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CALCITONIN REVISITED IN 2020

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Abstract

Calcitonin (CT) is a polypeptidic hormone specifically secreted by the thyroid parafollicular cells (C cells) and tangentially involved in human phosphocalcic and bone metabolism. CT from other species (e.g. salmon) is more potent than human CT and has limited therapeutic applications. The neoplastic proliferation of C cells leads to medullary thyroid carcinoma (MTC) generally characterized by an increase of CT secretion. Serum CT is therefore the ideal marker for MTC and can confirm its presence at an early stage, as well as the follow up of its remission or progression/relapse/survival after surgery. There are, however, controversies such as the necessity of CT screening in patients with thyroid nodules, or particular situations causing false positive or false negative results. Our minireview also deals with an up-to-date of surgical procedures for MTC, as well as with non-surgical therapy.

Key words: calcitonin, thyroid, medullary carcinoma, therapy.

Calcitonin as a hormone

First described in 1959 (1), the parafollicular C cells derive from the neural crest and ultimobranchial body ectoderm and are found within the thyroid follicles, comprising 1% of all thyroid cells (2). C cells specifically secrete a polypeptide hormone of 32 aminoacids, calcitonin (CT) from a larger precursor, pre-pro-CT (2). Calcitonin effects are mediated by G protein-coupled membrane CT receptors (CTR) found in multiple organs, including the brain, kidney and bone (2). In other species CT potently blocks kidney calcium reabsorption and osteoclastic activity, thereby antagonizing parathyroid hormone (PTH) (3), but in human adults its physiological role remains elusive (2, 3). Indeed, patients with long term hypercalcitoninemia due to medullary thyroid cancer (MTC), as well as thyroidectomized persons with very low CT levels have no modifications of their phosphocalcic profile or bone mineral density (3). CT seems, however, to play a protective role on maternal and fetal skeleton during pregnancy and lactation, when its circulating levels are increased. The sources for CT during pregnancy become the placenta and the fetus itself, while in lactation CT starts to be secreted by the mammary gland (4). Fish CT stimulates the CTR more efficiently than human CT. Salmon CT found its place in treating vertebral osteoporosis, also because of its antalgic central effects, hypercalcemia, as well as Paget's disease (5).

Calcitonin as a diagnosis marker for MTC

The neoplastic proliferation of C cells leads to MTC, contributing to 1-3% of total thyroid neoplasia (6). MTC can be caused by an activating mutation of the RET proto-oncogene, embracing a familial form in 25% of cases, either isolated or in the context of MEN2 syndromes. The majority (75%) of MTC appears, however, sporadically, with no mutation described (6). Neoplastic C cells generally do not lose their secretory capacity, therefore serum CT represents an excellent tumor marker for MTC, as well as for the early diagnosis of C cell proliferation, in the state of C cell hyperplasia (CCH) (6). Newer sandwich two-step techniques with monoclonal antibodies are more specific and accurate for CT evaluation, excluding the interference of precursor molecules (6). Normal CT levels are higher in children but decrease below10 pg/mL in most healthy adults, being slightly higher in males than in females (4, 6, 7).

When CT reaches values above 100-200 pg/mL, the presence of MTC is usually certified. CT levels generally parallel with tumor volume, as well as the appearance and amplitude of metastases (6,8). Very rarely, other non C cell-derived tumors, such as carcinoids or small cell lung cancers, may also be accompanied by very elevated CT levels (6). Lower CT values (between 10-40 pg/mL), although considered pathological, are more difficult to be

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interpreted, because normal range varies function of sex and the commercial kit used and slightly increased CT levels may be found in other non-malignant conditions (certain cases of autoimmune thyroiditis, chronic renal failure, chronic pulmonary disease, acute trauma, pregnancy, hypercalcemia, hypergastrinemia, hypercatecholaminemia, type 1A pseudohypoparathyroidism, mastocytosis, sepsis) (4, 6, 7, 9, 10).

Stimulation tests are useful for the differential diagnosis between MTC or CCH and the particular conditions accompanied by increased CT mentioned above. Pentagastrin stimulation test was abandoned due to its unavailability in many countries and its side effects and replaced by the rapid infusion (2.4 mg/kg iv) calcium test (6, 7). A surge of CT levels above 500 pg/mL in males and 80 pg/mL in females supports the diagnosis of CCH/MTC (11). A lower differentiation of TMC is reflected by a milder response to CT stimulation test (less than tenfold) suggesting an increased risk of invasion and metastases (6).

A subject of much debate is whether to routinely evaluate CT levels at all patients found with thyroid nodules (7). Thyroid nodules are very common and are recently found even more often during cervical ultrasound (over)investigation, but rarely turn out to be a MTC. Whether certain authors believe that CT screening may contribute to precocious diagnosis and cure of patients with MTC (12), others argue that the frequent false positive patients compared to the rare patients with MTC may increase the incidence of useless thyroidectomy, and that sporadic CCH is not proven to evolve toward MTC (13). Similarly, European Thyroid Association proposed CT screening in all thyroid nodules, whereas all other societies in the field agree that CT screening is not recommended and that CT should be measured only whenever the clinician considers it necessary (7). Moreover, the cost-effectiveness of such CT screening would be comparable to the colonoscopy or mammography screening (7). The personal opinion of one of the authors (DDB) is that CT should be evaluated in the following situations: [1] at all first degree relatives of patients diagnosed with sporadic MTC or familial MTC and with proven RET mutation, [2] at patients with clinical signs suggestive for MTC (large thyroid nodules and/or cervical lymph nodes, eventually accompanied by flushes, weight loss and motor diarrhea) [3] at patients with suspicious nodules by ultrasound investigation (irregular limits, large antero-posterior diameter, central vascularization, microcalcifications) and/or by fine needle aspiration biopsy (FNAB) and/or with non-suspicious nodules by ultrasound/FNAB but with quick volume increase. CT should not be evaluated [1] at first degree relatives of patients with familial MTC but not mutation carriers [2] at patients with non-suspicious thyroid nodules or with other thyroid pathology, e.g. autoimmune thyroiditis. CT can be also evaluated in the FNAB washout from a suspicious nodule (6, 8, 13).

Preoperative CT can also be used as a prognostic marker. The risk of lymph node metastases is minimal at CT levels below 53 pg/mL but increases at CT > 500 pg/mL (6). Preoperative CT > 1000 pg/mL suggests the presence of metastases and predicts failure to reach biochemical cure after surgery (8).

CT is not the only sensitive marker for MTC, since this type of cancer can secrete also carcinoembryonic antigen (CEA), neuron specific enolase (NSE), chromogranin A (CgA) and procalcitonin (proCT), all useful for MTC diagnosis and follow-up (9,10). Although CT is usually proportional with tumor volume, large MTC with only a mild or even absent increase of serum CT are also occasionally described. Albeit rare, non-secreting MTC is challenging because it is diagnosed later, and it is difficult to be followed. These anecdotic cases can be explained by: [1] a lack of CT synthesis, but an altered co-regulation of CgA ("chromograninomas") or CEA, which may be increased in serum or positively stain the tumor by immunohistochemistry, [2] a de-differentiation of a large tumor causing an aggressive evolution despite low CT, [3] the "hook effect" caused by very high CT levels through excessive usage of the first sandwich monoclonal antibody' leading to incorrectly low detection in the serum, [4] release of different types of CT, [5] capacity of CT synthesis, but not secretion, [6] a thymic origin of these tumors, [7] a CT negative neuroendocrine tumor (NET) of the thyroid. Many non-secreting MTC preserve the capacity to synthesize proCT and even CGRP, useful as follow-up markers (9, 10).

Up-to-date guidelines in the surgical approach of MTC

CT plays an important role in diagnosis and preoperative staging of sporadic or hereditary MTC by reflecting the tumor burden both in terms of primary tumor, lymph node (LN) involvement and distant metastasis. Moreover, CT seems to be, unlike any other biochemical marker, at least equal to imagistic findings helpful in adjusting the extent of surgical

treatment and as a parameter of response to local and systemic therapies.

Very recently Niederle *et al.* found early detection of MTC cutoff levels for baseline CT of 43 pg/mL for males and 23 pg/mL for females, while levels of >100 pg/mL and >85 pg/mL respectively were suggestive for predicting lateral neck LN metastasis (14).

Unlike in papillary thyroid carcinoma (PTC), in addition to total thyroidectomy (TT), central compartment (level VI) lymphadenectomy is advised routinely in cases of MTC confined to the thyroid and apparently (clinically and ultrasonographically) without LN metastasis (cN0) (15).

A normal postoperative basal serum calcitonin level (< 10 pg/mL) is defined as "biochemical cure" which may be reached in almost all N0 cases but in 20% or less in node-positive MTC after compartment-oriented surgery (16).

Absolute number of LN metastases was found to be a better predictor of biochemical cure than metastatic LN ratio (the number of metastatic nodes divided by the number of nodes dissected) or AJCC node category, after initial and revisional surgery for node-positive MTC. This effect may be surpassed only by the clinical impact of distant metastasis, a condition incompatible with biochemical cure. Revisional surgery is in itself an independent predictor of biochemical persistence/recurrence, posing the technical issues of removing residual tumor from a scarred fibrous operative field (especially in the central compartment) with significant nervous and parathyroid related morbidity.

Despite thorough neck dissection for node positive MTC, only 27.4 % of the patients with preoperative serum CT levels above 10 pg/mL were biochemically cured after initial operation, and 13.5 % after reoperation (8). Given the propensity to lymphatic spreading and high rates of occult nodal disease, "prophylactic" or routine central neck dissection (CND) is advised in MTC, although specific morbidity is significantly higher. In a recent review, Lombardi and colleagues found that TT with CND leads to a higher risk of complications when compared with TT alone, particularly related to hypoparathyroidism (hPT) rather than recurrent laryngeal nerve (RLN) injury (17).

Lateral neck (levels II-V) lymphadenectomy is advised when clinical or ultrasonographical LN involvement is obvious or related to high levels of CT. Machens and Dralle found that basal CT levels thresholds of 20, 50, 200, and 500 pg/mL were consistent with the presence of LN metastases in the ipsilateral central and lateral neck, contralateral central neck, contralateral lateral neck, and upper mediastinum respectively (18).

Patients with MTC have relatively high rates of nodal metastases and once the disease has escaped the thyroid gland, 'cure' rates drop considerably. This is particularly true if the disease is present in the lateral compartment. In fact, if there is contralateral lateral neck disease, patients are considered incurable irrespective of treatment approach. Despite of the local persistence /recurrence of the disease, long-term survival in these patients can be expected with 10-year survival over 70%. Therefore, a balance has to be made between the aggressiveness of treatment/ morbidity *versus* long-term benefit. Patients with MTC and evidence of nodal metastasis or high CT levels at presentation have low rates of biochemical cure, regardless of the extent of surgery (19).

The latest revised American Thyroid Association (ATA) recommendations state that patients with MTC confined to the neck and cervical lymph nodes should have a total thyroidectomy, dissection of the central LN compartment and of the involved lateral neck compartments. An apparently negative contralateral neck compartment should also be cleared if the basal CT level is above 200 pg/mL (15). Reinterventions for completing lymphadenectomy should be considered if the basal serum CT level is less than 1000 pg/mL and up to five metastatic LN were removed at the initial surgery.

The term "prophylactic" is actually used for thyroidectomy in children who have inherited a RET mutation before MTC develops or while it is clinically unapparent and confined to the gland. After completion of diagnosis of hereditary MTC by direct DNA analysis, the level of basal and stimulated CT is the most important factor in deciding the timing of prophylactic thyroidectomy (15).

Endoscopic and robotic techniques continuously developed and gained visibility in surgery of the thyroid and parathyroid in the last decade, initially for benign conditions, but recently total thyroidectomy and neck dissection were reported for malignant diseases including MTC (20). Besides the obvious cosmetic advantage resulting from the lack of visible scars on the neck, the oncological completeness and safety of the procedure are not biased due to superior visualization and articulate robotic arm that moves freely at various angles allowing delicate and precise gestures (20).

Calcitonin as a follow-up and prognosis marker for operated MTC

CT should not be evaluated immediately after tumor excision, due to its long half-life which impedes its fast clearance from the circulation. Low/normal CT 3 months after surgery suggests cure, and its normalization after only one week certifies the absence of lymph node metastasis (6, 8). CT evaluation 3 days after surgery was proven to have prognostic value by calculating the Calcitonin Ratio (CR), i.e. preoperative CT / postoperative CT 3 days after surgery (21). A CR above 0.15 implies a high risk of structural disease persistence after surgery (21). This prognosis method is simple, avoids measurement technique-dependent fluctuations and gives quick and accurate information about the prognosis (21). Follow-up should be continued every 6 months for the first year and then yearly in cases with undetectable or normal postoperative CT, eventually with a stimulation test for detectable CT < 10 pg/mL. The lack of CT evolution during the follow-up increases the chance of cure to 95%, however long-term CT measurement and ultrasound follow-up are recommended (6,8).

If postoperative CT is constantly above 10 pg/mL, then some degree of disease may persist after surgery and measurements should be performed every 3 months. At postoperative CT levels > 150 pg/mL, the presence of distant metastases is likely (6). The doubling time (DT) of CT and CEA levels reflects the growth rate of tumor tissue and the survival prognosis. A DT decreasing from 2 years to 6 months decreases survival four-fold (from 92% to 25% for 5-year survival and from 37% to 8% for 10 year survival) (6,8,21). If the DT is shorter for CEA, this reflects tumor de-differentiation and a more reserved prognosis (6). The very rare non-secreting MTC should be followed with pro-CT, CGRP, CgA and CEA measurement, as well as neck ultrasound, computerized tomography and 18 – fluorodeoxyglucose PET/CT (9,10).

Novelties in the medical therapy for MTC

Locoregional recurrence may benefit of surgical reintervention and external radiotherapy (8,15). Distant metastases are usually multifocal, but they may progress slowly. Cytotoxic chemotherapy has limited efficacy. Chemoembolization with adriamycin may be efficient in large liver metastases. Kinase inhibitors of tumor cells (RET and other kinases) or of endothelial cells (VEGFR) such as Cabozantinib or Vadentanib may be efficient in selected cases of progressive disease and should be used as first line intention (22, 23). MTC is an immunologically active tumor and has a specific immune profile which may be therapeutically targeted. Immune checkpoint blocker pembrolizumab (anti-PD1) is currently under investigation in MTC. Malignant C cells may have targetable antigens allowing adoptive T cell therapy in the near future (24).

In conclusion, CT is less important as a calcium and bone regulator in humans but is a very specific marker for the diagnosis and prognosis of MTC. CT evaluation should probably be performed in selected cases, at the clinician's advice. Presurgical CT levels of over 1000 pg/mL, numerous local lymph node metastases, a CR above 0.15 and a short DT suggest a high risk of tumor progression and distant metastases. Modern surgical techniques increase the chance of cure for more advanced disease stages. Newer therapeutic strategies may increase survival of non-operable patients with MTC.

Conflict of interest

The authors declare that they have no conflict of interest.

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