTC has not yet been reported.

Probably due to the relatively short follow-up period in our study, it is not possible to determine a prognostic impact of the delayed normalisation of basal CT levels. It may be of “biochemical” or “biological” nature, or both. However, our data suggest that delayed normalisation of basal CT levels might be of prognostic significance as can be seen in the patient with an increasing CT after 12 months. Wells et al. emphasised the importance of undetectable CT in demonstrating definitive cure [6]. Most of the patients, following total thyroidectomy due to differentiated carcinoma or goitre, did not show detectable CT levels even using very sensitive assays [3]. However, patients with detectable and even elevated postoperative CT levels after resection of an MTC without detectable recurrence or metastases are documented abundantly [20]. Therefore, CT normalisation has been used as an indicator for (biochemical) cure.

Conclusion

Delayed basal CT normalisation following resection of MTC does not depend on tumour size and number of lymph node metastases, but on the preoperative basal CT level. With respect to the half-life of CT, the interpretation of the delayed postoperative basal CT normalisation in some patients includes the possibility of pre- or intraoperative tumour cell dissemination. Due to the small number of patients and the short follow-up period, the

prognostic impact of the delay of CT normalisation remains unclear. In order to address this issue, repeated measurements of CT levels must be performed beginning on the first postoperative day. Further studies combining the evaluation of pre- or intraoperative tumour cell dissemination are required together with longer follow-up to determine a prognostic impact of the delay in CT normalisation and to explain the nature of this phenomenon.

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