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Review Article

Calcitonin: A useful old friend

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Abstract

Calcitonin regulates blood calcium levels and possesses certain clinically useful anti-fracture properties. Specifically, it reduces vertebral fractures in postmenopausal osteoporotic women significantly compared to a placebo. Nevertheless, the use of calcitonin has declined over the years and salmon calcitonin is no longer the first-line treatment for many of its indications. Commercial calcitonin only exists in intranasal or injectable preparations, which are less preferable for patients. Efficacy of a potential oral formulation has been under investigation but achieving adequate bioavailability remains a conundrum and the latest phase III trials have not shown promising evidence justifying its use. Associations with cancer have also derailed this treatment option. Furthermore, the rise of bisphosphonates and, more recently, monoclonal antibodies (such as denosumab), has revolutionised the treatment of osteoporotic fractures. Therefore, we are posed with an interesting question: is calcitonin a treatment of the past? This review aims to explore the reasons behind this paradigm shift and outline the potential role of calcitonin in the management of fractures and other conditions in the years to come.

Keywords: Analgesia, Calcitonin, Formulations, Fracture, Osteoporosis

Background

Calcitonin, in various preparations, has been used to treat metabolic bone disease for over forty years since its discovery in 1961 as a blood-calcium lowering hormone[1]. Salmon calcitonin, in particular, has been effective in treating postmenopausal osteoporosis, Paget's disease and hypercalcaemia[2,3]. Due to its ability to inhibit osteoclast activity, calcitonin reduces the risk of vertebral re-fracture, and it is also a powerful analgesic agent with proven efficacy in managing acute back pain caused by recent vertebral compression fractures[4,5].

By 1992, world sales of therapeutic calcitonin had exceeded 900 million US dollars[6]. However, the rise of bisphosphonates pushed calcitonin to the side; since the 1960s, etidronate has been utilised as a therapy, primarily for hypercalcaemia and Paget's disease, and in 1995, alendronate received approval by the US Food and Drug Administration (FDA) for the treatment of postmenopausal osteoporosis[7]. Since 2007, zoledronic acid has also been licensed for the treatment of postmenopausal osteoporosis, following evidence on its beneficial effects on bone mineral density (BMD), bone metabolism markers and a reduction in vertebral, hip and other fractures[8]. Multiple trials have demonstrated superior efficacy in bisphosphonates and alternative treatment options, which have consequently led to decreased use of calcitonin.

Although bisphosphonates possess multiple effects and are potent medications, there are significant adverse effects associated with long-term use, such as atypical femoral fractures and osteonecrosis of the jaw[7]. Therefore, it is interesting to see the extent to which these drugs have superseded calcitonin. This review aims to explore the reasons behind the decline of calcitonin and discuss its potential role in the years to come.

Biochemistry and pharmacology

Calcitonin is a single-chain polypeptide hormone which is made up of 32 amino acids. An N-terminal disulfide bridge between the cysteine residues at positions 1 and 7 create a 7-amino acid ring structure and there is also a C-terminal amidated proline[9]. The physiological effects of calcitonin are

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known to occur through receptor-mediated processes, and interactions involving the N-terminal ring and the C-terminus appear to be involved in receptor binding and signal transduction[9,10].

In humans, calcitonin is secreted by the para-follicular or C cells of the thyroid gland in response to an increase in serum calcium concentration[11]. Primarily, calcitonin targets the bone, where it profoundly inhibits osteoclast action and bone resorption. Actively resorbing osteoclasts secrete acid and acid hydrolases via their ruffled borders to degrade bone. Calcitonin promotes the internalisation of the osteoclasts' ruffled border proteins into intracellular vesicles, thereby thwarting acid release and preventing the demineralisation of bone matrix[12]. Calcitonin also acts via the kidneys, where it reduces the reabsorption of calcium, along with sodium, potassium, chloride and phosphate. Furthermore, the hormone works on the central nervous system to induce analgesia, stomach acid secretion and anorexia[1].

The exact mechanism behind the analgesic effects of calcitonin remains elusive, yet several theories have been proposed. A 2016 study on rats discovered that calcitonin decreases the number of serotonin transporters, whilst increasing the expression of thalamic serotonin receptors[13]. Other studies have proposed that nerve injuries activate a calcitonin-dependent signal, which reduces transcription of the sodium channel in the neurons of the dorsal root ganglion[14].

Calcitonin has been studied in numerous species including pig, rat, salmon and eel. Subtle structural differences massively affect their respective affinities for calcitonin receptors. For example, salmon calcitonin has a greater affinity to calcitonin receptors in all species, compared to mammalian calcitonin and therefore, its higher potency combined with its longer half-life has made salmon calcitonin the standard form used to treat bone disorders[9,12]. Although clinical resistance from circulating antibodies can form against non-human calcitonin, the use of human calcitonin is limited due to its susceptibility to precipitating as insoluble fibrils[9].

Salmon calcitonin has been commercially available in an injectable form and as a nasal spray, but developing an oral formulation of a peptide hormone, which can survive gastric enzymatic digestion and subsequently penetrate the intestinal mucosa, has been a challenge[2]. However, oral delivery of calcitonin has been shown to be feasible by linking salmon calcitonin with various additives, including permeation enhancers (e.g. a caprylic acid derivative), enzyme inhibitors and particulate systems[2,15,16].

The history of calcitonin

Parenteral calcitonin was the first FDA approved formulation, available as an intramuscular or subcutaneous injection. However, its use was associated with poor patient compliance and tolerability due to its extensive side effects, the most notable of which was gastrointestinal disturbance[17-20]. Numerous studies reported nausea, loss of appetite, abdominal pain and diarrhoea. In addition, patients also experienced flushing in the face and peripheries; local inflammatory reactions were also common at the site of administration[18,19]. Data on the efficacy of the injectable formulation is scarce. In a retrospective cohort study conducted by Kanis et al., a significant risk reduction in hip fractures (RR: 0.69, 95% CI: 0.51-0.92) was observed following a year of daily calcitonin injections, compared to control[21]. However, a similar magnitude of risk reduction was observed in patients receiving daily calcium supplementation (RR: 0.75, 95% CI: 0.60-0.94). It is important to note that, due to its extensive side effect profile, the use of injectable calcitonin has been mostly replaced by the later developed intranasal formulation.

The intranasal formulation has been the preferred method of administration over the parenteral route due to multiple factors. Firstly, it is more convenient and less invasive for the patient. Moreover, common side effects resulting from salmon calcitonin administration, such as nausea and vomiting, occur less frequently in studies using the intranasal formulation[4,22]. Collectively, these factors promote better drug tolerability and patient compliance. However, the nasal formulation has been reported to have lower bioavailability and slower absorption than the injectable formulation[23]. Mild nasal symptoms have also been observed in multiple studies, including nasal irritation, rhinitis and rhinorrhoea[4,18,22].

One of the important studies which led to the 1995 FDA approval of intranasal salmon calcitonin was the PROOF study (Prevent Recurrence of Osteoporotic Fracture)[4]. The PROOF study was an international, multi-centre trial which demonstrated that a 5-year daily 200IU dose of intranasal calcitonin, along with daily vitamin D and calcium supplementation, was able to reduce vertebral fracture risk by 36% compared to placebo in postmenopausal women living with osteoporosis. A significant but modest improvement in lumbar BMD was seen in all treatment arms (100 IU, 200 IU, and 400 IU), while serum bone resorption markers were also significantly reduced. This was the first large-scale, prospective study looking into the anti-fracture efficacy of calcitonin. Prior to this, studies demonstrating salmon calcitonin's anti-fracture properties were mostly retrospective or prospective with small sample sizes[21,24-26]. Interestingly, the efficacy of intranasal calcitonin was not dose-dependent. Patients receiving the daily 200 IU dose were able to benefit from a greater vertebral fracture risk reduction than patients on the daily 400 IU and 100 IU regimens. It is important to acknowledge that the PROOF study has been criticised for its high dropout rate of 59% by the end of the 5-year follow up. Although some of the main findings from this study, including its potential in increasing lumbar spine BMD and suppression of serum resorption markers, were consistent with the literature, evidence surrounding nasal calcitonin's vertebral anti-fracture efficacy have been conflicting[24,26-30]. Additionally, the effect of nasal calcitonin on non-vertebral fracture risk and BMD is unclear[31,32]. Aside from its effects on the vertebrae, nasal calcitonin has been

Table 1. Trials on the anti-fracture efficacy and analgesic effects of intranasal and oral calcitonin.

Reference	N	Intervention	Outcome
Chestnut et al. (2000)[4]	1255 (511 completed full 5-year follow up)	Daily nasal salmon calcitonin (100, 200 or 400 IU) vs placebo over 5 years	Daily 200 IU nasal calcitonin significantly reduced vertebral fracture risk. The 100 IU nasal calcitonin group experienced significantly fewer non-vertebral fractures compared to placebo. All dosages significantly increased vertebral BMD compared to placebo. Significant reductions in bone resorption markers were observed in 200 IU and 400 IU groups.
Henriksen et al. (2016)[37]	4665	Daily 0.8mg oral salmon calcitonin vs placebo over 36 months	Oral salmon calcitonin did not significantly reduce vertebral and non-vertebral fractures risk compared to placebo. The treatment group experienced a significantly greater increase in lumbar spine BMD than placebo but not in total hip or femoral neck BMD. Bone resorption markers were significantly lower in oral calcitonin arm than placebo arm at 12 and 24 months but not at 36 months.
Lyritis et al. (1991)[42]	56	Daily calcitonin 100 IU vs placebo injections for osteoporotic vertebral fractures, over 14 days	Calcitonin 100IU yielded significant reductions in pain ($p<0.001$) compared to placebo. These were apparent as early as day 2 of the treatment period. Urinary hydroxyproline and urinary calcium were significantly lower in the calcitonin group.
Lyritis et al. (1999)[43]	40	Daily 200 IU calcitonin suppositories vs placebo over 28 days	Daily calcitonin suppositories demonstrated significant analgesic efficacy on VAS scores compared to placebo in patients with recent osteoporotic vertebral fractures.
Karponis et al. (2015)[33]	41	Daily 200 IU intranasal calcitonin vs placebo over 3 months	Nasal calcitonin demonstrates a statistically significant analgesic efficacy after distal radius fractures when compared to placebo.

shown to have a significant analgesic effect during the early stages of treating distal radius fractures[33].

Oral calcitonin has raised interest as a result of a few factors. Firstly, bisphosphonates have received increasing levels of concern around their long-term, albeit rare, side effects, including osteonecrosis of the jaw and atypical femoral fractures[34,35]. This, therefore, renewed the interests in alternative therapies, including older treatment options such as calcitonin. Secondly, intranasal and injectable salmon calcitonin have been associated with suboptimal patient compliance[4]. Thus, a potentially more convenient and accepting method of delivery was explored. However, due to the peptide nature of calcitonin, achieving adequate bioavailability from the oral route has been the main challenge to tackle to date[36].

At the time of composing this review, evidence on oral calcitonin is limited and data from the latest phase III trials have not shown promising results, to the best of our knowledge. The most recent phase III trial, conducted by Henriksen et al., investigated the anti-fracture efficacy of oral salmon calcitonin in 4665 postmenopausal women over 3 years and is the only study hitherto to directly measure the anti-fracture efficacy of the oral formulation[37]. Achieving adequate bioavailability was a challenge and pharmacokinetic analysis demonstrated suboptimal drug exposure in subjects who were administered calcitonin. Overall, daily oral salmon calcitonin (0.8 mg/d) with calcium and vitamin D supplementation did not significantly alter new vertebral fracture and non-vertebral fracture incidence when compared to control ($p=0.94$). No significant differences in cumulative fracture risk were seen between the treatment and control groups across the 36-month study period. However, participants in the treatment arm had a statistically longer duration between baseline and the time of first hip fracture compared to placebo. The increase in lumbar spine BMD following oral calcitonin treatment was significantly greater in the treatment group than placebo (treatment: 1.02%, control: 0.18%, $p<0.0001$). Two studies conducted by Binkley et al. have demonstrated significant but mild improvement in lumbar spine BMD improvement and moderate suppression of bone resorption markers[38,39]. Anti-fracture efficacy was not assessed in these trials. Firstly, the ORACAL trial was a phase III study which showed that daily 0.2 mg oral formulation over 48 weeks induced a significantly greater improvement in lumbar spine BMD than the intranasal formulation ($p=0.027$) and placebo ($p=0.010$) groups. Yet, it is important to note that the absolute differences between the change in BMD of the oral, intranasal and placebo arms were modest (1.5%±3.2%, 0.78%±2.9%, 0.5%±3.2%, respectively). Similarly, the second and more recent trial conducted by Binkley et al. demonstrated a significant yet mild effect on lumbar spine BMD (1.03%, $p<0.001$) following 54-

week administration of daily 0.2mg recombinant salmon calcitonin. At non-vertebral sites, changes in BMD at the hip, femoral neck and trochanter sites were not statistically different between oral, nasal calcitonin and placebo groups in the ORACAL trial. At non-vertebral sites, Henriksen et al. observed a reduction in hip and femoral neck BMD in both treatment and placebo groups, but the reduction was greater in the placebo group. In all studies, a significant decrease in bone resorption markers was observed, including C-terminal telopeptides of collagen types I, II (CTX-I, CTX-II respectively) and N-terminal cross-linked telopeptide of type I collagen (NTx-I)[37-39]. In the ORACAL study, a significantly greater reduction in CTx-I was reported in the oral calcitonin group than the nasal calcitonin group. Henriksen et al. demonstrated that bone resorption markers in the oral calcitonin group were significantly lower than placebo at 6, 12 and 24 months, but not at 36 months. Whether differences in biochemistry translate to clinical significance, though, is a different question and, frankly, the one that should be asked.

To date, most studies have been conducted on postmenopausal women and very few have looked into calcitonin's therapeutic efficacy in other patient populations. A trial conducted by Trovas et al. assessed the efficacy of daily 200IU nasal calcitonin in 28 males with idiopathic osteoporosis over 12 months. Nasal calcitonin was able to significantly increase vertebral BMD compared to placebo (mean ± standard error of the mean (SEM): 7.1±1.7% and 2.4±1.5%, respectively, $p<0.05$). However, similar improvements in BMD were not observed in the femoral neck, trochanter and ward's triangle following calcitonin administration. Bone resorption markers, including CTX-1, NTX-1 and urinary deoxypyridinoline, were also suppressed and the reduction was significantly greater compared to placebo. This study was not powered to analyse nasal calcitonin's anti-fracture efficacy[40].

In the management of corticosteroid-induced osteoporosis, a Cochrane review conducted by Cranney et al. (including 9 trials) demonstrated that calcitonin was effective in improving vertebral BMD at 12 months, with a weighted mean difference of 3.2% (95% CI: 0.3 to 6.1) compared to placebo. However, no significant difference was observed at 24 months. Similar results were observed at the distal radius, where calcitonin exerted a significant improvement in BMD compared to placebo at 6 months only. No statistically significant difference in BMD was observed at the femoral neck compared to placebo. Additionally, no significant difference in relative risk for vertebral and non-vertebral fractures was observed in the treatment groups when compared to placebo[41]. Table 1 summarizes key findings from trials on the efficacy of calcitonin.

Current Indications

In the British National Formulary (BNF), calcitonin is indicated for use in hypercalcaemia of malignancy, Paget's disease of bone, and the prevention of acute bone loss due to sudden immobility. However, it is contraindicated in hypocalcaemia, and factors such as heart failure, a history of allergies and the risk of malignancy need to be taken into account.

Although calcitonin is not approved by the European Medicines Agency (EMA) for the treatment of postmenopausal osteoporosis, it is FDA-approved for managing patients who are at least 5 years postmenopausal and when the alternatives are contraindicated. This was largely based on the PROOF study in 2000 which showed a 30% reduction in vertebral fracture occurrence in participants with prior vertebral fractures[4]. However, due to meta-analyses reporting a potential, albeit non-definitive, link between salmon calcitonin and malignancy, it is no longer considered to be the first-line treatment and should only be used when the alternatives are contraindicated[44-46]. Calcitonin may still be preferred for acute osteoporotic fractures as several studies have observed significant analgesic effects in the acute setting[33,42,43,46]. In this instance, calcitonin is recommended for use until the pain resolves, at which point it should be substituted with a more effective long-term drug.

Calcitonin is EMA and FDA-approved in the treatment of hypercalcaemic emergencies. It is used due to its fast-acting calcium-lowering effect which is useful when calcium levels need to be lowered rapidly. After rehydrating the patient with saline, calcitonin is co-administered with a bisphosphonate and other calcium-lowering drugs such as loop diuretics. The osteoclast-inhibiting effect of calcitonin administration typically fades after 24-48 hours, but this coincides with when bisphosphonates' activity increases; as a result, co-administration produces a rapid fall in calcium due to calcitonin, and a sustained decrease over a few days from the bisphosphonate.

For Paget's disease of bone, calcitonin is authorised by the EMA for short-term use and it is the FDA-approved second-line treatment which should be administrated when the treatment of choice, zoledronic acid, is not tolerated or prompt surgery on the bone affected by the disease is necessary. A study involving 85 participants found that in the initial months of salmon calcitonin therapy for Paget's disease, the main markers of bone remodelling and turnover (alkaline phosphatase and urine hydroxyproline) decreased by approximately 50%. However, 22 of these patients eventually returned to pre-treatment levels despite continued treatment, and 19 of those 22 had high titres of anti-calcitonin antibodies[47]. This development of tolerance makes calcitonin a less viable long-term option in the treatment of Paget's disease compared to bisphosphonates, which are not vulnerable to antibodies. When administering calcitonin, serum alkaline phosphatase needs to be measured every 3 to 6 months until it normalises, after which it can be measured every 6 months; if levels rise again, antibody formation should be suspected.

Competitors in the treatment of postmenopausal osteoporosis

In comparison to calcitonin, the literature surrounding the anti-fracture efficacy of bisphosphonates has demonstrated more promising data. Bisphosphonates are pyrophosphate analogues, which exert their therapeutic effect by attaching to bone. Active resorption of these areas of bone leads to osteoclast inhibition via intracellular pathways[48,49]. Alendronate and risedronate are the two most commonly used bisphosphonates for postmenopausal osteoporosis in the UK. Due to the long half-life of bisphosphonates, convenient extended-interval dosing regimens, such as once weekly or once monthly options, are available on the market and some patient populations may also be eligible to undergo drug holidays[50]. Numerous studies have demonstrated anti-fracture efficacy in bisphosphonate use at both vertebral and non-vertebral sites[51-54]. Specifically, the Fracture Intervention Trial (FIT) highlighted that a daily alendronate regimen (5 mg/d for first 24 months, followed by 10 mg/d until 36 months) was able to induce a significant 50% reduction in vertebral fractures and 30% reduction in wrist and hip fractures in postmenopausal women with osteoporosis with at least one previous vertebral fracture[51]. Furthermore, femoral neck and lumbar spine BMD were also increased by 4.1% and 6.2%, respectively, throughout the study.

In the 3-year Vertebral Efficacy with Risedronate Therapy (VERT) trial, Risedronate (5mg/d) was able to reduce fracture incidence at both vertebral and non-vertebral sites by 41 % (95% CI: 18%-58%) and 39% (95% CI: 6%-61%), respectively, compared to placebo. Significant improvements in BMD were observed at the lumbar spine (5.4%), femoral neck (1.6%) and trochanter (3.3%) compared to placebo (1.1%, -1.2%, -0.7%, respectively)[53]. In the Hip Intervention Program (HIP) study, McClung et al. demonstrated that daily risedronate over 3 years was able to significantly lower hip fracture risk in elderly female patients with pre-diagnosed osteoporosis, compared to placebo. (RR: 0.6; 95% CI:0.4 to 0.9; P=0.009)[54].

Zoledronic acid is available as a convenient, once-yearly IV infusion which may be used in cases where oral bisphosphonates are contraindicated. In the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial, annual administration of zoledronic acid over 3-years demonstrated both vertebral and hip anti-fracture efficacy when compared to placebo (RR: 0.30; 95% CI: 0.24-0.38, HR: 0.59 95% CI: 0.42-0.83, respectively)[8]. Additionally, in the HORIZON Recurrent Fracture Trial, it was able to lower re-fracture incidence in patients with previous hip fractures (HR:0.65 95% CI 0.50-0.84)[55].

Ibandronate has been shown to exhibit vertebral anti-fracture efficacy compared to placebo[1] but there is a lack of strong evidence justifying its use for hip and non-vertebral fractures. The BONE study (Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe) was a 3-year trial conducted on 2946 postmenopausal women which demonstrated that oral daily (2.5 mg/d) and intermittent ibandronate (20 mg every other day for 12 doses every 3 months) were able to reduce vertebral fracture rates by 62% (p=0.0001) and 50% (p=0.0006), respectively, compared to placebo. Significant improvements in vertebral and hip BMD were also observed[56].

Evidence directly comparing the efficacy of bisphosphonates with calcitonin is limited. A study which directly compared alendronate with salmon calcitonin demonstrated a significantly greater increase in lumbar spine (p<0.001), trochanter (p<0.001) and femoral neck BMD (p<0.001) in patients who were administered the bisphosphonate compared to salmon calcitonin over 12 months[57]. Moreover, a significantly greater reduction in bone resorption markers within the alendronate group was observed compared to calcitonin following 12 months administration (p<0.001).

Denosumab, a fully human monoclonal antibody that inhibits RANKL, is not regarded as the standard first-line treatment for postmenopausal osteoporosis[58]. It has been shown to be very powerful at countering bone resorption, reducing fracture rates, increasing BMD and reducing serum bone resorption markers[59,60]. Notably, the FREEDOM study (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) was an international, multi-centre trial which compared the efficacy of denosumab against placebo in 7868 women with postmenopausal osteoporosis over 3 years[59]. The study showed that denosumab was able to significantly reduce vertebral (RR: 0.32 95% CI: 0.26-0.41) and hip (hazard ratio (HR): 0.60 95% CI: 0.37-0.97) fracture risk, increase lumbar and hip BMD and suppress bone resorption markers. An extension of the trial allowed the monitoring of an additional 7 years for 4550 participants from the FREEDOM study which demonstrated the long-term maintenance of low fracture incidence and continued rise in vertebral and non-vertebral BMD[60]. Yet, denosumab discontinuation is associated with 'rebound' bone resorption and anti-resorptive agents are often prescribed following withdrawal to minimise this effect[61].

Unlike the aforementioned anti-resorptive agents, different "anabolic" options are also available on the market, including teriparatide (PTH analogue) and abaloparatide (PTHrP analogue). PTH has two contrasting functions on bone turnover. Despite its net effect of bone resorption during continuous administration, it promotes bone formation when delivered intermittently[62]. In the UK, teriparatide is indicated for the treatment for postmenopausal osteoporosis and in males at high risk of fractures and corticosteroid-induced osteoporosis. The use of abaloparatide is approved by the FDA for the management of postmenopausal osteoporosis in the US. However, evidence surrounding its use was deemed insufficient by the EMA in 2017. In general, anabolic agents are not first-line for the treatment of osteoporosis, owing to a plethora of factors, such as the greater cost and inconvenient administration (subcutaneous injection) compared to most bisphosphonates[63]. Intriguingly, treatment withdrawal

often results in a progressive decline in BMD which requires management by anti-resorptive agents; this further limits the use of anabolic agents[64].

Teriparatide has been shown in numerous studies to possess anti-fracture efficacy at vertebral and non-vertebral sites[65-67]. Moreover, the Fracture Prevention Trial was an international, multi-centre randomized control trial which demonstrated that a daily regimen of 20 µg or 40 µg injection over 21 months considerably reduced new vertebral fracture risk by 65% (RR: 0.35 95%CI: 0.22-0.55) and 69% (RR: 0.31 95%CI: 0.19-0.50) compared to placebo, respectively[65]. Non-vertebral fracture RR in the 20 µg and 40 µg arms were 0.47 (95%CI: 0.25-0.88) and 0.46 (95%CI: 0.25-0.861), respectively. Daily 20 µg and 40 µg teriparatide were able to induce a dose-dependent and statistically significant increase in BMD measured at multiple sites including the lumbar spine, hip and femoral neck. Studies directly comparing teriparatide and calcitonin have shown a greater increase in lumbar BMD in patients treated with teriparatide compared to salmon calcitonin[68-70]. However, data comparing their efficacy on femoral neck and total hip BMD data has been inconsistent. Specifically, trials have shown an increase in serum bone formation markers including bone-specific alkaline phosphatase and osteocalcin in participants taking teriparatide but not in the calcitonin group[68-70]. However, it is important to question the external validity of these studies, which were mostly conducted on Asian populations and hence, a clinical benefit remains equivocal when generalising these findings to other populations.

Discussion

The decline in the use of calcitonin can be attributed to a variety of causes. There are issues intrinsic to the drug itself, including an association with cancer, and the lack of a widely-available oral formulation[2,4]. Additionally, there are extrinsic factors: primarily, the development of alternative drugs with greater efficacy.

Firstly, there is the potential risk of malignancy associated with calcitonin use. This was first brought to attention by the PROOF trial of nasal salmon calcitonin, where the results showed a higher risk of cancer in the active group (8.9%) compared to the placebo group (5.1%), with basal cell carcinomas being the major finding[4]. At the time, no action was taken by the FDA because the age and race of the participants were confounding factors, but the potential association was flagged up again after phase III trials for an oral formulation of calcitonin (SMC021) which reported cases of prostate cancer[71,72]. In addition to these findings, a 1994 study demonstrated a biological route through which calcitonin might stimulate the growth of prostate cancer cells[73]. Since then, the EMA commissioned a committee to review all of the salmon calcitonin studies and, in July 2012, stated that salmon calcitonin should no longer be recommended as a treatment option for postmenopausal osteoporosis, citing an increased malignancy risk as one of the paramount reasons. In March 2013, an advisory panel to the FDA also recommended that calcitonin should not be indicated for postmenopausal osteoporosis because the safety risk outweighed the fracture reduction. Although the FDA did not implement this recommendation, all calcitonin nasal spray products were withdrawn by Health Canada in October 2013 and two months later, the Taiwan FDA followed suit. Furthermore, a case-control study involving 28222 osteoporotic patients in Taiwan found that using a calcitonin nasal spray in women significantly elevated the risk of liver cancer, although the risk of breast cancer was reduced[74].

Another reason for the decline in use is that salmon calcitonin carries significant side-effects, many of which are related to the gastrointestinal tract such as abdominal pain, diarrhoea, nausea and vomiting in addition to arthralgia, musculoskeletal pain and flushing. Studies investigating the short-term and long-term side-effects of calcitonin have found that the unwanted effects of the nasal spray preparation were a lot milder and had a lower incidence compared to the subcutaneous injectable form of calcitonin[17]. However, there were some side-effects specific to the nasal spray including nasal irritation, sneezing and rhinitis. As previously mentioned, randomised control trials involving oral calcitonin found it to be well-tolerated in general but it was still associated with hot flushes and gastrointestinal symptoms like nausea and dyspepsia. In the ORACAL trial, a higher incidence of nausea and dyspepsia was reported in participants who took the oral calcitonin than the nasal spray group[38].

One of the most important factors which diverted healthcare professionals away from the use of calcitonin was the lack of strong evidence justifying its use, along with the simultaneous presence of other treatment options which demonstrated more promising data showing superior efficacy in increasing multifocal BMD and anti-fracture efficacy. Whilst the PROOF study was able to illustrate calcitonin's anti-fracture efficacy, many other studies did not show consistent results. In most studies, the fracture rate was either too low to allow meaningful statistical analysis or that statistical analysis did not show a significant change in vertebral fracture rates from calcitonin use. Although calcitonin has been shown in various trials to increase lumbar spine BMD and decrease bone resorption markers, including CTX-I and CTX-II, the clinical utility of using BMD and serum bone resorption markers in predicting fracture risks have been questioned[75-77].

Future direction

In the future, it is likely that calcitonin will continue to be used in combination with bisphosphonates for the treatment of emergency hypercalcaemia and hypercalcaemia of malignancy due to its rapid action. It is unlikely that calcitonin will become the first-line treatment for postmenopausal osteoporotic fractures or Paget's disease, mainly due to the proven greater efficacy of bisphosphonates. However, its

powerful analgesic effect should not be overlooked and if a safe oral formulation that can achieve adequate bioavailability is found, which would potentially be more beneficial and acceptable to patients than the nasal spray, then there could be renewed interest in this drug.

The efficacy of calcitonin in treating acute pain associated with fractures has already been discussed, but calcitonin may also be a useful alternative in the treatment of acute and chronic neuropathic pain with recent studies having been conducted to look at the potential mechanisms behind this. This benefit of calcitonin has previously been demonstrated in the treatment of phantom limb pain where a double-blinded crossover study showed efficacy in the early post-operative period[78]. Additionally, a case report by Visser et al. illuminated a patient's recovery from post-herpetic neuralgia after being administered calcitonin following the failure of traditional analgesics, and a 2011 case series highlighted the role of calcitonin in treating acute neuropathic pain associated with spinal cord injury[79,80]. Other reports which have indicated potential uses of calcitonin in neuropathic pain include diabetic neuropathy, lumbar spinal canal stenosis, reflex sympathetic dystrophy, post-operative pain and trigeminal neuralgia[81].

Finally, in addition to calcitonin's effects on reducing bone resorption, a 2005 study found that an oral form of salmon calcitonin significantly reduced the urinary excretion of CTx-II, suggesting that it could decrease the degradation of cartilage and act as a treatment for osteoarthritis[82]. Furthermore, calcitonin has been shown to reduce the levels of rheumatoid factor and interleukin-1b in patients with rheumatoid arthritis, but ancillary work is necessary at this stage to establish it in the armamentarium of anti-rheumatic medications[83,84]. This is another example of how successfully creating a viable oral formulation of calcitonin could be key to the future of the drug, although achieving adequate concentrations in the joints of interest may be another challenge.

Conclusion

Since its discovery by Douglas Harold Copp, calcitonin has been a useful treatment for various metabolic bone diseases. However, similar to many other medications, it has been derailed by associations with cancer and superseded by newer and more potent alternatives. There will still be a role for calcitonin when patients are unsuitable candidates for first-line therapies. Furthermore, the development of an oral formulation could herald a new interest in the drug. Although calcitonin will be used less for its original purpose of increasing BMD and reducing fracture risk, its unique analgesic efficacy means that there may still be a future for this old friend.

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