

RESEARCH OUTPUTS / RÉSULTATS DE RECHERCHE

Calcitonin

Faour, Omar; Gilloteaux, Jacques

Published in:

Translational Research in Anatomy

DOI:

[10.1016/j.tria.2017.01.001](https://doi.org/10.1016/j.tria.2017.01.001)

Publication date:

2017

Document Version

Publisher's PDF, also known as Version of record

[Link to publication](#)

Citation for pulished version (HARVARD):

Faour, O & Gilloteaux, J 2017, 'Calcitonin: Survey of new anatomy data to pathology and therapeutic aspects', *Translational Research in Anatomy*, vol. 6, pp. 4-15. <https://doi.org/10.1016/j.tria.2017.01.001>

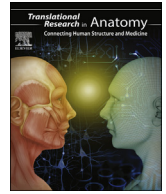
General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.



Calcitonin: Survey of new anatomy data to pathology and therapeutic aspects



Omar Faour ^a, Jacques Gilloteaux ^{a, b, *}

^a Department of Anatomical Sciences, St Georges' University School of Medicine, KBT Global Scholar's Program, Newcastle upon Tyne, United Kingdom

^b Unité de Recherche en Physiologie Moléculaire (URPhyM), Faculté de Médecine, Université de Namur, Place du Palais de Justice, B-5000 Namur, Belgium

ARTICLE INFO

Article history:

Received 11 November 2016

Accepted 30 January 2017

Available online 2 February 2017

Keywords:

Calcitonin
Endoderm
Calcemia
Salmon calcitonin
Carcinoma
Osteoporosis
ECMO
Perinatal
Pro calcitonin

ABSTRACT

Since the discovery of calcitonin (CT) reports have questioned the physiological role of human CT in regulating calcemia. This peptide is produced out of the CT/CGRP gene splicing along with other factors or hormones, including somatostatin by synonymously called parafollicular cells, C thyrocytes or C cells located in the thyroid glands. The C cells have recently been proven to originate out of the ultimobranchial anlage of the pharyngeal endoderm instead of the neural crest cells as indicated in all textbooks. Both blood and urine CT and procalcitonin (proCT) found in human and other mammals can also be secreted by cells located outside the thyroid glands. Taking account of dietetic calcium intake, CT assists in the homeostasis of bone mineral mass during growth, lactation, and pregnancy, hypo- and hyper gravity along with other paracrine thyroid secretions. Excess CT level in tissue fluids, needle aspirations and, now proCT, can diagnose sepsis, medullary thyroid or other carcinomas; caution to be taken with ectopic CT and gender-difference levels. Salmon CT as diurnal oral delivery seems, if proven not toxic, best suited to continue preventing or treating several defects, especially osteoporosis, orthopedic-related pains, perinatal or acute, fatal hypercalcemia. Contemplating old with recent physiological clinical results, human longitudinal morphologic and molecular data dealing with C cells and their paracrine interactions are few while only animal studies make us know much about CT. Human samples out of biopsies or cadavers should be further endeavored from development to aging to fully correlate normal with extreme or peculiar pathologies.

© 2017 The Authors. Published by Elsevier GmbH. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Contents

1. Introduction	5
2. The anatomical basis: terminology, discovery, new developmental aspects	5
2.1. Terminology and location	5
2.2. Discovery	5
2.3. Newly found developmental origin and histology of the C thyrocytes	6
3. Calcitonin production	6
4. Calcitonin physiology	6
5. CT and human growth and ageing	7
5.1. Fetal	7
5.2. Peri- and postnatal	8
5.3. Calcitonin's effect on bone tissue is age and sex dependent	8
5.4. Calcitonin is not solo player but performs with others members of the same family	8
6. CT and gravity	9
7. CT measurement through its precursor peptide pro-calcitonin (proCT)	9
8. Medullary thyroid carcinoma (MTC) and other CT defects	9

* Corresponding author. Department of Anatomical Sciences, St George's University School of Medicine, UNN-Life Sciences, Drill Hall 013, Newcastle upon Tyne NE1 8ST, United Kingdom.

E-mail addresses: jgilloteaux@sgu.edu, jacques.gilloteaux@unamur.be (J. Gilloteaux).

9.	Chronic kidney disease (CDK) and calcitonin	9
10.	Calcitonin as a therapeutic agent	10
10.1.	Calcemia	10
10.2.	Osteoporosis	10
10.3.	Orthopedic or bone-related defects	10
10.4.	Low calcemia and ECMO	10
11.	Toxic effects of sCT?	10
12.	Conclusion	10
	Acknowledgements	10
	References	10

1. Introduction

'Plus est en vous' [There is more in you]

House Van Gruuthuse, Brugge.

Like many other hormones, pathologic observations and experiments that lead to the discovery of the calcitonin (CT) were performed under pathologic rather than normal physiological conditions out of small mammals (e.g. dogs, rats, pig, guinea pig). Initial observations were made by removal of the thyroid and parathyroid glands of dogs in Sanderson's laboratory [1,2]. Later, further observations about CT involved the delivery of a very high dose of calcium to dogs, rats and sheep that resulted in a significant fall in blood calcium and regulated phosphate uptake observed after parathyroidectomy [1–15]. These data led these authors to claim the existence of a new hormone whose crucial role is to control the body fluids' level or 'tone' of calcium, i.e. calcemia. Originally, and wrongly though, this hormone has been thought to be released by the parathyroid glands, so the large number of publications dealing with parathyroid [e.g. Refs. [1–13]]. It was only a year later after the original observations [3] that the same group followed by others demonstrated that the C cells in rat and dog thyroid glands were the true source of CT [13]. This 32-amino acid protein hormone was isolated and purified out and proven to originate from those C cells of the thyroid gland. Hence the name 'thyrocalcitonin' or 'calcitonin' to indicate its origin and function of the hormone [16–20]. Both terms are accepted by the World Health Organization and used in pharmaceuticals.

Sources of CT have also been extracted from ultimobranchial bodies of domestic fowl and fishes and this CT have been formulated to be used as medication [21–23]. Salmon CT (sCT) has been found to be most physiologically active CT to treat hypercalcemia [21,22] and osteoporosis [23].

This survey was initiated after previous observations describing crinophagy in the thyroid glands in both C and T thyrocytes of genetically obese rats [24] where one became intrigued about CT functions since this rat strain survived with high, toxic calcemia [22,23,25,26].

Based on earliest data, this report adds not only the newest information about the embryological origin of the C cells with the intent to comfort and stimulate further morphologic biomedical studies and their interrelationships with the adjacent thyroid gland cells and tissues to encourage further studies to clarify some paracrine functions and pathology already known through comparative physiology or histopathology.

Even though CT was the topic of several reviews [e.g. Ref. [27]], especially, another more recent one [28], it was found necessary to add this survey to encompass not only those very recent crucial developmental findings in regards with normal development but

also to convey the difficulties to obtain precious old data out of human tissues buried in archival state. Data from C cells from fetal to aging are needed to comfort the physiologic status of C cells, found to be interacting with the T thyrocytes because CT can regulate calcemia and is a marker for other pathologic etiologies of neo- or perinatal status and other diseases, including sepsis, bone repairs, ageing, and cancers. Finally, the usage of synthetic CT (sCT) is also evoked because this medication needed to acutely reduce a high and toxic serum calcium level, to treat osteoporosis as well as pain associated with bone surgeries may have a carcinogenetic activity. However, this warning based on statistics [29] appears in another study to suggest no such toxicity [30]. This ambiguity is hopefully further evaluated for possible therapy against osteoporosis along with toxic influence needs to be further verified to exploit its clinical utilization.

2. The anatomical basis: terminology, discovery, new developmental aspects

2.1. Terminology and location

The most recently published international Terminologia Histologica [31] has recommended naming the thyroid follicle's epithelial components T thyrocytes or follicular cells. Adjacent to these follicle cells are pale-wedged shaped cells. In human samples, these cells are few, often isolated or paired within the same epithelial lining, named C thyrocytes, C cells or parafollicular cells. These C cells encompass the same gland's epithelium but typically are prevented by T thyrocytes' junctional complexes to reach the follicles' lumina while their secretory apices discharge CT and small quantities of other peptides such as serotonin, thyrotropin-releasing hormone [7,8] as well as somatostatin [32–39] associated with the *Calcitonin-Gene Related Peptide/Calcitonin (CGRP/CT)* gene products as in the circulatory system via fenestrated capillaries located near the basal aspects of the thyroid follicles and with facilitated paracrine diffusion or through undefined, intercellular contacts as shown in rodents [24,32–37,39]. In rabbit [38], like in rat [39], a unique colocalization of CT with somatostatin or somatostatin-like peptide was also demonstrated. In addition, more C cells are in the right lobe than the left thyroid lobe and none in the isthmus [40].

2.2. Discovery

Hazard [41] recalled the detection of the C thyrocytes or C cells in 1875 by E Creswell Baber [42] in dog thyroid glands and named them 'parenchymatous cells'. The C thyrocytes were also recognized in the thyroid gland follicles by many authors [e.g. out of [41]]: 'parafollicular cells' [43–45], 'macrothyrocytes' [46], 'inter-follicular cells' [47], 'neurohormonal cells' [48], 'giant-light cells' [49], 'argyrophil cells' [50,51], 'light cell' [52] and, surprisingly,

'mitochondrion-rich cell' (Hürthle cell?) [53]. Normal C cells' histology, histochemistry and ultrastructural aspects can be read along with many publications dealing with the thyroid structure, some are old, very interesting when accessible often with high cost [for example, in Refs. [54–96]]. It is unfortunate that a very large number of publications describing the microscopic anatomy of human and animal C cells are currently considered as archives in most large libraries and in biomedical citation sites because many of these pioneered ultrastructural studies date from the 1960s'. Their content is often available as titles in those sites and eventually only available at high cost for today's investigators. The frustration about these unreadable archives is that significant information become ignored by new investigators or considered 'archaic' even though they could comfort other current data. Similar studies done in the past with ultrastructure aspects must ignominiously recommence, in animals and human samples, at cost of people's efforts and grants of research agencies or charities.

2.3. Newly found developmental origin and histology of the C thyrocytes

Today many textbooks still proclaim that C cells derived from Amine Precursor Uptake and Decarboxylase (APUD) aka Diffuse Neuroendocrine System (DNES) cells [97–101]. These cells were thought to arise from the mesectodermal neural crest [102–104] which then settle the T thyrocytes within the same basal lamina. Using immunohistochemistry with molecular markers along with a detailed morphologic thyroid development and his broad basis of data obtained throughout his career on the thyroid tissues, Kameda and collaborators [105–110] demonstrated in murine and other mammals that not only C thyrocytes but also T thyrocytes and thymus would derive from the ultimobranchial anlage, out of the pharyngeal endoderm lineage and producing, among others, chromogranin A, CGRP, somatostatin along with CT. These endodermal precursor cells required, among others, the transcription factors and signaling molecules Pax9, Tbx1, Ripply3, Pbx1, Mash1 (Ascl1), Hes1, Nkx2.1 (TTF-1), Pax3, Shh, FRS2 α , Eya1, EphA4, Hox3 paralogs (Hoxa3, Hoxb3, Hoxd3), Pax8. Others already found that *Eya1* gene is needed to differentiate into functional C cells [111]. Without specific molecular markers C cells' origin was also evoked by others [32,33,112–114] with the possibility evolving into different subtypes in normal development or interactive paracrine and endocrine influences [32,33,38,40,93,113–115] as noted in Ref. [24]. The influence of the pituitary on C cells has already been assumed in one old reference [116]. In addition, with somatostatin [38,40,93] another publication indicated that sympathetic activity can modify their activity [117].

While teaching human microscopic anatomy to students, it has always been intriguing to note that C thyrocytes were scarce among the thyroid follicles, contrarily to most small mammals that displayed many C cells taking residence within the thyroid follicles' epithelia. In some cases, their population appears large enough to become as replacing part of the interstitial, loose connective tissue adjacent to the follicles. Histometry and non-equal distribution among the twin lobes of the thyroid gland have been studied [40,118–121]. A recent review (without text access) seems to confirm Kameda's group and others, cited above, however without study of the migration and interactions with connective and nerve tissues [122].

Extracted from Ref. [24] on can illustrate this large population of C thyrocytes in Zucker rats as found in the FA/? (Fig. 1) less abundant than in the *fa/fa* thyroid (Fig. 2 a–b) as recently studied compared with those found in dog (Fig. 3) and in human thyroids (Fig. 4) [123]. One can recall that *fa/fa* rats carry a leptin receptor homozygous defect associated with a complex metabolic syndrome

that favors obesity caused by non-insulin dependent diabetes mellitus and hypothyroidism in which crinophagy was discovered in both C and T thyrocytes [24]. Furthermore, other undetermined cell types were noted aggregated with the typical C cells in these obese rats.

These observations can comfort much earlier data that showed a significant reduction of CT expression and serum release in the obese rats [124–127]. These obese rats develop reproductive deficiency but can survive by some unclear homeostatic balance bearing near toxic, high serum calcium levels [123–133] while assuming, as reported, a typical aging bone structure [124]. In addition, eluded in Ref. [24] as reviewed in diverse mammals, including human, where some functional interdependence between both C and T thyrocytes are reported [32,34,35,93,134–137]. Somatostatin can similarly modulate CT as, for example, insulin-growth factors and thyroid hormone [32,34,36–39,133]. Thus, interactions between C and T thyrocytes can also be suspected with connective tissue cells and innervation [93,138].

Incidentally, this survey on functions of CT in human was originally stimulated by this unpredicted, bizarre physiology found in the obese rodents because if calcium receptors are found on the C cells, these cells seem deficient in the leptin mutated *fa/fa* rats as noted in Ref. [24].

3. Calcitonin production

The human C thyrocytes produce the alpha-calcitonin gene that encodes a small family of peptides that include calcitonin (CT), katalcacin and calcitonin-gene related peptide (CGRP). Both CT and katalcacin peptides are produced from one precursor along with CGRP from the alternative splicing of the *CGRP/CT* gene located on human chromosome 11, that brings either alpha and beta CGRP isoforms, categorized as neuropeptides [35–37,137]. The regulation of CT gene expression and activities has already been studied in the peculiar obese Zucker rats [128–130]. CT half-life is quite short and level varies with age and sex [139–143], per thyroid damage or excision [145–148].

4. Calcitonin physiology

The following paragraphs are to note that most data about CT seems to indicate that this hormone alone, with interrelated ectopic one – possibly along with some of the co-secreted superfamily of CT and sex steroids with calcium-rich food intake - antagonizes parathyroid hormone (PTH) activities. CT is regulating a normal calcemia through maintenance of bone mineralization, and preventing its depletion like in osteolysis which results in calcium release in serum that can be balanced by capture of calcium from nutrients as well as retrieving phosphate in vivo and in vitro. Altogether, these activities make a valuable, significant physiologic role in skeletal homeostasis during the entire mammal's life cycle, especially when dynamic bone remodeling occurs during pregnancy and lactation. However, due to some overall decreased actions or of their receptors and intracellular messengers, CT and hormone co-adjuvants (superfamily, estrogens, etc) are unable to prevent the progressive decay favoring osteoporosis or other pathologies. Indeed, in normal physiology, CT stimulates the production of calcitriol or 1, 25-dihydroxycholecalciferol (1, 25(OH) 2D) after calcidiol is transported to the proximal tubules of the kidneys where it is hydroxylated at the 1- α position. The enzyme 25-hydroxyvitamin D3 1-alpha-hydroxylase catalyzes the conversion of calcidiol into calcitriol, the active hormonally active metabolite as vitamin D. Activation of the ligand of the vitamin receptor enhances the level of calcium (Ca²⁺) in the blood by increasing the uptake of calcium from the gut into the blood.

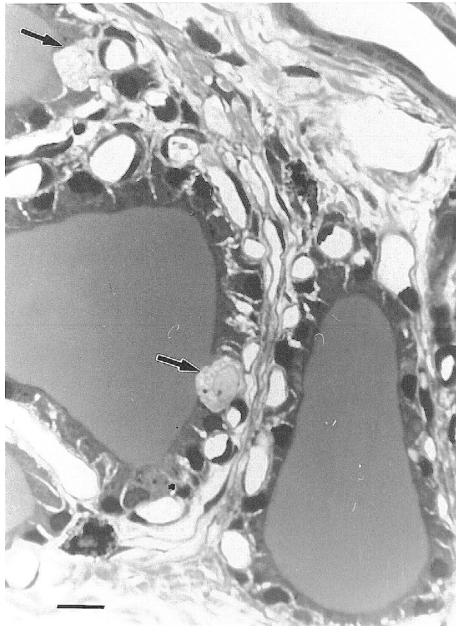


Fig. 1. One- μ m thick section of lean (Fa/?) young male Zucker rat thyroid; toluidine blue stain. A well-contrasted, simple cuboidal epithelium lines the follicles and, amongst them, a few poorly contrasted clusters of C cells are easily recognized (arrows). Note the numerous capillaries dilated but empty due to the perfusion. Scale is 10 μ m.

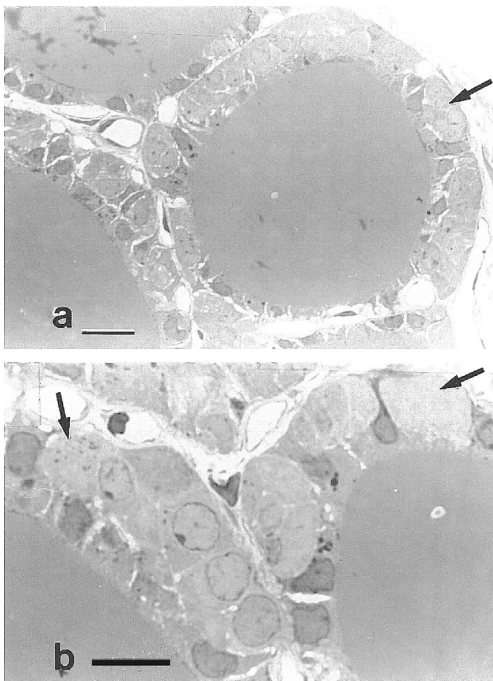


Fig. 2. A–B: One- μ m thick sections of obese (fa/fa) young male Zucker rat thyroid; toluidine blue stain. Both A and B micrographs illustrate the abundance of C cells surrounding the thyroid follicles compared with the lean thyroids. The well-contrasted T thyrocytes (T) appear distorted by the swollen, poorly used colloid of the follicles and by their surrounded crowds of parafollicular or C cells that show less stained. Many C cells appear with small and blue dark variable sized granulations and organize as if cell layers are in arcuate rows (arrows) under the stretched follicular cells also containing accumulated dark granulations. The vascular component appears poorly represented around these follicles when compared to those viewed lean rats. Scales equal 10 μ m [out of 24].

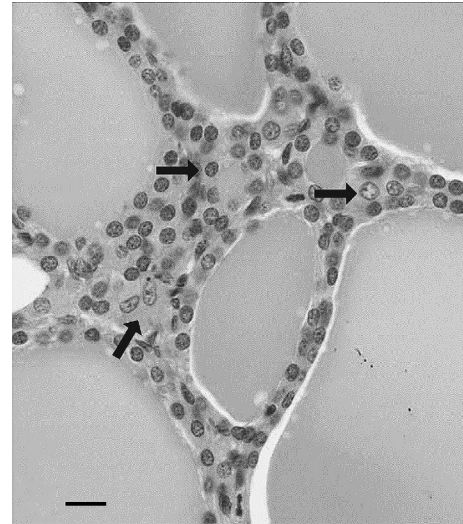


Fig. 3. Five μ m thick paraffin section of a dog thyroid, stained by H&E with Saffron C cells are indicated by arrows.

Calcitriol level also augments during pregnancy and lactation. Through their receptors, CT main function appears to control the inhibition of the osteoclasts' activity with the consequence of lowering the serum calcium level [1,5,13,145–148] even though CT half-life and signaling is somewhat short as opposed to that of PTH.

5. CT and human growth and ageing

5.1. Fetal

Building a bone skeleton already suggests that during the fetal and early postnatal periods a likely transient increased population of C thyrocytes with abundant secretion occurs mainly until some late adolescent age while ossification and maturation of the bone skeleton attained its greatest extent, then this cell population

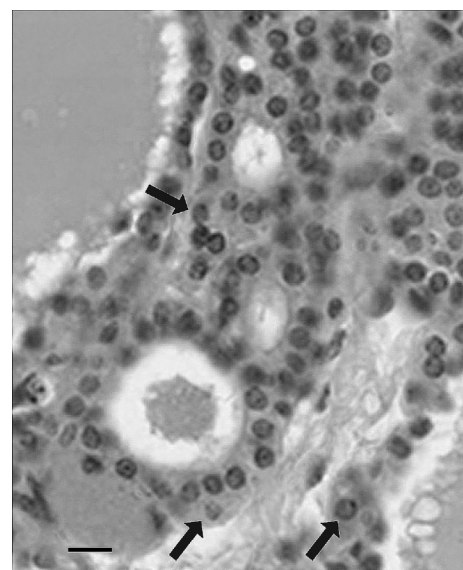


Fig. 4. Five μ m thick paraffin section of a human thyroid, stained by H & E with Saffron. Both 3 and 4 scales equal 10 μ m and kindly obtained from an area of the digital microscope histology set www.histology.be of the University of Namur Medical School C cells are indicated by arrows.

would probably decrease unless pathology occurs. Overall, one can note the absence of any morphologic correlations in human longitudinal studies that ultimately would correlate with the obvious, less invasive physiologic studies. Kameda and collaborators showed that both C thyrocytes and T thyrocytes derived from the ultimobranchial pharyngeal endoderm lineage and can produce somatostatin along with CT as well as other paracrine or co-localized hormones. This somatostatin production appears transiently in the murine fetus and gradually decreases with age, also in other mammals [107–110]. However, other studies have indicated somatostatin production postnatally and throughout life [32–34,37–39,134–137].

Kovacs and others [149–151] indicated that, pregnancy elevates serum CT and fetal CT level is higher than maternal levels in utero. They also wrote that ‘... apart from responding appropriately to changes in the serum calcium concentration, little evidence of an essential role for CT in fetal mineral homeostasis can be found’. Altogether one can suggest that the increased CT with sex steroids, prolactin, placental lactogen and IGF-1 (as well as other unknown factors) associate each other's activity in a sort of ballet where each hormone/dancer accomplishes a choreographic figure that is well defined (but not known entirely) and, in the course of each arabesque, interacts with some or all of the other hormones/components in a performance that results in the increased absorption of calcium by intestines, kidneys and from the skeletal system progressive bone mineralization as early as two-months in-utero. Biopsies demonstrated osteoclastic activity occurring as early as 10-week gestation while bone mass density studies did not adequately describe this physiological axis in-utero [149–151]. However, they also indicated that acute changes in bone mineralization during pregnancy do not seem to cause long-term changes in skeletal calcium content. One would here interpret that this bone remodeling can be viewed to accommodate dynamic developmental changes while increasing bone mineralization occurs in the growing skeletal tissues. As scant as the data are, only a few significant in vitro observations with human fetal tissues and trans iliac crest biopsies verified that CT has anti-osteoclastic activity [152,153].

5.2. Peri- and postnatal

In several readings [149–152,154] one noted that ‘... In humans, 1, 25(OH) 2D rises to adult levels over the first 48 h of postnatal life, likely in response to the rise in parathyroid hormone (PTH). Serum CT rises 2- to 10-fold over cord blood levels over the same time interval and then gradually declines. However, ‘... in infants that are premature, often develop hypocalcemia along with asphyxia and need extracorporeal oxygenation (or ECMO). These ‘premies’ can develop seizures [149–151,154,155] because the loss of placental regulation and other defects, including maternal diabetes and hypomagnesemia with high perinatal CT [150]. Consequently, hypercalcitoninemia has been suggested to cause neonatal hypocalcemia. However, other studies indicate that the postnatal rise in CT levels does not correlate to the fall in serum calcium [152–154]. In addition, these premature babies could eventually maintain fetal pulmonary neuroepithelial bodies with secretions that perturb homeostatic calcemia [156]. The same authors indicated that about ‘6-week postpartum, CT level returns to normal level’ [151,154,155]. Reports in veterinary investigations seem to comfort human data [157,158]. In some cases, hyperparathyroidism and pseudohypoparathyroidism require increased calcitriol in view of absent PTH [151,154,155]. Finally, it is noted that ‘... mice lacking CT gene lose twice the normal amount of bone mass calcium during lactation’. Thus, CT physiological action seems to protect against an excessive bone mineral resorption during that life period [159–162]. It is well-noted by the same authors [152,161–163]: ‘... whether CT

plays a similar role in human physiology is unknown’ but most of these important physiologic data are unfortunately without morphologic support in humans.

5.3. Calcitonin's effect on bone tissue is age and sex dependent

In adolescents, whether male or female, serum CT decreases with age [139–146,164–167]. However, CT maintains a higher level in male than females, especially during postmenopausal ages. There is a similar difference after a hypercalcemic challenge where the response in males is more significant than in females [139,142,168,169].

Through its receptors, and from a few critical data in vitro [81,146,154], CT's main function again appears to control the inhibition of the osteoclasts' activity or formation out of stem monoblasts in the marrow with the resulting, general effect of lowering the serum calcium and phosphate levels [1,5,13,81,170] even though CT half-life is somewhat short [18,145,146,159].

If most biochemical or clinical measurements are sporadically available since long ago from aged humans, one had no opportunities obtaining some published morphologic reports dealing with normal human aging C cells [e.g. Refs. [66,67]] but only old animals.

The hypo calcemic effect of CT - along with CGRP - in mature animals is minimal against osteopenia [169, 170] like CT null mice [171–174]. Calcitriol or vitamin D receptors also inhibits the release of CT as noted in cats [175], thus reducing blood calcium primarily by inhibiting calcium release from bone [176] while the effect of CT on renal excretion is disputed and response is age-dependent unless an active osteolytic bone disease is present [166–168,177].

The major effect of menopause on the skeletal bone mass is a dominant increase in bone turnover with resorption. This may be contributed by both the reduction of intestinal and renal absorption of calcium, hence the body is more prone to fracture. It is more frequent in women than men, probably caused by the decreased anabolic actions of estrogens, thyroxin and other bone growth factors on osteoblasts or their hormonal desensitization as osteoporosis sets [166,167], reviewed in Ref. [168]. In a few clinical studies, a prolonged recovery time for CT out of induced hypercalcemia in longer during ageing [e.g. Ref. [169]]. Furthermore, the mean basal CT level in women is generally lower than that of men. The infusion of calcium or pentagastrin in women resulted in a minimal or undetectable response in plasma CT whereas men showed a significantly greater increase. This relative deficiency in women may likely predispose them to an increase in osteoclast activity and bone loss, especially after menopause through low CT in osteoporosis [166–168].

5.4. Calcitonin is not solo player but performs with others members of the same family

The CT family members are small peptide hormones, involved in calcium homeostasis, vertebrate osteogenesis and osteoblast function [178]. In mammals, six CT family member peptides have been identified, which include calcitonin gene-related peptide alpha and beta (α CGRP and β CGRP), amylin, adrenomedullin 1 (ADM1), adrenomedullin 2 (ADM2 or intermedin) and calcitonin receptor-stimulating peptide (CRSP) [178,179] with distinct effects on bone cells. Calcitonin superfamily also encompasses amylin, calcitonin gene-related peptide, and adrenomedullin [180,181]. There are 2 types of receptors for CT, one for the CT (type I) and another for the sCT (type II). Even though type II provide a CT preferred conformation, type I requires other activity-modifying proteins [182–185].

Whether in conjunction with calcium and phosphate homeostasis, the distribution of CT receptors – along with the CT ectopic sites –

along with the interactions of CT superfamily of hormones, throughout the body of mammals and human is vast, puzzling, and still in need of further clarifications. Morphologic investigations and the support of newest molecular tools should further allow exciting discoveries that can still be made in endocrine studies. Let us mention as examples the CT receptors detected among diverse tissues and organs: bone marrow osteocytes [152,171,173,180,181,186–188], lymphocytes [189], central nervous system and pituitary [190], GI tract (especially stomach oxyntic and G cells and pathology [191–194], kidney [177,195,196], lung [156,197,198] and heart [199–201].

Taking a specific example in relationship with what is stated in the former paragraph, an intramuscular CT injection interferes to decrease gastrin production in old patients (60 and 82 years of age). One could also question: is it only the stomach and intestinal gastrin without the gastrin made in the central nervous system? [see Ref. [230]]. In addition, large doses of pentagastrin or glucagon have been shown to stimulate CT secretion but only cause a slight increase in plasma CT in comparison to calcium infusion. However, the relationship between gastrin and CT has yet to be identified and but it could be ectopic in cases of peptic defects [192,194].

CT receptor diversity and its association to cancers can be of diagnostic but also complicated by its ectopic sources [156,178]. One can think at the recent discovery about the endodermal origin of the C cells [110]. This basic find alone could reshuffle studies about CT paracrine and endocrine interrelationships with thyroid and other hormones.

Looking back in some comparative endocrine reports [202], one cannot ignore some apparent contradictory function of CT on calcemia homeostasis that has been published long ago: CT does not directly alter calcium metabolism in thyroidectomized pigs [203]. In rodents, a meal results in a reduced PTH secretion due to calcium entry via absorption in the digestive tract [204,205] or antibodies against CT comforted those data [206]. Other observations in hypocalcemia and hypothyroidism do not necessarily assist in understanding CT functions [207,208] because C cells metabolic interactions have been reported with T thyrocytes in many mammals and even human thyroid [24,32,33,108,110]. Curiously, extra-thyroidal tissues producing CT, found long ago [109,111,112], then detected in humans and monkeys [209–212] have not been granted more recent investigations using combined morphology and molecular tools, including ultrastructure to further understand these intriguing structures.

6. CT and gravity

Long duration of spaceflights with hypo gravity could have deleterious osteoclastic actions [213], in part caused by atrophy or loss of C cells during hypo gravity and, strangely, also caused by hyper gravity [214]. In the meantime, some sort of protection seems possible through the secretion of an inducible 18-kDa heparin-binding cytokine, namely pleiotrophin, also a platelet-derived growth factor [215–217]. Following the changes causing bone demineralization, then a recovery period to reconstruct the bone matrix lasting several weeks is needed [218].

7. CT measurement through its precursor peptide pro-calcitonin (proCT)

In clinical laboratories, diverse methods evolved with advances in technologies to evaluate CT plasma and urine level [219,228]. Early data displayed variability due to product degradation or technical procedures among laboratories [177,180,219,220]. Later, normal and cancer patients CT can be found as monomer and dimer

forms in both body fluids as well as the presence of pro-calcitonin (proCT) [185,221–224].

Incidentally, patients who underwent thyroidectomy have been found to have detectable CT in both serum and urine. These observations suggest that human CT can be secreted by extrathyroidal tissues [209–212,225] as it can be found in some bronchial tumors bearing ‘carcinoid’ cells [156,197,209,210,224]. Similarly, the detection out of lung, thymus and other tissues [109,225] could explain an alteration in the human interpretation of clinical results [210–215]. Furthermore, these ectopic CT data cannot be surprising since one again should recall the endodermal origin of the C cells [107–110]; these should help understanding some of these results [196,202–212,225]. High CT and receptors can be found in some forms of inflammations, especially highly toxic sepsis [225–229] and cancers, e, g. thyroid and medullary tumors [224,230,240–255], ovary [231–235] and prostate [236,237].

Innovative tests have been devised by Trimboli and collaborators in measuring the precursor of CT, pro-calcitonin (proCT), instead of CT and to be less laborious and sensitive technique, indicative of pathophysiologic disorders [237–239]. In all, fine needle aspiration (FNA) technique [228,238–240] is consistent with measurements of the fluidic samples for CT or, likely proCT. Difficult clinical cases can be resolved with imaging as technetium scintigraphy, PET and other combined methodologies, preceding or after surgical intervention [238].

8. Medullary thyroid carcinoma (MTC) and other CT defects

When high CT serum concentration is routinely measured in patients, it is mostly caused by a medullary thyroid carcinoma (MTC) [147,220,228–252]. This type of tumor does cause hypocalcaemia and some of the clinical symptoms include flushing, diarrhea, and/or weight loss.

Although serum CT concentration is being used to diagnose MTC, it is a sensitive test but not a specific marker because other pathologies than MTC, such as neuroendocrine tumors and hypergastrinemia, can also result in high basal CT levels, as noted in several previous paragraphs. For uncommon clinical cases, CT-negative MTC, it has been recommended to perform an ultrasound evaluation of the cervical region and calcium stimulus with measurements using electroluminescence immunoassay (ECLIA) for the follow-up of such cases [228,238,252].

Deficiency of CT is rare and occurs after total excision of the thyroid in some MTC, then serum CT level obviously disappears [147,210] (if no ectopic sources) proving again that CT is essentially produced by C cells.

Finally, in both female and male patients, serum CT can be found elevated in progression along with malignant ovarian [231–235] and prostate cancer [236,237] as a response to high calcemia.

9. Chronic kidney disease (CDK) and calcitonin

CDK is characterized by a loss of renal functions over a long period and results in inability to excrete wastes, to reabsorb minerals, and to form calcitriol. This insufficiency of calcitriol, with hypocalcemia and hyperphosphatemia, causes an increase in PTH synthesis and secretion [253,254]. Renal failure can often result in local parathyroid hypertrophy, cysts or benign parathyroid carcinomas. Thus, in patients with CKD, this secondary hyperparathyroidism with high serum PTH level causes an imbalance in the homeostatic mechanisms controlling bone minerals eventually leading to renal osteodystrophy [255]. CT does not seem to play a protective role in these patients and stay at normal serum level despite the high levels PTH. Hence, does CT protect the body from excessive PTH activity or would this alteration

balanced by nutrients?

10. Calcitonin as a therapeutic agent

10.1. Calcemia

There is little doubt that CT can balance calcemia through internal secretions especially in regards of acute or malignant hypercalcemia [148,256,257] but does not appear to act while osteopetrosis is developed [258].

10.2. Osteoporosis

Out of the original discovery, natural sources have been searched for it to be applied therapeutically against osteoporosis [259–262]. Testing slaughtered fowl and out of fisheries, salmon, extracted salmon CT (sCT) was found to be best source and more active [1,14,20–23] to help maintain bony skeleton while osteoporosis develops [263–272]. The fish sCT either oral or spray seems adequate clinically for managing acute hypercalcemia in patients but its effect lasts only for a week, longer than human CT for its favorable pharmaceutical properties [263–273]. A series of ongoing studies started in 2008 showed sCT taken orally by day seems favorable against osteoporosis or osteoarthritis defects [262–271]. However, new data are developed while this survey is written and submitted to this journal.

10.3. Orthopedic or bone-related defects

Other osteopathic defects have been experimented with sCT to treat vertebral fractures [274,275], pertrochanteric or other bone fractures [276,277]. In addition to the management of lumbar spinal stenosis (LSS) [278,279]. Insofar multiple studies have shown that sCT reduces pain caused by osteoporotic vertebral compression fractures, bone metastases, Paget's disease of bone [256] and adolescent idiopathic scoliosis [280].

Several researchers evaluated the effect of salmon CT using the visual analogue scale (VAS) in patients who suffer from lumbar spinal stenosis (LSS). One of the studies concluded that intramuscular injection of low dose CT on patients with LSS does improve bone pain in patients suffering from severe low back pain but has no effect on walking distance [279]. Another group investigated the effect of sCT as a therapeutic agent to alleviate anastrozole-induced bone pain in patients who suffer breast cancer – they found CT can act as an analgesic and effective to reduce bone pain; they also reported it had no effect on bone loss during cancer treatment [281] or bone pain associated with diabetes [282].

10.4. Low calcemia and ECMO

In case of hypocalcemia the adjustments made in critical illness calls for intravenous calcium [283–285], no mention is made about CT level [284] contrarily with premature infants [149–151,154,155,286,287] when high CT occurs perinatally.

11. Toxic effects of sCT?

CT is most widely used parenterally, however oral and nasal formulations are also available [21–23,262,263]. An isolated study reported an association between sCT use and cancer [29]. However, another recent study claims no carcinogenetic association [30]. This point of contention or ambiguous data should also be reviewed soon considering the ongoing sCT clinical trials [272].

12. Conclusion

The function of CT in humans is to be associated or to control the dynamics of bone growth and its homeostasis during fetal, youth, adulthood and decreased in ageing. It seems to prevail during the periods of high calcium demands dealing with bone remodeling, especially after fractures and the physiologic calcemia needed during lactation. In these instances, some animal studies suggest CT acts on the kidneys to favor an increased production of the active form of vitamin D to help meet the high body calcium demands along with some of the PTH activities by intervening in colonic reabsorption of calcium from the diet instead of using bone minerals as a mineral source. Other influences of paracrine hormones or signaling factors can interact with the C cells where most synthesis and release of CT occurs, including of some ectopic sites, likely lungs and thymus.

Even though a plethora of studies have been made on the human thyroid in basic and clinical investigations and some aspects of C cells and CT physiology remain a puzzle [27,28] The newly discovered common endodermal origin from the ultimobranchial body of the C and T thyrocytes (and other associated cells that probably disappear in fetus or soon after birth in human) may induce some studies. Especially new C cells' developmental and longitudinal human research studies to be done, first noninvasive, such as fluid measurements. In addition, morphology and molecular techniques added to ethical cadaveric studies would improve the understanding of ageing aspects about those C cells regarding the thyroid gland and the etiology of rare pathologies to foreseen new therapeutic strategies.

Acknowledgements

This study was done through scholarly activities sponsored by St George's University School of Medicine, at Northumbria University, Newcastle upon Tyne, UK and Grenada, WI along with the Unité de Recherche en Physiologie Moléculaire (URPhyM), Faculté de Médecine, Université de Namur, Namur, Belgium. O. Faour has made a major contribution while in Newcastle and Grenada campuses, now completing his medical studies. We are grateful for the teaching internet site www.histology.be of the University of Namur Medical School, Namur, Belgium for obtaining both Figs. 3 and 4 and with the assistance of Elise Scaillet, Infographist, for the setting of the illustrations.

References

- [1] D.H. Copp, Calcitonin and calcium metabolism, *C.M.A.J.* 103 (1970) 821–824.
- [2] P.H. Sanderson, F. Marshall 2nd, R.E. Wilson, Calcium and phosphorus homeostasis in the parathyroidectomized dog; evaluation by means of ethylenediamine tetraacetate and calcium tolerance tests, *J. Clin. Invest.* 39 (1960) 662–670.
- [3] D.H. Copp, A.G. Davidson, Direct humoral control of parathyroid function in the dog, *Proc. Soc. Exp. Biol. Med.* 107 (1961) 342–344.
- [4] D.H. Copp, E.C. Cameron, B.A. Cheney, A.G.F. Davidson, K.G. Henze, Evidence for calcitonin – a new hormone from the parathyroid that lowers blood calcium, *Endocrinology* 70 (1962) 638–649.
- [5] D.H. Copp, B. Cheney, Calcitonin—a hormone from the parathyroid which lowers the calcium level of the blood, *Nature* 193 (1962) 381–382.
- [6] D.H. Copp, Calcitonin—a new hormone from the parathyroid which lowers blood calcium, *Oral Surg. Oral Med. Oral Pathol.* 16 (1963) 872–877.
- [7] D.H. Copp, The parathyroid glands and regulation of blood calcium, *Oral Surg. Oral Med. Oral Pathol.* 16 (1963) 1249–1254.
- [8] D.H. Copp, S.S. Shim, The homeostatic function of bone as a mineral reservoir, *Oral Surg. Oral Med. Oral Pathol.* 16 (1963) 738–744.
- [9] D.H. Copp, Calcitonin – a new hormone from the parathyroid and its function in regulating blood calcium, *Rein Foie* 6 (1963) 23–30.
- [10] D.H. Copp, Parathyroids, calcitonin, and control of plasma calcium, *Recent Prog. Horm. Res.* 20 (1964) 59–88.
- [11] D.H. Copp, K.G. Henze, Parathyroid origin of calcitonin. Evidence from perfusion of sheep glands, *Endocrinology* 75 (1964) 49–55.

- [12] B.M. Carruthers, D.H. Copp, H.W. McIntosh, Diurnal variation in urinary excretion of calcium and phosphate and its relation to blood level, *Lab. Clin. Med.* 63 (1964) 959–968.
- [13] P.F. Hirsch, E.F. Voelkel, P.L. Munson, Thyrocalcitonin: hypocalcemic hypophosphatemic principle of the thyroid gland, *Science* 146 (1964) 412–413.
- [14] D.H. Copp, D.H. Hormonal control of hypercalcemia. Historic development of the calcitonin concept, *Am. J. Med.* 43 (1967) 648–655.
- [15] D.H. Copp, *Calcit. Adv. Intern. Med.* 14 (1968) 55–82.
- [16] M.A. Kumar, G.V. Foster, I. MacIntyre, Further evidence for calcitonin. A rapid-acting hormone which lowers plasma-calcium, *Lancet* ii (1963) 480–482.
- [17] P.F. Hirsch, G.F. Gauthier, P.L. Munson, Thyroid hypocalcemic principle and recurrent laryngeal nerve injury as factors affecting the response to parathyroidectomy in rats, *Endocrinology* 73 (1963) 244–252.
- [18] M.A. Aliapoulos, E.F. Voelkel, P.L. Munson, Assay of human thyroid glands for thyrocalcitonin activity, *J. Clin. Endocrinol. Metab.* 26 (1966) 897–901.
- [19] J.T. Potts jr, H.D. Niall, H.T. Keurmann, H.B. Brewer jr, L.J. Deftos, The amino acid sequence of porcine thyrocalcitonin, *Proc. Natl. Acad. Sci. U. S. A.* 59 (1968) 1321–1328.
- [20] H.D. Niall, H.T. Keutmann, D.H. Copp, J.T. Potts jr, Amino acid sequence of salmon ultimobranchial calcitonin, *Proc. Natl. Acad. Sci. U. S. A.* 64 (1969) 771–778.
- [21] O.L. Silva, K.L. Becker, Salmon calcitonin in the treatment of hypercalcemia, *Arch. Intern. Med.* 132 (1973) 337–339.
- [22] L.A. Wisneski, Salmon calcitonin in the acute management of hypercalcemia, *Calcif. Tissue Int.* 46 (1990) 26–30.
- [23] K. Henriksen, A.C. Bay-Jensen, C. Christiansen, M.A. Karsdal, Oral salmon calcitonin – pharmacology in osteoporosis, *Expert Opin. Biol. Ther.* 10 (2010) 1617–1629.
- [24] J. Gilloteaux, D. Pardham, Crinophagy in thyroid follicular and parafollicular cells in male obese Zucker rat, *Ultrastruct. Pathol.* 39 (2015) 255–269.
- [25] C.W. Cooper, J.F. Obie, A.R. Hughes, D.L. Margules, J.J. Flynn, Secretion of calcitonin in the genetically obese Zucker rat (fa/fa), *Proc. Soc. Exp. Biol. Med.* 173 (1983) 48–55.
- [26] J.J. Flynn, D.L. Margules, T.C. Peng, C.W. Cooper, Serum calcitonin, calcium and thyroxine in young and old Zucker fatty rats (fa/fa), *Physiol. Behav.* 31 (1983) 79–84.
- [27] J. Kirk, C. Hepfinger, *Calcit. Clin. Rev. Bone Mineral. Metab.* 3 (2005) 39–49.
- [28] A.J. Felsenfeld, B.S. Levine, Calcitonin, the forgotten hormone: does it deserve to be forgotten? *Clin. Kidney J.* 8 (2015) 180–187.
- [29] R.A. Overman, M. Borse, M.L. Gourlay, Salmon calcitonin use and associated cancer risk, *Ann. Pharmacother.* 47 (2013) 1675–1684.
- [30] G. Wells, J. Chernoff, J.P. Gilligan, D.S. Krause, Does salmon calcitonin cause cancer? A review and meta-analysis, *Osteoporos. Int.* 27 (2016) 13–19.
- [31] FICAT or Federative International Committee on Anatomical Terminology (now FIPAT), Terminologia Histologica – International Terms for Human Cytology and Histology, Wolters Kluwer/Lippincott Williams & Wilkins, Philadelphia, 2008, p. 82.
- [32] J.M. Fernandez-Santos, J. Morillo-Bernal, R. Garcia-Marin, et al., Paracrine regulation of thyroid hormone synthesis by C cells, in: N.K. Agrawal (Ed.), *Thyroid Hormone*, Chapter 3, Intech Open Access, 2012, pp. 51–83, <http://dx.doi.org/10.5772/46178>.
- [33] J.C. Utrilla, J. Morillo-Bernal, F. Gordillo-Martínez, R. García-Marín, J.L. Herrera, J.M. Fernández-Santos, J.M.E. Díaz-Parrado, C. Garnacho, M. De Miguel, M.I. Martín-Lacave, Expression of hypothalamic regulatory peptides in thyroid C cells of different mammals, *Gen. Comp. Endocrinol.* 187 (2013) 6–14.
- [34] S.G. Amara, V. Jonas, M.G. Rosenfeld, E.S. Ong, R.M. Evans, Alternative RNA processing in calcitonin gene expression generates mRNAs encoding different polypeptide products, *Nature* 298 (1982) 240–244.
- [35] A. Ali-Rachedi, I.M. Varndell, P. Facer, C.J. Hillyard, R.K. Craig, I. MacIntyre, J.M. Polak, Immunocytochemical localisation of katecalcitonin, a calcium-lowering hormone cleaved from the human calcitonin precursor, *Clin. Endocrinol. Metab.* 57 (1983) 680–682.
- [36] M. Zabel, Ultrastructural localization of calcitonin, somatostatin and serotonin in parafollicular cells of rat thyroid, *Histochem J.* 16 (1984) 1265–1272.
- [37] I. MacIntyre, M. Alevizaki, P.J. Bevis, M. Zaidi, Calcitonin and the peptides from the calcitonin gene, *Clin. Orthop. Relat. Res.* 217 (1987) 45–55.
- [38] R. Buffa, J.A. Chayvialle, P. Fontana, L. Usellini, C. Capella, E. Solcia, Parafollicular cells of rabbit thyroid store both calcitonin and somatostatin and resemble gut D cells ultrastructurally, *Histochemistry* 62 (1979) 281–288.
- [39] J. Seidel, M. Zabel, A. Kasprzak, R. Spachacz, The expression of calcitonin, calcitonin gene-related peptide and somatostatin in the thyroids of rats of different ages, *Folia Morphol. Warsz.* 62 (2003) 485–487.
- [40] E. Albi, F. Curcio, R. Spelat, R. Lazzarini, E. Loret, I. Ferri, F.S. Ambesi-Impimbato, The thyroid lobes: the different twins, *Arch. Biochem. Biophys.* 518 (2012) 16–22.
- [41] J.B. Hazard, The C cells (parafollicular cells) of the thyroid gland and medullary thyroid carcinoma, *Am. J. Pathol.* 88 (1977) 214–250.
- [42] E.C. Baber, Contributions to the minute anatomy of the thyroid gland of the dog, *Proc. Roy. Soc. Lond. B* 24 (1875) 240–241.
- [43] G.E. Wilson, The thyroid follicle in man. Its normal and pathological configuration, *Anat. Rec.* 37 (1927) 31–61.
- [44] J.F. Nonidez, The origin of the 'parafollicular' cell, a second epithelial component of the thyroid gland of the dog, *Am. J. Anat.* 49 (1932) 479–505.
- [45] W.E.W. Roediger, The oxyphil and C-cells of the human thyroid gland: a cytochemical and histopathologic review, *Cancer* 36 (1975) 1758–1770.
- [46] G. Zechel, Observations on the follicular cycle and on the presence of the 'macrothyrocyte' in the human thyroid, *Anat. Rec.* 56 (1933) 119–130.
- [47] R.N. Baillif, Cytological changes in the rat thyroid following exposure to heat and cold, and their relationship to the physiology of secretion, *Am. J. Anat.* 61 (1937) 1–20.
- [48] P. Sunder-Plassmann, Ueber neuro-hormonale Zellen des Vagusystems in der Schilddrüse, *Dtsch. Z. Chir.* 252 (1939) 210–223.
- [49] H.W. Altman, Die Parafollikuläre Zelle der Schilddrüse und ihre Beziehungen zu der gelben Zellen des Darmes, *Beitr. Pathol. Anat.* 104 (1940) 420–454.
- [50] W. Sandritter, K.H. Klein, Ueber argyrophile Zellen in der Schilddrüse, *Frankf. Z. Pathol.* 65 (1954) 204–218.
- [51] W. Sandritter, E. Kummer, G. Pilat, L. Rowe, Zür Histochemie und Funktion der parafollikulären Zellen in der Schilddrüse, *Klin. Wschr.* 34 (1956) 871–872.
- [52] M. Stux, B. Thompson, H. Isler, C.P. Leblond, The 'light cells' of the thyroid gland in the rat, *Endocrinology* 68 (1961) 292–308.
- [53] G.V. Foster, I. MacIntyre, A.G.E. Pearce, Calcitonin production and the mitochondrion-rich cell of the dog, *Nature* 203 (1964) 1029–1030.
- [54] G.S. Williamson, H.I. Pearce, The structure of the thyroid organ in man, *J. Pathol. Bacteriol.* 4 (1923) 459–469.
- [55] L.v. Bakay, Die parafollikulären Zellen des Kropfes, *Virchows Arch. Pathol. Anat. Physiol. Klin. Med.* 314 (1947) 329–344.
- [56] M. Gabe, M. Données histochimiques sur les cellules parafolliculaires de la glande thyroïde du chien, *Acta Anat. (Basel)* 38 (1959) 332–344.
- [57] G. Azzali, Prime osservazioni al microscopio elettronico sulle cellule parafollicolari della tiroide (First observation with the electron microscope of the parafollicular cells of the thyroid), *Boll. Soc. Biol. Sper.* 88 (1962) 1319–1324. Article in Italian.
- [58] S.L. Wissig, The fine structure of parafollicular (light) cells of the rat thyroid gland, *Electron Microscopy*, in: 5th Int. Congr. Electr Micros, Academic Press, New York, 1962.
- [59] G. Azzali, Ultrastructure des cellules parafolliculaires de la thyroïde chez quelques mammifères, *Ann. Endocrinol.* 25 (Suppl) (1964) 8–13.
- [60] L. Luciano, E. Reale, Elektronenmikroskopische Beobachtungen am parafollikulären Zellen der Rattenschilddrüse, *Z. Zellforsch. Mikrosk. Anat.* 64 (1964) 751–766.
- [61] M. Tashiro, Electron microscopic studies of the parafollicular cells in the thyroid gland of the dog, *Okajimas Folia Anat. Jpn.* 39 (1964) 191–211.
- [62] G. Bussolati, A.G.E. Pearce, Immunofluorescent localization of calcitonin in the 'C' cells of the pig and dog thyroid, *J. Endocrinol.* 37 (1967) 205–209.
- [63] A.F. Cavalleira, A.G.E. Pearce, The cytology and cytochemistry of the C cells in the thyroid gland of the pig, *J. Roy. Microsc. Soc.* 86 (1967) 203–209.
- [64] J. Kracht, U. Hachmeister, H.J. Breustadt, M. Lenke, Immunohistological studies on thyrocalcitonin in C-cells, *Endokrinologie* 52 (1967) 396–401.
- [65] T. Matsuzawa, K. Kurosomi, Morphological changes in the parafollicular cells of the rat thyroid glands after administration of calcium shown by electron microscopy, *Nature* 213 (1967) 927–928.
- [66] M. Beskid, A. Rosciszewska, C cells in the normal animal and human thyroid gland, *Folia Histochem Cytochem* 6 (1968) 461–468.
- [67] H. Braunstein, C.L. Stephens, Parafollicular cells of human thyroid, *Arch. Pathol.* 86 (1968) 659–666.
- [68] E. Solcia, R. Sampietro, New methods for staining secretory granules and 5-hydroxytryptamine in the thyroid C cells, in: S. Taylor (Ed.), *Calcitonin. Proc Symp Thyrocalcitonin and the C Cells*, Heinemann, London, 1968, pp. 127–132.
- [69] Y. Kameda, Parafollicular cells of the thyroid as studied with Davenport's silver impregnation, *Arch. Histol. Jpn.* 30 (1968) 90–94.
- [70] H. Lietz, H. Zippel, Cytochemische Untersuchungen zur vergleichenden Morphologie der C-Zellen in der Schilddrüse, *Z. Zellforsch. Mikrosk. Anat.* 102 (1969) 85–98.
- [71] H. Lietz, C-cells: source of calcitonin. A morphological review, *Curr. Top. Pathol.* 55 (1971) 109–146.
- [72] U. Welsch, E. Flitney, A.G.E. Pearce, Comparative studies on the ultrastructure of the thyroid parafollicular C-cells, *J. Microsc.* 89 (1969) 83–94.
- [73] E. Altenähr, H. Lietz, H. Vergleichende experimentelle Untersuchungen zur Ultrastruktur von Epithelkörperchen und C-Zellen der Schilddrüse bei verschiedenen Funktionszuständen, *Verh. Dtsch. Ges. Path.* 54 (1970) 360–367.
- [74] Y. Kameda, Increased mitotic activity of the parafollicular cells of the dog in experimentally induced hypercalcemia, *Arch. Histol. Jpn.* 32 (1970) 179–182.
- [75] A.S. Chan, P.E. Conen, Ultrastructural observations on cytodifferentiation of parafollicular cells in the human fetal thyroid, *Lab. Invest.* 25 (1971) 249–259.
- [76] N.M. Kalina, A.G.E. Pearce, Ultrastructural localisation of calcitonin in C-cells of dog thyroid; an immunocytochemical study, *Histochemie* 26 (1971) 1–8.
- [77] Y. Kameda, The occurrence and distribution of the parafollicular cells in the thyroid, parathyroid IV and thymus IV in some mammals, *Arch. Histol. Jpn.* 33 (1971) 283–299.
- [78] R. Krstić, O. Buecher, Parafollicular cells of the Wistar rat under the influence of cold, *C.R. Assoc. Anat.* 149 (1970) 1084–1087.
- [79] P. Nève, S.H. Wollman, Fine structure of ultimobranchial follicles in the thyroid gland of the rat, *Anat. Rec.* 171 (1971) 259–272.
- [80] Y. Kameda, Electron microscopic studies on the parafollicular cells and

- parafollicular cell complexes in the dog, *Arch. Histol. Jpn.* 36 (1973) 89–105.
- [81] S. Blähsner, Morphology and function of thyrocytes and calcitonin cells (C-cells) in the rat. Serum analysis following injections of thyrotropic hormone, tocopherol, calcium chloride of phosphate [Article in German], *Endokrinologie* 62 (1973) 327–349.
 - [82] W.E.W. Roediger, A comparative study of the normal human neonatal and the canine C-cell, *J. Anat.* 115 (1973) 255–276.
 - [83] R. Krstić, O. Bucher, J. Kazimierzczak, Morphodynamics of the C-cells of the thyroid and the cells of the parathyroid glands of rats after calcitonin administration for one to eight weeks (author's transl), *Z. Anat. Entwicklungsgesch.* 144 (1974) 19–38 [Article in German].
 - [84] O. Bucher, R. Krstić, Ultrastructural changes of C-cells in the rat during a 2-month administration of calcitonin, *Verh. Anat. Ges.* 68 (1974) 799–803.
 - [85] P.B. De Grandi, J.P. Kraehenbuhl, M.A. Campiche, Ultrastructural localization of calcitonin in the parafollicular cells of pig thyroid gland with cytochrome c-labelled antibody fragments, *J. Cell Biol.* 50 (1971) 446–456.
 - [86] R.K. Jordan, B. McFarlane, R.J. Scothorne, An electron microscopic study of the histogenesis of the ultimobranchial body and of the C-cell system in the sheep, *J. Anat.* 114 (1973) 115–136.
 - [87] M. Petkó, Morphological and histochemical changes of ultimobranchial follicles of the rat thyroid in the course of postnatal life, *Acta Morphol. Acad. Sci. Hung.* 23 (1975) 123–131.
 - [88] E.A. Nunez, M.D. Gershon, Cytophysiology of thyroid parafollicular cells, *Int. Rev. Cytol.* 52 (1978) 1–80.
 - [89] V.I. Bykov, Heterogeneity of the mammalian thyroid gland and changes in the organ with age, article in Russian, *Arkh. Anat. Gistol. Embriol.* 77 (1979) 61–77.
 - [90] Y. Kameda, Development and cytodifferentiation of C cells complexes in dog fetal thyroids. An immunohistochemical study using anti-calcitonin, anti-thyroglobulin and anti-19S thyroglobulin antisera, *Cell Tissue Res.* 206 (1980) 403–415.
 - [91] Y. Kameda, A. Ikeda, Immunohistochemical reactions of C-cell complexes in dogs after induced hypercalcemia, antithyroid drug treatment and hypophysectomy, *Cell Tissue Res.* 208 (1980) 417–432.
 - [92] Y. Kameda, Distribution of C cells in monkey thyroid glands as studied by the immunoperoxidase method using anti-calcitonin and anti-C-thyroglobulin antisera, *Arch. Histol. Jpn.* 46 (1983) 221–228.
 - [93] M. Zabel, Ultrastructural localization of calcitonin, somatostatin and serotonin in parafollicular cells of rat thyroid, *Histochem. J.* 16 (1984) 1265–1272.
 - [94] J.E. Garrett, H. Tamir, O. Kifor, R.T. Simin, K.V. Rogers, A. Mithal, R.F. Gagel, E.M. Brown, Calcitonin-secreting cells of the thyroid express an extracellular calcium receptor gene, *Endocrinology* 136 (1985) 5202–5211.
 - [95] Y. Kameda, Ontogeny of immunoreactive calcitonin gene-related peptide C in thyroid C cells from dogs, rabbits and Guinea pigs, *Anat. Rec.* 220 (1988) 76–86.
 - [96] A.V. Pavlov, The mitotic activity of the follicular and parafollicular (C) cells in the thyroid of rats with hypercalcemia [in Russian], *Morfologiya* 102 (1992) 99–105.
 - [97] A.G.E. Pearse, The cytochemistry and ultrastructure of polypeptide hormone-producing cells of the APUD series and the embryologic, physiologic and pathologic implications of the concept, *J. Histochem Cytochem* 17 (1969) 303–313.
 - [98] A.G.E. Pearse, T.T. Takor, Neuroendocrine embryology and the APUD concept, *Clin. Endocrinol. (Oxf)* 5 (Suppl) (1976) 229S–244S.
 - [99] A.G.E. Pearse, T.T. Takor, Embryology of the diffuse neuroendocrine system and its relationship to the common peptides, *Fed. Proc.* 38 (1979) 2288–2294.
 - [100] A.G.E. Pearse, A.F. Carvalheira, Cytochemical evidence for an ultimobranchial origin of rodent thyroid C cells, *Nature* 214 (1967) 929–930.
 - [101] A.G.E. Pearse, J.M. Polak, Cytochemical evidence for the neural crest origin of mammalian ultimobranchial C-cells, *Histochemie* 27 (1971) 96–102.
 - [102] N.M. Le Douarin, C.S. Le Lièvre, Démonstration de l'origine neurale des cellules à calcitonine du corps ultimobranchial chez l'embryon de poulet, *C. R. Séances Acad. Sci. Paris Sér. D.* 270 (1970) 2857–2860.
 - [103] M.E. Stoeckel, A. Porte, Origine embryonnaire et différenciation sécrétoire des cellules à calcitonine (cellules C) dans la thyroïde foetale du rat. Etude au microscope électronique, *Z. Zellforsch. Mikrosk. Anat.* 106 (1970) 251–268.
 - [104] C.S. Le Lièvre, N.M. Le Douarin, Mesenchymal derivatives of the neural crest: analysis of chimaeric quail and chick embryos, *J. Embryol. Exp. Morph.* 34 (1975) 125–154.
 - [105] R. Calvert, Structure of rat ultimobranchial bodies after birth, *Anat. Rec.* 181 (1975) 561–579.
 - [106] Y. Kameda, Localization of immunoreactive calcitonin gene-related peptide in thyroid C cells from various mammalian species, *Anat. Rec.* 219 (1987) 204–212.
 - [107] Y. Kameda, T. Nishimaki, M. Miura, S.X. Jiang, F. Guillemot, Mash1 regulates the development of C cells in mouse thyroid glands, *Dev. Dyn.* 236 (2007) 262–270.
 - [108] Y. Kameda, T. Nishimaki, O. Chisaka, S. Iseki, H.M. Sucov, Expression of the epithelial marker E-cadherin by thyroid C cells and their precursors during murine development, *J. Histochem. Cytochem.* 55 (2007) 1075–1088.
 - [109] Y. Kameda, M. Ito, T. Nishimaki, N. Gotoh, *FRS2α* is required for the separation, migration, and survival of pharyngeal-endoderm derived organs including thyroid, ultimobranchial body, parathyroid, and thymus, *Dev. Dyn.* 238 (2009) 503–513.
 - [110] Y. Kameda, Cellular and molecular events on the development of mammalian thyroid C cells, *Dev. Dyn.* 245 (2016) 323–341.
 - [111] P.X. Xu, W. Zheng, C. Laclef, P. Maire, R.L. Maas, H. Peters, X. Xu, *Eya1* is required for the morphogenesis of mammalian thymus, parathyroid and thyroid, *Development* 129 (2002) 3033–3044.
 - [112] L. Galante, T.V. Gudmundsson, E.W. Matthews, A. Tse, E.D. Williams, N.J.Y. Woodhouse, I. MacIntyre, Thymic and parathyroid origin of calcitonin in man, *Lancet* ii (1968) 537–539.
 - [113] L. Andersson, Embryonic Origin and Development of Thyroid Progenitor Cells. An Experimental Study Focused on Endoderm, EphA4 and Foxa2, PhD Thesis, Göteborgs University, Sweden, 2010, pp. 1–54.
 - [114] E. Johansson, L. Andersson, J. Örnros, T. Carlsson, C. Ingesson-Carlsson, S. Liang, J. Dahlberg, S. Jansson, L. Parrillo, P.Z. Zoppoli, G.O. Barila, D.L. Altschuler, D. Padula, H. Lickert, H. Fagman, M. Nilsson, Revising the embryonic origin of thyroid C cells in mice and humans, *Development* 142 (2015) 3519–3528.
 - [115] J.M. Fernández-Santos, J. Morillo-Bernal, R. García-Marín, J.C. Utrilla, I. Martín-Lacave, Paracrine regulation of thyroid-hormone synthesis by C cells, in: N.K. Agrawal (Ed.), *Thyroid Hormone*, Intech Open Access; Chapter 3, 2012, pp. 51–83.
 - [116] B. Thompson, H. Isler, S.K. Sarkar, Effect of hypophysectomy and growth hormone on the light cells of the thyroid gland, *Endocrinology* 70 (1962) 786–795.
 - [117] B.V. Aleshin, L.A. Us, Effect of sympathetic impulses on parafollicular cells (C-cells) of the thyroid gland, *Bull. Eksp. Biol. Med.* 91 (1981) 726–727. In Russian.
 - [118] E. Conde, I. Martín-Lacave, R. Gonzalez-Campora, H. Galera-Davidson, Histometry of normal thyroid glands in neonatal and adult rats, *Am. J. Anat.* 191 (1991) 384–390.
 - [119] P.A. Monsour, B.J. Kruger, A. Barnes, Calcitonin cell population and distribution in the thyroid gland of the rat, *J. Morphol.* 186 (1985) 271–278.
 - [120] E. Conde, I. Martín-Lacave, J.C. Utrilla, A. Moreno, R. Gonzalez-Campora, H. Galera-Davidson, Mitotic activity of the endocrine cells in rat thyroid glands during postnatal life, *Endocrinology* 13 (1992) 436–440.
 - [121] E. Conde, I. Martín-Lacave, J.C. Utrilla, R. González-Campora, H. Galera-Davidson, Postnatal variations in the number and size of C-cells in the rat thyroid gland, *Cell Tissue Res.* 280 (1995) 659–663.
 - [122] M. Nilsson, D. Williams, On the origin of cells and derivation of thyroid Cancer: C cell story revisited, *Eur. Thyroid. J.* 5 (2016) 79–93.
 - [123] The Digital Microscope, Université de Namur, Belgium. www.histology.be.
 - [124] J.J. Flynn, D.L. Margules, T.C. Peng, C.W. Cooper, Serum calcitonin, calcium, and thyroxine in young and old Zucker fatty rats (fa/fa), *Physiol. Behav.* 31 (1963) 79–84.
 - [125] R.J. Martin, P.J. Wangsness, J.H. Gahagan, Diurnal changes in serum metabolites and hormones in lean and obese Zucker rats, *Horm. Metab. Res.* 10 (1978) 187–192.
 - [126] C.W. Cooper, J.F. Obie, A.R. Hughes, D.L. Margules, J.J. Flynn, Secretion of calcitonin in the genetically obese Zucker rat (fa/fa), *Proc. Soc. Exp. Biol. Med.* 173 (1983) 48–55.
 - [127] S. Durbin-Naltchayan, J. Bounnik, R. Michel, Thyroid status in the obese syndrome of rats, *Horm. Metab. Res.* 15 (1983) 547–549.
 - [128] P.K. Seitz, C.W. Cooper, Calcitonin, calcitonin gene-related peptide and renal calcitonin receptors in the Zucker rat, *Bone Min.* 2 (1987) 53–62.
 - [129] N. Segond, A. Jullienne, E.H. Tahri, J.M. Garel, Calcitonin mRNA activity in young obese (fa/fa) Zucker rats, *FEBS Lett.* 174 (1984) 86–89.
 - [130] N. Segond, E.H. Tahri, P. Besnard, B. Legendre, A. Jullienne, J.M. Garel, Calcitonin mRNA activity in genetically obese rats, *Biomed. Pharmacother.* 40 (1986) 207–214.
 - [131] P. Chomard, J.L. Beltramo, R. Ben Cheikh, N. Autissier, Changes in thyroid hormone and thyrotrophin in the serum and thyroid glands of developing genetically obese male and female Zucker rats, *J. Endocrinol.* 142 (1994) 317–324.
 - [132] J.A. Tamasi, B.J. Arey, D.R. Bertolini, J.H. Feyen, Characterization of bone structure in leptin receptor-deficient Zucker (fa/fa) rats, *J. Bone Min. Res.* 18 (2003) 1605–1611.
 - [133] P. Martin, J. Gahagan, Serum hormone levels and tissue metabolism in paired lean and obese Zucker rats, *Horm. Metab. Res.* 9 (1977) 181–187.
 - [134] Y. Kameda, H. Shigemoto, A. Ikeda, Development and cytodifferentiation of C cells complexes in dog fetal thyroids. An immunohistochemical study using anti-calcitonin, anti -C-thyroglobulin and anti-19S thyroglobulin antisera, *Cell Tissue Res.* 206 (1980) 403–415.
 - [135] P.J. Gkonos, M.A. Tavianini, C.C. Liu, B.A. Roos, Thyrotropin-releasing hormone gene expression in normal thyroid parafollicular cells, *Mol. Endocrinol.* 3 (1989) 2101–2109.
 - [136] P. Bernd, M.D. Gershon, E.A. Nunez, H. Tamir, Separation of dissociated thyroid follicular and parafollicular cells: association of serotonin binding protein with parafollicular cells, *J. Cell Biol.* 88 (1981) 499–508.
 - [137] J. Morillo-Bernal, J.M. Fernández-Santos, J.C. Utrilla, M. de Miguel, R. García-Marín, I. Martín-Lacave, Functional expression of the thyrotropin receptor in C cells: new insights into their involvement in the hypothalamic-pituitary-thyroid axis, *J. Anat.* 215 (2009) 150–158.
 - [138] M. Kalisnik, O. Vraspir-Porenta, T. Kham-Lindtner, M. Logonder-Mlinsek, Z. Pajer, D. Stiblar-Martincic, R. Zorc-Pleskovic, M. Trobina, The interdependence of the follicular, parafollicular, and mast cells in the mammalian thyroid gland: a review and a synthesis, *Am. J. Anat.* 183 (1988) 148–157.

- Erratum in: *Am J Anat* 185 (1989) 101.
- [139] H. Heath 3rd, G.W. Sizemore, Plasma calcitonin in normal man. Differences between men and women, *J. Clin. Invest.* 60 (1977) 1135–1136.
- [140] H. Hunter III, W.S. Glen, Plasma calcitonin in normal man, *J. Clin. Invest.* 60 (1977) 1135–1141.
- [141] F. Loré, M. Galli, B. Franci, M.T. Martorelli, Calcitonin levels in normal subjects according to age and sex, *Biomed. Pharmacother.* 38 (1984) 261–263.
- [142] L.J. Deftos, M.H. Weisman, G.W. Williams, D.B. Karpf, A.M. Frumar, B.J. Davidson, J.G. Parthemore, H.L. Judd, Influence of age and sex on plasma calcitonin in human beings, *N. Engl. J. Med.* 302 (1980) 1351–1353.
- [143] J.J. Body, H. Heath 3rd, Estimates of circulating monomeric calcitonin: physiological studies in normal and thyroidectomized man, *J. Clin. Endocrinol. Metab.* 57 (1983) 897–903.
- [144] R.D. Tiegs, J.J. Body, J.M. Barta, H. Heath 3rd, Secretion and metabolism of monomeric human calcitonin: effects of age, sex, and thyroid damage, *J. Bone Min. Res.* 1 (1986) 339–349.
- [145] C.R.K. Kleeman, S.G. Massry, J.W. Coburn, The clinical physiology of calcium homeostasis, parathyroid hormone, and calcitonin. I, *Calif. Med.* 114 (3) (1971) 16–43.
- [146] C.R.K. Kleeman, S.G. Massry, J.W. Coburn, The clinical physiology of calcium homeostasis, parathyroid hormone, and calcitonin. II, *Calif. Med.* 114 (4) (1971) 19–30.
- [147] L. Fugazzola, A. Pinchera, F. Luchetti, P. Iacconi, P. Miccoli, C. Romei, M. Puccini, F. Pacini, Disappearance rate of serum calcitonin after total thyroidectomy for medullary thyroid carcinoma, *Int. J. Biol. Markers* 9 (1994) 21–24.
- [148] H. Sternlicht, I.G. Glezerman, Hypercalcemia of malignancy and new treatment options, *Ther. Clin. Risk Manag.* 11 (2015) 1779–1788.
- [149] C.S. Kovacs, H.M. Kronenberg, Maternal-fetal calcium and bone metabolism during pregnancy, puerperium, and lactation, *Endocr. Rev.* 18 (1997) 833–872.
- [150] K.R. McDonald, N.J. Fudge, J.P. Woodrow, J.K. Friel, A.O. Hoff, R.F. Gagel, C.S. Kovacs, Ablation of calcitonin/calcitonin gene related peptide impairs fetal magnesium but not calcium homeostasis, *Am. J. Physiol. Endocrinol. Metab.* 287 (2004) E218–E226.
- [151] C.S. Kovacs, H.M. Kronenberg, American Society for Bone and Mineral Research, in: C.S. Kovacs, H.M. Kronenberg (Eds.), *Skeletal Physiology: Pregnancy and Lactation*, 2006, pp. 63–64. Chapter 10.
- [152] R.J. Murills, E. Shane, R. Lindsay, D.W. Dempster, Bone resorption by isolated human osteoclasts in vitro: effects of calcitonin, *J. Bone Min. Res.* 4 (1989) 259–268.
- [153] M.E. Holthrop, L.G. Raisz, H.A. Simmons, The effects of parathyroid hormone, colchicine, and calcitonin on the ultrastructure and the activity of osteoclasts in organ culture, *J. Cell Biol.* 60 (1974) 346–355.
- [154] C.S. Kovacs, *Skeletal physiology: fetus and neonate*, in: C.S. Kovacs, H.M. Kronenberg (Eds.), *American Society for Bone and Mineral Research*, 2006, pp. 50–55. Chapter 8.
- [155] C.S. Kovacs, Calcium, phosphorus, and bone metabolism in the fetus and newborn, *Early Hum. Dev.* 91 (2015) 623–628.
- [156] M. Stahlman, M.E. Grey, A.G. Kasselberg, Immunoreactive bombesin and calcitonin paracrine cells of human fetal and newborn airways, *Pediatr. Pulmonol.* (1 Suppl) (1985) S6–S12.
- [157] C.C. Capen, D.M. Young, Fine structural alterations in thyroid parafollicular cells of cows in response to hypercalcemia induced by vitamin D, *Am. J. Pathol.* 57 (1969) 365–382.
- [158] E.M. Rodríguez, A. Bach, M. Devant, A. Aris, Is calcitonin an active hormone in the onset and prevention of hypocalcemia in dairy cattle? *J. Dairy Sci.* 99 (2016) 3023–3030.
- [159] J.P. Woodrow, C.S. Noseworthy, N.J. Fudge, A.O. Hoff, R.F. Gagel, C.S. Kovacs, Calcitonin/calcitonin gene-related peptide protects the maternal skeleton from excessive resorption during lactation, *J. Bone Min. Res.* 18 (2003) S2–S37.
- [160] J.N. VanHouten, P. Dann, A.F. Stewart, C.J. Watson, M. Pollak, A.C. Karaplis, J.J. Wysolmerski, Mammary-specific deletion of parathyroid hormone-related protein preserves bone mass during lactation, *J. Clin. Invest.* 112 (2003) 1429–1436.
- [161] J.P. Woodrow, C.J. Sharpe, N.J. Fudge, A.O. Hoff, R.F. Gagel, C.S. Kovacs, Calcitonin plays a critical role in regulating skeletal mineral metabolism during lactation, *Endocrinology* 147 (2006) 4010–4021.
- [162] J.P. Woodrow, A.O. Hoff, R.F. Gagel, C.S. Kovacs, Calcitonin treatment rescues calcitonin-null mice from excessive bone resorption during lactation, *J. Bone Min. Res.* 19 (S1) (2004) SA518.
- [163] B.J. Kirby, Y. Ma, H.M. Martin, K.L. Buckle Favaro, A.C. Karaplis, C.S. Kovacs, Upregulation of calcitriol during pregnancy and skeletal recovery after lactation do not require parathyroid hormone, *J. Bone Min. Res.* 28 (2013) 1987–2000.
- [164] D.A. Nelson, S.A. Norris, V. Gilsanz, American Society for Bone and Mineral Research, in: C.S. Kovacs, H.M. Kronenberg (Eds.), *Childhood and Adolescence*, 2006, pp. 55–63. Chapter 9.
- [165] J. Gilloteaux, M.H. Linz, Histology of Aging. IV. Cartilage and bone tissues, *Gerontol. Geriatr. Edu.* 3 (1983) 313–319.
- [166] S. Bord, S. Beavan, D. Ireland, A. Horner, J.E. Compston, Mechanisms by which high-dose estrogen therapy produces anabolic skeletal effects in postmenopausal women: role of locally produced growth factors, *Bone* 29 (2001) 216–222.
- [167] A. LaRochelle, P. Sprumont, J. Gilloteaux, Exercice after 50 years (Exercice après 50 ans), In French, in: C.M. Thiebaud, P. Sprumont (Eds.), *Endocrinology of Aging*, DeBoeck-Dessain, Brussels-Louvain la Neuve, Belgium, 2005, pp. 68–74. Chapter 8.
- [168] I.R. Reid, Menopause, in: C.S. Kovacs, H.M. Kronenberg (Eds.), *American Society for Bone and Mineral Research*, 2006, pp. 68–70. Chapter 11.
- [169] F. Takou, O. Hajime, O. Masahiro, Y. Masaki, A test on the recovery from hypercalcemia for evaluation of thyrocalcitonin activity in man, *Endocrinol. Jpn.* 14 (1967) 246–250.
- [170] A.O. Hoff, P. Catala-Lehnen, P.M. Thomas, M. Priemel, J.M. Rueger, I. Nasonkin, A. Bradley, M.R. Hughes, N. Ordóñez, G.J. Cote, M. Amling, R.F. Gagel, Increased bone mass is an unexpected phenotype associated with deletion of the calcitonin gene, *J. Clin. Invest.* 110 (2002) 1849–1857.
- [171] Z. Mone, S.M. Baljit, A. Etsuko, Calcitonin and bone formation: a knockout full of surprises, *J. Clin. Invest.* 110 (2002) 1769–1771.
- [172] T. Schinke, S. Liese, M. Priemel, M. Haberland, A.F. Schilling, P. Catala-Lehnen, D. Blicharski, J.M. Rueger, R.F. Gagel, R.B. Emeson, M. Amling, Decreased bone formation and osteopenia in mice lacking alpha-calcitonin gene-related peptide, *J. Bone Min. Res.* 19 (2004) 2049–2056.
- [173] A.K. Huebner, J. Keller, P. Catala-Lehnen, S. Perkovic, T. Streichert, R.B. Emeson, M. Amlin, T. Schinke, The role of calcitonin and alpha-calcitonin gene-related peptide in bone formation, *Arch. Biochem. Biophys.* 15 (2008) 210–217.
- [174] L. Wang, X. Shi, R. Zhao, B.P. Halloran, D.J. Clark, C.R. Jacobs, W.S. Kingery, Calcitonin-gene-related peptide stimulates stromal cell osteogenic differentiation and inhibits RANKL induced NF-kappaB activation, osteoclastogenesis and bone resorption, *Bone* 46 (2010) 1363–1379.
- [175] C. Pineda, E. Aguilera-Tejero, A.I. Raya, F. Guerrero, M. Rodriguez, I. Lopez, Assessment of calcitonin response to experimentally induced hypercalcemia in cats, *Am. J. Vet. Res.* 74 (2013) 1514–1521.
- [176] D. Voet, J. Voet, Biochemistry, in: *Biomolecules, Mechanisms of Enzyme Action, and Metabolism*, third ed., vol. 1, John Wiley & Sons, New York, 2004, pp. 663–664. ISBN 0-471-25090-2.
- [177] S.L. Carney, Calcitonin and human renal calcium and electrolyte transport, *Min. Electrolyte Metab.* 23 (1997) 43–47.
- [178] R. Muff, W. Born, J.A. Fisher, Calcitonin, calcitonin gene-related peptide, adrenomedullin and amylin: homologous peptides, separate receptors and overlapping biological actions, *Eur. J. Endocrinol.* 133 (1995) 17–20.
- [179] S.J. Wimalawansa, Amylin, calcitonin gene-related peptide, calcitonin, and adrenomedullin: a peptide superfamily, *Crit. Rev. Neurobiol.* 11 (1997) 167–239.
- [180] D. Naot, J. Cornish, The role of peptides and receptors of the calcitonin family in the regulation of bone metabolism 43 (2008) 813–818.
- [181] S. Grantholm, P. Henning, U.H. Lerner, Comparisons between the effects of the calcitonin receptor-stimulating peptide and intermediate and other peptides in the calcitonin family on bone resorption and osteoclastogenesis, *J. Cell Biochem.* 112 (2011) 3300–3312.
- [182] T. Qi, G. Christopoulos, R.J. Bailey, A. Christopoulos, P.M. Sexton, D.L. Hay, Identification of N-terminal receptor activity-modifying protein residues important for calcitonin gene-related peptide, adrenomedullin, and amylin receptor function, *Mol. Pharmacol.* 74 (4) (2008) 1059–1071.
- [183] E. Johansson, J.L. Hansen, A.M. Hansen, A.C. Shaw, P. Becker, L. Schäffer, S. Reedt-Runge, Type II turn of receptor-bound salmon calcitonin revealed by X-ray crystallography, *J. Biol. Chem.* (2016 May 4) pii: jbc.M116.726034.
- [184] S.M. Lee, D.L. Hay, A.A. Pioszak, Calcitonin and amylin receptor peptide interaction mechanisms: insights into peptide-binding modes and allosteric modulation of the calcitonin receptor by receptor activity-modifying proteins, *J. Biol. Chem.* 291 (2016) 8686–8700.
- [185] S.M. Lee, D.L. Hay, A.A. Pioszak, Calcitonin and amylin receptor peptide interaction mechanisms. Insights into peptide-binding modes and allosteric peptide-binding modes and allosteric modulation of the calcitonin receptor by receptor activity-modifying proteins, *J. Biol. Chem.* 291 (2016) 16416, <http://dx.doi.org/10.1074/jbc.A115.71362>.
- [186] A. Samura, S. Wada, S. Suda, M. Iitaka, S. Katayama, Calcitonin receptor regulation and responsiveness to calcitonin in human osteoclast-like cells prepared in vitro using receptor activator of nuclear factor-kappaB ligand and macrophage colony-stimulating factor, *Endocrinology* 141 (2000) 3774–3782.
- [187] R.A. Davey, D.M. Findlay, Calcitonin: physiology or fantasy? *J. Bone Min. Res.* 28 (2013) 973–979.
- [188] S.J. Marx, G.D. Aurbach, J.R. Gavin 3rd, D.W. Buell, Calcitonin receptors on cultured human lymphocytes, *J. Biol. Chem.* 249 (1974) 6812–6816.
- [189] S.R. Terra, J.C. Cardoso, R.C. Félix, L.A. Martins, D.O. Souza, F.C. Guma, A.V. Canário, V. Schein, STC1 interference on calcitonin family of receptors signaling during osteoblastogenesis via adenylate cyclase inhibition, *Mol. Cell Endocrinol.* 403 (2015) 78–87.
- [190] J.A. Fischer, P.H. Tobler, M. Kaufmann, W. Born, H. Henke, P.E. Cooper, S.M. Sagar, J.B. Martin, Calcitonin: regional distribution of the hormone and its binding sites in the human brain and pituitary, *Proc. Natl. Acad. Sci. U. S. A.* 78 (1981) 7801–7805.
- [191] O. Toshiro, S. Masataka, I. Hideki, T. Kikuko, O. Hajime, Calcitonin inhibition of gastrin secretion in man, *Endocrinol. Jpn.* 20 (1973) 625–627.
- [192] H. Ito, J. Hata, H. Yokozaki, E. Tahara, Calcitonin in human gastric mucosa and carcinoma, *J. Cancer Res. Clin. Oncol.* 112 (1986) 50–56.
- [193] S. Kopic, J.P. Geibel, Gastric acid, calcium absorption, and their impact on

- bone health, *Physiol. Rev.* 93 (2013) 189–268.
- [194] V.V. Chernin, L.A. Fomina, The calcium-regulating system and recurrent peptic ulcer, *Article in Russian, Ter. Arkh.* 88 (2016) 10–15.
- [195] A.B. Borle, Effects of thyrocalcitonin on calcium transport in kidney cells, *Endocrinology* 85 (1969) 194–199.
- [196] G.D. Aurbach, D.A. Heath, Parathyroid hormone and calcitonin regulation of renal function, *Kidney Int.* 6 (1974) 331–345.
- [197] C. Goran, M. Dragan, K. Aleksandra, Z. Svetlana, S.D. Mirjana, T. Svetislav, T. Aleksandar, P.S. Danica, J. Danka, Ectopic calcitonin secretion in a woman with large cell neuroendocrine lung carcinoma, *Hormones* 12 (2013) 584–590.
- [198] M. Fouchereau-Peron, M.S. Moukhtar, A.A. Benson, G. Milhaud, Characterization of specific receptors for calcitonin in porcine lung, *Proc. Natl. Acad. Sci. U. S. A.* 178 (1981) 3973–3975.
- [199] A. Hakim, Effect of human calcitonin on the sarcoplasmic reticulum of the human heart, *Naturwissenschaften* 60 (1973), 53–53.
- [200] W. Barabanova, The mechanism of action of thyrocalcitonin on myocardial cells, *Fiziol. Zh. SSSR Im. I. M. Sechenova* 61 (1975) 1381–1386. *Article in Russian.*
- [201] P.A. Smirnov, E.V. Chaikovskaia, V.S. Shestak, Influence of thyrocalcitonin on the adenosine triphosphatase activity and the electrolyte balance of the rat myocardium [Article in Russian], *Farmakol. Toksikol.* 39 (1976) 44–45.
- [202] P.J. Bentley, *Comparative Vertebrate Endocrinology*, second ed., Cambridge University Press, Cambridge, 1982, pp. 250–268.
- [203] R. Swaminathan, R.F.L. Bates, A.R. Care, Fresh evidence for a physiological role for calcitonin in calcium homeostasis, *J. Endocr.* 54 (1972) 525–526.
- [204] M.A. Kumar, W.C. Sturtridge, The physiological role of calcitonin assessed through chronic deficiency in rats, *J. Physiol. Lond.* 233 (1973) 33–43.
- [205] C. Harper, S.U. Toverud, Ability of thyrocalcitonin to protect against hypercalcemia in adult rats, *Endocrinology* 93 (1973) 1354–1359.
- [206] B.A. Roos, M. Yoon, S.V. Cutshaw, D.N. Kalu, Calcium regulatory action of endogenous calcitonin demonstrated by passive immunization with calcitonin antibodies, *Endocrinology* 107 (1980) 1320–1326.
- [207] L.J. Deftos, D. Powell, J.G. Parthemore, J.T. Potts Jr., Secretion of calcitonin in hypocalcemic states in man, *J. Clin. Invest.* 52 (1973) 3109–3114.
- [208] N. Demeester-Mirkine, P. Bergmann, J.J. Body, J. Corvilain, Calcitonin and bone mass status in congenital hypothyroidism, *Calcif. Tissue Int.* 46 (1990) 222–226.
- [209] J. Ham, M.L. Ellison, J. Lumsden, Tumour calcitonin. Interaction with specific calcitonin receptors, *Biochem. J.* 190 (1980) 545–550.
- [210] O. Silva, L.A. Wisneski, J. Cyrus, R.H. Snider, C.F. Moore, K.L. Becker, Calcitonin in thyroidectomized patients, *Am. J. Med. Sci.* 275 (1978) 159–164.
- [211] K.L. Becker, R.H. Snider, C.F. Moore, K.G. Monaghan, O.L. Silva, Calcitonin in extrathyroidal tissues of man, *Acta Endocrinol.* 92 (1979) 746–751.
- [212] K.L. Becker, G. Geelhoed, W. O'Neill, K.G. Monaghan, R.H. Snider, C.F. Moore, O.L. Silva, Calcitonin in tissues of thyroidectomized monkey, *Experientia* 36 (1980) 609–610.
- [213] F. Strollo, Hormonal changes in humans during spaceflight, *Adv. Space Biol. Med.* 7 (1999) 99–129.
- [214] E. Albi, F. Curcio, R. Spelat, A. Lazzarini, S. Cataldi, E. Loreti, I. Ferri, F.S. Ambesi-Implombato, Loss of parafollicular cells during gravitational changes (microgravity, hypergravity) and the secret effect of pleiotrophin, *PLoS One* 7 (2012) e48518, <http://dx.doi.org/10.1371/journal.pone.0048518>.
- [215] K. Meng, A. Rodriguez-Peña, T. Dimitrov, W. Chen, M. Yamin, M. Noda, T.F. Deuel, Pleiotrophin signals increased tyrosine phosphorylation of beta catenin through inactivation of the intrinsic catalytic activity of the receptor-type protein tyrosine phosphatase beta/zeta, *Proc. Natl. Acad. Sci. U. S. A.* 97 (2000) 2603–2608.
- [216] T.F. Deuel, N. Zhang, H.J. Yeh, I. Silos-Santiago, Z.Y. Wang, Pleiotrophin: a cytokine with diverse functions and a novel signaling pathway, *Arch. Biochem. Biophys.* 397 (2002) 162–171.
- [217] P. Perez-Pinera, J.R. Berenson, T.F. Deuel, Pleiotrophin, a multifunctional angiogenic factor: mechanisms and pathways in normal and pathological angiogenesis, *Curr. Opin. Hematol.* 15 (2008) 210–214.
- [218] M. Lamprou, A. Kaspiris, E. Panagiotopoulos, P.V. Giannoudis, E. Papadimitriou, The role of pleiotrophin in bone repair, *Injury* 45 (2014) 1816–1823.
- [219] R.H. Snider, O.L. Silva, C.F. Moor, K.L. Becker, Immunochemical heterogeneity of calcitonin in man: effect on radioimmunoassay, *Chim. Acta* 76 (1977) 1–14.
- [220] R.H. Snider, C.F. Moore, O.L. Silva, K.L. Becker, Radioimmunoassay of calcitonin in normal human urine, *Anal. Chem.* 50 (1978) 449–454.
- [221] M.S. Moukhtar, A. Jullienne-Moukhtar, D. Raulais, J. Taboulet, C. Calmettes, G. Milhaud, Heterogeneity of human calcitonin [Article in French], *C. R. Acad. Sci. Hebd. Seances Acad. Sci. D.* 280 (9) (1975) 1127–1130.
- [222] A. Jullienne, D. Raulais, C. Calmettes, M.S. Moukhtar, G. Milhaud, Heterogeneity of immunoreactive calcitonin in normal human thyroid, *Horm. Metab. Res.* 10 (1978) 456–457.
- [223] A. Jullienne, N. Segond, C. Calmettes, M.S. Moukhtar, G. Milhaud, Biosynthesis of human calcitonin: evidence for a prohormone, *Biochem. Biophys. Res. Commun.* 95 (1980) 932–937.
- [224] P.H. Tobler, F.A. Tschopp, M.A. Dambacher, W. Born, J.A. Fischer, Identification and characterization of calcitonin forms in plasma and urine of normal subjects and medullary carcinoma patients, *J. Clin. Endocrinol. Metab.* 57 (1983) 749–754.
- [225] C. Calmettes, Calcitonin cancers: definition, history, various forms [Article in French], *Bull. Cancer* 71 (1984) 114–121.
- [226] E.S. Nylen, K.T. Whang, R.H. Snider Jr., P.M. Steinwald, J.C. White, K.L. Becker, Mortality is increased by procalcitonin and decreased by an antiserum reactive to procalcitonin in experimental sepsis, *Crit. Care Med.* 26 (1998) 1001–1006.
- [227] K.T. Whang, P.M. Steinwald, J.C. White, E.S. Nylen, R.H. Snider, G.L. Simon, R.L. Goldberg, K.L. Becker, Serum calcitonin precursors in sepsis and systemic inflammation, *J. Clin. Endocrinol. Metab.* 83 (1998) 3296–3301.
- [228] P.M. Steinwald, K.T. Whang, K.L. Becker, R.H. Snider, E.S. Nylen, J.C. White, Elevated calcitonin precursor levels are related to mortality in an animal model of sepsis, *Crit. Care* 3 (1999) 11–16.
- [229] K.T. Whang, P.M. Steinwald, J.C. White, E.S. Nylen, R.H. Snider, G.L. Simon, R.L. Goldberg, K.L. Becker, Serum calcitonin precursors in sepsis and systemic inflammation, *J. Clin. Endocrinol. Metab.* 83 (9) (1998 Sep) 3296–3301.
- [230] Y.Y. Cho, H.W. Jang, J.Y. Jang, T.H. Kim, J.H. Choe, J.H. Kim, J.S. Kim, S.W. Kim, J.H. Chung, Clinical outcomes of patients with hypercalcitoninemia after initial treatment for medullary thyroid cancer and postoperative serum calcitonin cutoffs for predicting structural recurrence, *Head. Neck* (2016), <http://dx.doi.org/10.1002/hed.24469> [Epub ahead of print].
- [231] D. Wynn, G.D. Everett, R.A. Boothby, Small cell carcinoma of the ovary with hypercalcemia causes severe pancreatitis and altered mental status, *Gynecol. Oncol.* 95 (2004) 716–718.
- [232] A. Bourgain, O. Acker, E. Lambaudie, M. Boukerrou, A. Chevalier-Place, P. Meignie, M. Parent, M.C. Baranzelli, V. Cabaret, J.L. Wemeau, D. Querleu, Small cell carcinoma of the ovary of the hypercalcemic type revealed by a severe acute pancreatitis: about one case, *Gynecol. Obstet. Fertil.* 33 (2005) 35–38 [Article in French].
- [233] J.M. McDonald, R.G. Karabakhtian, H.H. Pierce, J.A. Iocono, C.P. Desimone, S.L. Bayliff, F.R. Ueland, Small cell carcinoma of the ovary of hypercalcemic type: a case report, *J. Pediatr. Surg.* 47 (2012) 588–592.
- [234] J.G. Pressey, D.R. Kelly, H.T. Hawthorne, Successful treatment of preadolescents with small cell carcinoma of the ovary hypercalcemic type, *J. Pediatr. Hematol. Oncol.* 35 (2013) 566–569.
- [235] M.B. Ilić, D.V. Jovanović, M.Z. Milosavljević, V. Stanković, G. Djordjević, Z. Protrka, J. Nedović, S.L. Mitrović jr, Hypercalcemic type of small cell carcinoma of the ovary, *Vojnosanit. Pregl.* 72 (2015) 295–298.
- [236] H.K. Kim, W.K. Bae, Y.D. Choi, H.J. Shim, J.H. Yoon, H.C. Kang, Serum calcitonin may falsely estimate tumor burden in chronic hypercalcemia: a case of prostatic and multiple bone metastases from medullary thyroid cancer, *Thyroid* 24 (2014) 599–603.
- [237] A. Aljameeli, A. Thakkar, S. Thomas, V. Lakshmikanthan, K.A. Iczkowski, G.V. Shah, Calcitonin receptor-zonula occludens-1 interaction is critical for calcitonin-stimulated prostate cancer metastasis, *PLoS One* 11 (3) (2016) e0150090, <http://dx.doi.org/10.1371/journal.pone.0150090>.
- [238] M. Kihara, A. Miyauchi, T. Kudo, M. Hirokawa, A. Miya, Reference values of serum calcitonin with calcium stimulation test by electroluminescence immunoassay before/after total thyroidectomy in Japanese patients with thyroid diseases other than medullary thyroid carcinoma, *Endocr. J.* (2016), <http://dx.doi.org/10.1507/endocrj.EJ16-0197>.
- [239] L. Giovannella, F.A. Verburg, M. Imperiali, S. Valabrega, P. Trimboli, L.C. Ceriani, Comparison of serum calcitonin and procalcitonin in detecting medullary thyroid carcinoma among patients with thyroid nodules, *Clin. Chem. Lab. Med.* 51 (2013) 1477–1478.
- [240] P. Trimboli, E. Seregni, G. Treglia, M. Alevizaki, L. Giovannella, Procalcitonin for detecting medullary thyroid carcinoma: a systematic review, *Endocr. Relat. Cancer* 22 (2015) R157–R164.
- [241] P. Trimboli, L. Guidobaldi, N. Locuratolo, F.R. Piro, M. Giordano, L. Giovannella, Serum markers measured in FNA fluids of medullary thyroid carcinoma occurring as a cyst, *Int. J. Biol. Markers* 31 (2) (2016 May 28) e224–e227, <http://dx.doi.org/10.5301/ijbm.5000205>.
- [242] J.R. Goellner, H. Gharib, C.S. Grant, D.A. Johnson, Fine needle aspiration cytology of the thyroid, 1980 to 1986, *Acta Cytol.* 31 (1987) 587–590.
- [243] H.J. Wolfe, R.A. Delellis, Familial medullary thyroid carcinoma and C cell hyperplasia, *Clin. Endocrinol. Metab.* 10 (1981) 351–365.
- [244] K. Emmertsen, Medullary thyroid carcinoma and calcitonin, *Dan. Med. Bull.* 32 (1985) 1–28.
- [245] R. Madhuchanda, C. Herbert, S.S. Rebecca, Current understanding and management of medullary thyroid cancer, *Oncol.* 18 (2013) 1093–1100.
- [246] K. Lorenz, M. Elwert, A. Machens, M. Abuazab, H.J. Holzhausen, H. Dralle, Hypercalcitoninemia in thyroid conditions other than medullary thyroid carcinoma: a comparative analysis of calcium and pentagastrin stimulation of serum calcitonin, *Langenbecks Arch. Surg.* 398 (2013) 403–409.
- [247] A.L. Maia, D.R. Siqueira, M.A. Kulcsar, A.J. Tincani, G.M. Mazeto, L.M. Maciel, Diagnosis, treatment, and follow-up of medullary thyroid carcinoma: recommendations by the thyroid Department of the Brazilian Society of Endocrinology and Metabolism, *Arq. Bras. Endocrinol. Metabol.* 58 (2014) 667–700.
- [248] F. Raue, K. Frank-Raue, Long-term follow-up in medullary thyroid carcinoma, *Recent Res. Cancer Res.* 204 (2015) 207–225.
- [249] Y.J. Bae, M. Schaab, J. Kratzsch, Calcitonin as biomarker for the medullary thyroid carcinoma, *Recent Res. Cancer Res.* 204 (2015) 117–137.
- [250] C. Nozières, L. Chardon, B. Goichot, F. Borson-Chazot, V. Hervieu, K. Chikh, C. Lombard-Bohas, T. Walter, Neuroendocrine tumors producing calcitonin:

- characteristics, prognosis and potential interest of calcitonin monitoring during follow-up, *Eur. J. Endocrinol.* 174 (2016) 335–341.
- [251] P. Lennon, S. Deady, N. White, D. Lambert, M.L. Healy, A. Green, J. Kinsella, C. Timon, J.P. O'Neill, Aggressive medullary thyroid cancer, an analysis of the Irish National Cancer Registry, *Ir. J. Med. Sci.* (2016 Apr 15) [Epub ahead of print].
- [252] M.T. Samà, R. Rossetto Giaccherino, M. Gallo, F. Felicetti, F. Maletta, N. Bonelli, A. Piovesan, N. Palestini, E. Ghigo, E. Arvat, Clinical challenges with calcitonin-negative medullary thyroid carcinoma, *J. Cancer Res. Clin. Oncol.* (2016) [Epub ahead of print].
- [253] T. Sarah, Secondary Hyperparathyroidism and chronic kidney disease, *Diabetes Spectr.* 21 (2008) 19–25.
- [254] M.S. Stuart, L.S. Arnold, A.S. Fahd, D. Radhika, P.T. Samir, P. Martin, J.M. Eric, A.W. Jay, Z.M. Joel, W.B. Charles, Modified-release calcifediol effectively controls secondary hyperparathyroidism associated with vitamin D insufficiency in chronic kidney disease, *Am. J. Nephrol.* 40 (2014) 535–545.
- [255] S.M. Chittal, D.G. Oreopoulos, G.A. DeVeber, P. Thomas, S. Rabinovich, G.J. Lloyd, M.A. Kumar, A. Rapoport, Plasma calcitonin in renal osteodystrophy, *CMAJ J.* 104 (1971) 1098–1100.
- [256] L.A. Wisneski, Salmon calcitonin in the acute management of hypercalcemia, *Calcif. Tissue Int.* 46 (1973) 337–339.
- [257] A. Tagiyev, H. Demirbilek, B. Tavil, G. Buyukyilmaz, F. Gumruk, F.M. Cetin, Severe hypercalcemia in a child with acute lymphoblastic leukemia relapse: successful management with combination of calcitonin and bisphosphonate, *J. Pediatr. Hematol. Oncol.* 38 (2016) 232–234.
- [258] F. Shapiro, M.J. Glimcher, M.E. Holtrop, A.H. Tashjian Jr, D. Brickley-Parsons, J.E. Kenzora, Human osteopetrosis: a histological, ultrastructural, and biochemical study, *J. Bone Jt. Surg. Am.* 62 (1980) 384–399.
- [259] G.M. Palmieri, J.A. Pitcock, P. Brown, J.G. Karas, L.J. Roen, Effect of calcitonin and vitamin D in osteoporosis, *Calcif. Tissue Int.* 45 (1989) 137–141.
- [260] K. Siminoski, R.G. Josse, Prevention and management of osteoporosis: consensus statements from the Scientific Advisory Board of the Osteoporosis Society of Canada. Calcitonin in the treatment of osteoporosis, *CMAJ* 155 (1996) 962–965.
- [261] J.M. Cardona, E. Pastor, Calcitonin versus etidronate for the treatment of postmenopausal osteoporosis: a meta-analysis of published clinical trials, *Osteoporos. Int.* 7 (1997) 165–174.
- [262] M. Muñoz-Torres, G. Alonso, M.P. Raya, Calcitonin therapy in osteoporosis, *Treat. Endocrinol.* 3 (2004) 117–132.
- [263] M.A. Karsdal, I. Byrjalsen, B.J. Riis, C. Christiansen, Investigation of the diurnal variation in bone resorption for optimal drug delivery and efficacy in osteoporosis with oral calcitonin, *BMC Clin. Pharmacol.* 8 (2008) 12.
- [264] M.A. Karsdal, I. Byrjalsen, B.J. Riis, C. Christiansen, Optimizing bioavailability of oral administration of small peptides through pharmacokinetic and pharmacodynamic parameters: the effect of water and timing of meal intake on oral delivery of Salmon Calcitonin, *BMC Clin. Pharmacol.* 9 (2008) 5.
- [265] L. Bandeira, E.M. Lewiecki, J.P. Bilezikian, Pharmacodynamics and pharmacokinetics of oral salmon calcitonin in the treatment of osteoporosis, *Expert Opin. Drug Metab. Toxicol.* 18 (2016) 1–9.
- [266] M.A. Karsdal, I. Byrjalsen, K. Henriksen, B.J. Riis, C. Christiansen, A pharmacokinetic and pharmacodynamic comparison of synthetic and recombinant oral salmon calcitonin, *J. Clin. Pharmacol.* 49 (2009) 229–234.
- [267] M.A. Karsdal, I. Byrjalsen, K. Henriksen, B.J. Riis, C. Christiansen, Investigations of inter- and intraindividual relationships between exposure to oral salmon calcitonin and a surrogate marker of pharmacodynamic efficacy, *Eur. J. Clin. Pharmacol.* 66 (2010) 29–37.
- [268] M.A. Karsdal, I. Byrjalsen, K. Henriksen, B.J. Riis, E.M. Lau, M. Arnold, C. Christiansen, The effect of oral salmon calcitonin delivered with 5-CNAC on bone and cartilage degradation in osteoarthritic patients: a 14-day randomized study, *Osteoarthr. Cartil.* 18 (2010) 150–159.
- [269] M.A. Karsdal, K. Henriksen, A.C. Bay-Jensen, B. Molloy, M. Arnold, M.R. John, I. Byrjalsen, M. Azria, B.J. Riis, P. Qvist, C. Christiansen, Lessons learned from the development of oral calcitonin: the first tablet formulation of a protein in phase III clinical trials, *J. Clin. Pharmacol.* 51 (2011) 460–471.
- [270] K.V. Andreassen, S.T. Hjulær, S.G. Furness, P.M. Sexton, A. Christopoulos, O. Nosjean, M.A. Karsdal, K. Henriksen, Prolonged calcitonin receptor signaling by salmon, but not human calcitonin, reveals ligand bias, *PLoS One* 9 (2014) e92042, <http://dx.doi.org/10.1371/journal.pone.0092042> eCollection 2014.
- [271] M.A. Karsdal, I. Byrjalsen, P. Alexandersen, A. Bihlet, J.R. Andersen, B.J. Riis, A.C. Bay-Jensen, C. Christiansen, CSMC021C2301/2 investigators. Treatment of symptomatic knee osteoarthritis with oral salmon calcitonin: results from two phase 3 trials, *Osteoarthr. Cartil.* 23 (2015) 532–543.
- [272] K. Henriksen, I. Byrjalsen, J.R. Andersen, A.R. Bihlet, L.A. Russo, P. Alexandersen, I. Valter, P. Qvist, E. Lau, B.J. Riis, C. Christiansen, M.A. Karsdal, MA. SMC021 investigators. A randomized, double-blind, multicenter, placebo-controlled study to evaluate the efficacy and safety of oral salmon calcitonin in the treatment of osteoporosis in postmenopausal women taking calcium and vitamin D, *Bone* 91 (2016) 122–129.
- [273] K. Sascha, P.G. John, Gastric acid, calcium absorption, and their impact on bone health, *Physiol. Rev.* 93 (2013) 189–268.
- [274] M. Laroche, S. Cantogrel, B. Jamard, A. Constantin, L. Zabraniecki, A. Cantagrel, B. Mazières, Comparison of the analgesic efficacy of pamidronate and synthetic human calcitonin in osteoporotic vertebral fractures: a double-blind controlled study, *Clin. Rheumatol.* 25 (2006) 683–686.
- [275] H. Hassanzadeh, V. Puvanesarajah, A.C. Dakin, Medical management of osteoporosis for elective spine surgery, *Clin. Spine Surg.* 29 (2016) 134–140.
- [276] T. Karachalios, G.P. Lyritis, J. Kaloudis, N. Roidis, M. Katsiri, The effects of calcitonin on acute bone loss after peritrochanteric fractures, *J. Bone Jt. Surg.* 86 (2004) 350–358.
- [277] A. Karponis, S. Rizou, D. Pallis, C.P. Zafeiris, D.F. Georgiou, A. Galanos, F. Giannoulis, G.P. Lyritis, Analgesic effect of nasal salmon calcitonin during the early post-fracture period of the distal radius fracture, *J. Musculosk. Neur. Interact.* 15 (2015) 186–189.
- [278] A. Alireza, K. Mehdi, S. Amin, N. Mahshid, N. Ali, Efficacy of intramuscular calcitonin injection in management of lumbar spinal stenosis, *Asian Spin J.* 9 (2015) 75–82.
- [279] P. Kun, C. Long, P. Jing, X.F. Fei, X. Zhou, Effects of calcitonin on lumbar spinal stenosis: a systemic review and meta analysis, *Int. J. Clin. Exp. Med.* 8 (2015) 2536–2544.
- [280] A. Goździalska, J. Jaśkiewicz, M. Knapik-Czajka, J. Drąg, M. Gawlik, M. Cieślą, A. Kulis, D. Zarzycki, E. Lipik, Association of calcium and phosphate balance, vitamin D, PTH, and calcitonin in patients with adolescent idiopathic scoliosis, *Spine (Phila Pa 1976)* 41 (2016) 693–697.
- [281] P. Liu, D.Q. Yang, F. Xie, B. Zhou, M. Liu, Effect of calcitonin on anastrozole-induced bone pain during aromatase inhibitor therapy for breast cancer, *Gen. Mol. Res.* 13 (2014) 5285–5291.
- [282] M.A. Abbassy, I. Watari, A.S. Bakry, T. Ono, A.H. Hassan, Calcitonin and vitamin D3 have high therapeutic potential for improving diabetic mandibular growth, *Int. J. Oral Sci.* 8 (2016) 39–44.
- [283] G.P. Zaloga, Hypocalcemia in critically ill patients, *Crit. Care Med.* 20 (1992) 251–262.
- [284] R.N. Dickerson, L.G. Morgan, A.D. Cauthen, K.H. Alexander, M.A. Croce, G. Milnard, R.O. Brown, Treatment of acute hypocalcemia in critically ill multiple-trauma patients, *J. Parenter. Enter. Nutr.* 29 (2005) 436–441.
- [285] R.N. Dickerson, L.G. Morgan, M.A. Croce, G. Milnard, R.O. Brown, Treatment of moderate to severe acute hypocalcemia in critically ill trauma patients, *J. Parenter. Enter. Nutr.* 31 (2007) 228–233.
- [286] J.N. Meliones, F.W. Moler, J.R. Custer, S.J. Snyder, M.K. Dekeon, S.M. Donn, R.A. Chapman, R.H. Bartlett, Hemodynamic instability after the initiation of extracorporeal membrane oxygenation: role of ionized calcium, *Crit. Care Med.* 19 (1991) 1247–1251.
- [287] J. Rambaud, I. Guellec, J. Guilbert, P.L. Léger, S. Renolleau, Calcium homeostasis disorder during and after neonatal extracorporeal membrane oxygenation, *Indian J. Crit. Care Med.* 19 (2015) 513–517.