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Current Pharmacological Options for the Management of Primary Hyperparathyroidism

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Abstract

Drugs for treating primary hyperparathyroidism can be divided into two main groups: (i) antiresorptive drugs that inhibit the increased bone turnover, which can be divided into estrogen-like compounds (estrogen, oral contraceptives and selective estrogen receptor modulators [SERMs]), bisphosphonates and calcitonin; and (ii) drugs that interfere with parathyroid hormone (PTH) secretion (currently only cinacalcet is available). No drugs that interfere with PTH action are currently available.

Available studies suggest that all classes of drugs are able to lower serum calcium levels. However, calcitonin does so only temporarily. Estrogen-containing compounds (hormone replacement therapy) may be less attractive because of the potential risk of breast cancer, cardiovascular disease and deep vein thromboembolism. Oral contraceptives have not been shown to be able to prevent fractures in the general population, and no data are available on their effect in women with primary hyperparathyroidism. The only SERM marketed for hyperparathyroidism is raloxifene and this has not been associated with an increased risk of breast cancer and cardiovascular diseases, and has been shown to be able to prevent vertebral fractures in postmenopausal women with osteoporosis. Two small trials suggest that raloxifene may increase bone mineral density (BMD) and decrease serum calcium levels in patients with primary hyperparathyroidism. Bisphosphonates have been shown to decrease serum calcium and increase BMD in patients with primary hyperparathyroidism, but PTH levels may increase.

Cinacalcet effectively induces a sustained decrease in serum calcium and PTH for up to 1 year. However, BMD does not seem to increase.

No data on hard endpoints such as fractures, kidney stones, cardiovascular disease etc. are available for any of the drugs available for the treatment of primary hyperparathyroidism.

When managing primary hyperparathyroidism, the target of treatment needs to be borne in mind: the hypercalcaemia, the complications of the disease (e.g. osteoporosis), or the increased parathyroid hormone (PTH) level. This review focuses on the pharmacological management of primary hyperparathyroidism at all levels. Firstly the pathophysiology, symptoms and organ manifestations (complications) are discussed, and then pharmacological treatment is reviewed.

1. Pathophysiology

In primary hyperparathyroidism there is increased PTH secretion from one or more parathyroid glands despite elevated serum calcium levels,[1] i.e. the normal feedback mechanism mediated by the calcium sensing receptor (CaSR) is disturbed.[2] The

sensitivity of the CaSR to calcium is decreased, i.e. elevated serum calcium level is perceived by the receptor as being normal.[2] The increased PTH secretion leads to increased bone turnover[3] with increased resorption and increased calcium efflux from the skeleton.[4] In mild primary hyperparathyroidism, both calcium influx and efflux from the skeleton are increased as part of the increased turnover.[3] Patients with primary hyperparathyroidism experience a negative calcium balance, which is also seen in healthy controls.[4] However, progressive bone loss is not a common observation in patients with untreated mild primary hyperparathyroidism[5] because mild primary hyperparathyroidism is a state with an increased bone turnover and a new equilibrium in bone mineral density (BMD). After surgical treatment of primary hyperparathyroidism, BMD increases.[6] To what extent the increased bone turnover in mild primary hyperparathyroidism poses a risk to the skeleton with an increased risk of fractures remains to be demonstrated.[7]

Antiresorptive drugs (see section 5) decrease the calcium efflux from the skeleton and thus decrease the calcium load presented for excretion. For every 3 mmol of calcium presented for excretion, 1 mmol is retained in the serum and increases serum calcium levels. As a consequence, the decrease in serum calcium with antiresorptive drugs will be modest compared with a calcimimetic (see section 6), which reduces the renal threshold for calcium reabsorption.[3]

The increased calcium efflux from the skeleton leads to increased urinary calcium excretion.[4] In the kidney, PTH induces an increased threshold for calcium excretion, which also contributes to the increase in serum calcium levels.[1] PTH induces increased calcium reabsorption and increased phosphate excretion.[1] The increased renal tubular calcium reabsorption is the main mechanism behind hypercalcaemia in the early stages of primary hyperparathyroidism. However, over time, despite the increased renal calcium threshold and calcium reabsorption, there is an increased total calcium excretion in the urine.[4]

The increased PTH level also induces 1-α-hydroxylase, which increases the conversion of 25-hydroxy-vitamin D to 1,25-dihydroxy-vitamin D leading to an increased level of 1,25-dihydroxy-vitamin D.[8]

2. Symptoms and Organ Manifestations

Primary hyperparathyroidism has gone from the classical picture with 'bones, stones and psychiatric groans' to an often asymptomatic disease, which is discovered incidentally upon biochemical screening with measurements of serum calcium levels.[9]

Surgery with removal of the affected parathyroid gland(s) remains the treatment of choice.[10] However, with the change in mode of presentation, surgery may not always be desirable, and alternative methods are needed to control, for example, osteoporosis in an otherwise asymptomatic patient who does not want surgery or from a medical point of view cannot undergo surgery.

By organ, the symptoms and organ manifestations of primary hyperparathyroidism are:

- Kidneys: polyuria, thirst, polydipsia, dehydration, nephrocalcinosis, urinary tract calcifications[11] and reduced kidney function.
- Cardiovascular system: increased risk of arteriosclerosis,[12] angina pectoris, myocardial infarction (MI), hypertension[12,13] and cardiac arrhythmias.
- Intestine: constipation, nausea and vomiting.
- Stomach and duodenum: increased acid secretion and ulcers.
- Pancreas: acute and chronic pancreatitis,[14] pancreas insufficiency and diabetes mellitus.[15]
- Skeleton: osteoporosis and fractures.[16]
- CNS: confusion, loss of memory, dementia and psychotic symptoms.

- Muscles and joints: fatigue, and muscle and joint pain.

It has been debated whether all of these truly represent features of primary hyperparathyroidism or whether some, e.g. ulcers, have just by coincidence been associated with primary hyperparathyroidism.

All of these symptoms and findings contribute to increased mortality in patients with primary hyperparathyroidism, especially from cardiovascular causes.[17] Surgically treated patients with primary hyperparathyroidism tend to have a lower mortality than conservatively managed patients.[18,19]

Symptoms of hypercalcaemia may often be subtle or mimic otherwise common symptoms such as fatigue and difficulties in concentrating.

3. Indications for Surgery or Medical Management

Current US guidelines state that symptomatic patients should undergo surgery, while in otherwise asymptomatic patients, surgery should be advised in those with high albumin adjusted serum calcium levels (≥1 mg/mL [0.25 mmol/L] above upper normal range), high urine calcium excretion (>400 mg/day), osteoporosis, creatinine clearance reduced by more than 30%, or age <50 years.[10] It should be noted that these guidelines have been subject to debate.[20] The evidence for surgical versus conservative management is at present limited because it is only based on randomised controlled trials (RCTs) rather than on epidemiological data from cohort studies.

Medical management has its place: (i) in patients who cannot tolerate surgery, e.g. because of comorbidity which prevents anaesthesia (although this group nowadays is rather small as a result of improvements in anaesthesia and the advent of minimally invasive surgical procedures); (ii) in patients who do not want to undergo surgery; (iii) in the waiting time from diagnosis to surgery in patients with severe hypercalcaemia; and (iv) in patients with recurrent or persistent hypercalcaemia despite surgery and in whom repeat surgery is not possible or desirable.

However, drugs may also be used in patients who have already undergone surgery, or are about to undergo surgery, in order to treat specific conditions, and in this case osteoporosis is the most frequent condition that needs attention.

4. Drugs for the Treatment of Primary Hyperparathyroidism

In the evaluation of drugs used for the treatment of primary hyperparathyroidism, we should be aware that often only small and uncontrolled trials are available. The endpoints used in the studies have often been biochemical and the study duration limited. The effects of individual drugs are evaluated in section 5 in terms of their effect on serum calcium levels, urine calcium excretion (as a measure of bone resorption), biochemical markers of bone turnover (also as a measure of bone resorption), BMD and 'hard' endpoints such as fractures.[19] Systematic searches of MEDLINE, EMBASE, the Cochrane Library and Web of Science were performed for each drug combined with the term 'primary hyperparathyroidism'. The search date was 30 April 2006. The tables in this article present an overview of studies on drugs to control primary hyperparathyroidism.

The drug classes used to treat primary hyperparathyroidism can be divided into:

1. Drugs to treat the consequences of elevated calcium levels (i.e. treatment of the elevated calcium itself or osteoporosis). For example, these drugs may be antiresorptive drugs, which are usually administered for the prevention and treatment of osteoporosis.[21] The main emphasis will be on the effects of antiresorptive drugs, as little experience is available for the effects of other drugs (for example, drugs

to prevent renal stone formation in primary hyperparathyroidism).
2. Drugs to treat the increased PTH level. These drugs can decrease PTH synthesis or secretion, or block the effects of PTH either by interfering with itself (e.g. an antibody) or its receptor and the post-receptor pathways. The only available drug in this class is cinacalcet, which is a calcimimetic that interferes with the CaSR.

5. Antiresorptive Drugs

Antiresorptive drugs act through inhibition of osteoclasts, thus decreasing calcium efflux from the skeleton and, thereby, decreasing serum calcium levels and urine calcium excretion.[22] The decreased resorption leads to increased BMD of the skeleton.

5.1 Estrogen and Estrogen-Like Substances, including Selective Estrogen Receptor Modulators (SERMs)

Estrogen and estrogen-like substances have been tested only in postmenopausal women. They may perhaps be less likely to be effective in premenopausal women who are not estrogen deficient. Most studies were small 'before-and-after studies' without a control group.

5.1.1 Ethinylestradiol (Oral Contraceptives)

Effects

From table I, it can be seen that only a few small studies have been conducted with oral contraceptives.[23-25] All studies have been before-and-after trials without a comparison group. The mean decrease in serum calcium level was 0.22 mmol/L over a period of 3 weeks to 20 months. The effect was due to a decrease in bone turnover (resorption) with a concomitant decrease in urine calcium excretion and serum calcium levels. PTH levels remained unchanged. No studies with 'hard endpoints' are available.

Effects in Patients without Primary Hyperparathyroidism

From studies in women in general, ethinylestradiol seems associated with an increased BMD.[32] However, such studies have not shown that oral contraceptives are effective in preventing fractures,[33-36] and this is of particular importance in patients with primary hyperparathyroidism as one of the main manifestations that one is trying to prevent is osteoporosis and fractures.

Adverse Effects

The adverse effects of oral contraceptives include nausea, mastalgia, migraine, breakthrough bleeding, venous thromboembolism and oedema.[37] In rare cases, stroke and MI may be seen.[37]

Conclusions

Oral contraceptives containing ethinylestradiol may lower serum calcium levels in postmenopausal women with primary hyperparathyroidism. The association of ethinylestradiol with stroke and MI is a cause for concern, as the risk of arteriosclerosis is increased in primary hyperparathyroidism. Given the lack of evidence for an effect on hard endpoints and the potential adverse effects, this class of drugs should not be considered in general for the treatment of primary hyperparathyroidism. Treatment with oral contraceptives started for other reasons than primary hyperparathyroidism may be continued.

5.1.2 Estradiol and Conjugated Equine Estrogens

Effects

Estrogen-containing compounds may be used as hormone replacement therapy (HRT: estrogen in combination with a progestogen) or as estrogen alone (estrogen replacement therapy [ERT]). Estrogen may be used as estradiol or as conjugated equine estrogens.

From table I it can be seen that only a few studies have been conducted with estrogens in postmenopausal women. The mean decrease in serum calcium level was 0.10 mmol/L. In addition to the

Table I. Effects of oral contraceptives (ethinylestradiol) and estrogens on serum calcium levels, bone turnover markers, bone mineral density (BMD) and hard endpoints in primary hyperparathyroidism (mean ± SEM)

Regimen	Patient characteristics	Baseline albumin-adjusted calcium (mmol/L)	Study duration	Decrease in serum calcium (mmol/L)	PTH changes	Change in urine calcium excretion	Change in bone turnover markers	Change in BMD	Effect on hard endpoints	Ref.
Ethinylestradiol										
Ethinylestradiol 50 μg/day in 3 of 4wk cycles	10 PM women, all treated	3.00	16wk	0.19*	NA	Urine 24h calcium/creatinine ratio 0.402 : 0.228*	↓ urine hydroxyproline*, ↓ ALP (2p = 0.05)	NA	NA	23
Ethinylestradiol 50 μg/day in 3 of 4wk cycles	8 PM women, all treated	2.95	3–20mo	0.27*	NA	↓ fasting urine calcium/creatinine	↓ urine hydroxyproline, NS	NA	NA	24
Ethinylestradiol 30 μg/day	6 PM women, all treated	2.77 ± 0.07	3wk	0.19 ± 0.09*	721 ± 264 to 624 ± 206 pg/mL (NS)	Fasting urine calcium/creatinine ratio 0.47 ± 0.09 to 0.30 ± 0.07*	↓ urine hydroxyproline, NS	NA	NA	25
Estrogens										
CEE 0.625–2.5 mg/day (on average 1.25 mg/day)	14 PM women, all treated	2.75 ± 0.02	4mo	0.13	1098 ± 109 to 1164 ± 181 pg/mL (NS)	Urine 24h calcium excretion 321 ± 36 to 243 ± 36 mg	↓ urine hydroxyproline*, ↓ ALP*	NA	NA	26
CEE 0.625mg in 2 pts, estriol 1mg in 1 pt, ethinylestradiol 50μg in 1 pt	5 elderly women, all treated	2.90 ± 0.10	3wk	0.21 ± 0.11*	NA	↓ urine 24h calcium/creatinine	NA	NA	NA	27

Continued next page

Table I. Contd

Regimen	Patient characteristics	Baseline albumin-adjusted calcium (mmol/L)	Study duration	Decrease in serum calcium (mmol/L)	PTH changes	Change in urine calcium excretion	Change in bone turnover markers	Change in BMD	Effect on hard endpoints	Ref.
CEE 0.625 mg/day + medroxyprogesterone 5 mg/day	42 PM women, RCT	HRT: 2.56 ± 0.03 Placebo: 2.62 ± 0.03	2y	HRT: 0.04 ± 0.04* Placebo: 0.03 ± 0.04, NS	HRT: 8.5 ± 1.1 to 11.6 ± 1.4* Placebo: 7.9 ± 0.8 to 10.9 ± 1.0*	NA	HRT: ↓ urine hydroxyproline*, ↓ ALP*	Total body BMD: +3.6 ± 0.8%, spine +6.6 ± 1.6%, hip 4.8 ± 2.3%, forearm 5.4 ± 1.6%	More mastalgia and vaginal bleedings with HRT than placebo	28
CEE 0.3–0.625 mg/day	15 PM women, 5 CEE, 10 surgery	CEE: 2.70 ± 0.03 Surgery with calcitriol: 2.84 ± 0.07 Surgery without calcitriol: 2.75 ± 0.03	12mo	CEE: 0.04 ± 0.08, NS Surgery: 0.50 ± 0.09*	CEE: 11.0 ± 3.5 to 11.7 ± 3.4, NS Surgery: 11.0 ± 1.5 to 3.2 ± 0.05*	Urine calcium/ creatinine CEE: 0.37 ± 0.03 to 0.18 ± 0.06* Surgery: 0.58 ± 0.08 to 0.40 ± 0.05*	↓ ALP with CEE, NS, ↓ BGP with CEE, NS	↑ lumbar spine (5.3%/y), ↑ femoral neck (5.5%/y)	NA	29
Other estrogens										
Cyclofenil 200mg tid	8 pts, all treated	2.79 ± 0.07	5–13wk	0.17 ± 0.10*	NA	Urine 24h calcium 6.5 ± 3.2 to 4.7 ± 2.2 mmol*	↓ urine hydroxyproline*	NA	NA	30
Methallenestril 3mg bid	6 PM women, all treated	2.74 ± 0.08	5–24wk	0.26 ± 0.09*	NA	Urine 24h calcium 5.7 ± 1.0 to 3.9 ± 1.0 mmol	↓ urine hydroxyproline*	NA	NA	31

ALP = alkaline phosphatase; **BGP** = bone Gla protein (osteocalcin); **bid** = twice daily; **CEE** = conjugated equine estrogens; **HRT** = hormone replacement therapy; **NA** = not available; **NS** = not statistically significantly different; **PM** = postmenopausal; **PTH** = parathyroid hormone; **pts** = patients; **RCT** = randomised controlled trial; **tid** = three times daily; ↓ indicates decrease; ↑ indicates increase; * 2p < 0.05 for change over time.

longitudinal studies mentioned in table I, one cross-sectional trial has been conducted in 59 postmenopausal women with or without HRT/ERT treatment.[38] This trial reported equal serum calcium levels in women both taking and not taking HRT/ERT (2.68 ± 0.03 mmol/L in both groups), and PTH levels were also similar.[38] Lumbar spine, femoral neck and distal radius BMD all tended to be higher in women on HRT/ERT than in women not receiving HRT/ERT. The effect of estrogens in all trials in table I was a decrease in bone turnover with a concomitant decrease in urine calcium excretion and serum calcium levels. Only one randomised controlled trial has been conducted.[28] This trial showed a very limited decrease in serum calcium levels of 0.04 mmol/L, which was not different from that with placebo.[28] There was an increase in total body, lumbar spine, hip and forearm BMD.[28] No studies with hard endpoints are available.

Effects in Patients without Primary Hyperparathyroidism

From studies on postmenopausal women in general, a reduction in fracture risk can be anticipated for both vertebral (relative risk [RR] = 0.67; 95% CI 0.45, 0.98; $p < 0.01$) and non-vertebral fractures (RR = 0.73; 95% CI 0.56, 0.94; $p < 0.01$).[39-44]

Adverse Effects

The adverse effects of ERT and HRT are numerous when used to treat postmenopausal osteoporosis (and thus not primary hyperparathyroidism). HRT is associated with an increased risk of breast cancer (RR = 1.27; 95% CI 1.03, 1.56[45] in one meta-analysis, and RR = 1.26; 95% CI 1.00, 1.59[39] in a large, randomised, controlled trial), an increased risk of cardiovascular disease (RR = 1.29; 95% CI 1.02, 1.63 in a large, randomised trial),[39] an increased risk of cerebrovascular disease (RR = 1.41; 95% CI 1.07, 1.85[39]), and an increased risk of deep venous thrombosis/pulmonary embolism (RR = 2.07; 95% CI 1.49, 2.87[39]). The increased risk of cardiovascular events is rather concerning given the already increased risk of cardiovascular deaths in patients with primary hyperparathyroidism.[17]

ERT does not seem associated with an increased risk of breast cancer (RR 0.77; 95% CI 0.59, 1.01[41]), and no association with cardiovascular disease seems present based on results from a large, randomised, controlled trial (RR = 0.91; 95% CI 0.75, 1.12).[41] However, an increased risk of deep venous thrombosis/pulmonary embolism is seen with ERT (RR = 1.47; 95% CI 1.04, 2.08[41]), as well as a trend towards an increase for cerebrovascular disease (RR = 1.33; 95% CI 0.99, 1.79[41]). However, one should be aware that unopposed ERT should not be used in women with an intact uterus as it has been associated with an increase in the risk of endometrial cancer (RR = 2.3; 95% CI 2.1, 2.5[46]).

These adverse effects related to cardiovascular events make use of HRT and ERT less attractive because patients with primary hyperparathyroidism have an increased risk of arteriosclerosis.

Conclusions

Long-term use of HRT and ERT cannot be recommended in patients with primary hyperparathyroidism.

5.1.3 Other Estrogen-Like Substances

Only a few studies have been performed (table I) with other estrogen-like substances in postmenopausal women. None of the studies had a control group and no data on hard endpoints are available. The mean decrease in serum calcium level was 0.21 mmol/L. The drugs acted by decreasing bone turnover and, thus, reducing urine calcium excretion and serum calcium levels. The concerns are the same as for the other estrogens. In particular, because of the low level of evidence, these compounds cannot be recommended for the treatment of primary hyperparathyroidism at present.

5.1.4 Progestogens

Only a few studies with progestogens have been performed (table II). They have demonstrated a

Table II. Effects of progestogens, selective estrogen receptor modulators (SERM), and calcitonin on serum calcium levels, bone turnover markers, bone mineral density (BMD) and hard endpoints in primary hyperparathyroidism (mean ± SEM)

Regimen	Patient characteristics	Baseline albumin-adjusted calcium (mmol/L)	Study duration	Decrease in serum calcium (mmol/L)	PTH changes	Change in urine calcium excretion	Change in turnover markers	Change in BMD	Effect on hard endpoints	Ref.
Progestogens										
Norethindrone 5 mg/day	11 PM women, all treated	2.93 ± 0.08	3wk	0.09 ± 0.11*	From 886 ± 174 to 1014 ± 220 pg/mL, NS	Fasting urine calcium/creatinine from 0.58 ± 0.10 to 0.32 ± 0.08*	↓ urine hydroxyproline*	NA	NA	25
Norethindrone 5 mg/day	20 PM women, all treated	2.65 ± 0.03	3mo	0.10 ± 0.04*	NA	Fasting 2h urine calcium/creatinine from 0.38 ± 0.04 to 0.16 ± 0.03*	↓ urine hydroxyproline*	↑ forearm BMD*	NA	47
SERM										
Raloxifene 60–120 mg/day	3 PM women, all treated	2.76 ± 0.05	12mo	0.18 ± 0.07	From 65.3 ± 4.4 to 68.7 ± 11.0 IU/L	Fasting urine calcium/creatinine from 0.18 ± 0.04 to 0.08 ± 0.02*	↓ ALP (NS), ↓ urine desoxypyridinoline*	↑ lumbar spine (3.4%), ↑ hip (2.5%)	NA	48
Raloxifene 60 mg/day	18 PM women, RCT	Raloxifene: 2.69 ± 0.05 Placebo: 2.65 ± 0.03	8wk	Raloxifene: 0.10 ± 0.07* Placebo: 0.06 ± 0.06	Raloxifene from 25.9 ± 6.1 to 29.8 ± 7.6 pmol/L, NS Placebo from 20.7 ± 4.4 to 22.0 ± 4.4 pmol/L, NS	Urine 24h calcium/creatinine Raloxifene from 0.24 ± 0.04 to 0.24 ± 0.04, NS Placebo from 0.24 ± 0.05 to 0.23 ± 0.05, NS	↔ ALP, ↓ BGP, ↓ serum NTX	NA	NA	49
Calcitonin										
Calcitonin 100IU IM as a bolus or 100IU IV as continuous infusion	10 patients	Bolus: 3.04 ± 0.03 Infusion: 3.12 ± 0.03	5d	Bolus: 0.02 ± 0.02, NS Infusion: 0.07 ± 0.02*	Bolus: increased 15.0 ± 6.9 ng/L* Infusion: increased 42.2 ± 5.8 ng/L*	Fasting urine calcium/creatinine: Bolus: decreased 0.12 ± 0.04* Infusion: decreased 0.11 ± 0.04*	↓ urine hydroxyproline, NS	NA	NA	50

ALP = alkaline phosphatase; **BGP** = bone Gla protein (osteocalcin); **IM** = intramuscular; **IV** = intravenous; **NA** = not available; **NS** = not statistically significantly different; **NTX** = N-terminal cross links of collagen; **PM** = postmenopausal; **PTH** = parathyroid hormone; **RCT** = randomised controlled trial; ↓ indicates decrease; ↑ indicates increase; ↔ indicates unchanged; * $2p < 0.05$ for change over time.

modest decrease in serum calcium of around 0.10 mmol/L. The mechanism of action is similar to that of the estrogens, with a decrease in bone turnover and concomitant decrease in urine calcium excretion and serum calcium levels. Given the low level of evidence for these drugs and the potential adverse effects of progestogens discussed in the sections on estrogens (5.1.1–3), progestogens cannot be recommended for the treatment of primary hyperparathyroidism.

5.1.5 SERMs: Raloxifene

Effects

Table II presents the two trials that have been performed using raloxifene in patients with primary hyperparathyroidism.[48,49] In the first trial, the decrease in serum calcium levels seemed to be maintained at both 6 and 12 months after treatment start.[48] However, this trial was very small.[48] Indeed, both studies were small, and the results on changes in urine calcium excretion and bone turnover markers were inconsistent. However, in general one should expect that the decrease in serum calcium was mediated through a decrease in bone turnover with a decrease in urine calcium excretion. PTH levels remained constant. The first small trial reported an increase in BMD of the spine and femoral neck.[48]

Effects in Patients without Primary Hyperparathyroidism

From a large randomised controlled trial in patients with osteoporosis (not primary hyperparathyroidism) there is evidence that raloxifene prevents vertebral fractures,[51,52] but not non-vertebral fractures,[51,52] hip[52] or forearm fractures.[52]

Adverse Effects

In contrast to HRT, in postmenopausal women, raloxifene reduces the risk of invasive breast cancer and estrogen receptor-positive invasive breast cancer over 8 years by 66% (HR 0.34; 95% CI 0.22, 0.50) and 76% (HR 0.24; 95% CI 0.15, 0.40), respectively.[53] This is the effect of the estrogen-receptor antagonistic effects of raloxifene. Raloxifene does not influence the risk of cardiovascular events (RR = 0.86; 95% CI 0.64, 1.15 for 60 mg/day; and RR = 0.98; 95% CI 0.74, 1.30 for 120 mg/day).[54] Raloxifene, like ERT and HRT, increases the risk of deep venous thromboembolism/pulmonary embolism (RR = 3.1; 95% CI 1.5, 6.2[51]). Raloxifene increases the risk of hot flushes as a result of the antagonistic effect on the estrogen receptor (RR = 2.4; 95% CI 1.9, 3.0). The risk of leg cramps is also increased with raloxifene (RR = 1.3; 95% CI 1.1, 1.6). As raloxifene, in contrast to HRT, is not associated with cardiovascular events and increased breast cancer risk, raloxifene may provide a better alternative than estrogens for the medical management of primary hyperparathyroidism.

Conclusions

Raloxifene may be an alternative to estrogen-containing compounds to lower serum calcium levels and prevent osteoporosis in postmenopausal women. However, more evidence is needed before raloxifene is entered into routine treatment practice for primary hyperparathyroidism.

5.2 Calcitonin

5.2.1 Effects

Calcitonin has been studied in two trials in patients with primary hyperparathyroidism. The first study compared the effects of either intramuscular calcitonin 100IU or intranasal calcitonin 110, 200 or 400IU.[55] This study demonstrated a decrease in 24-hour area under the plasma concentration-time curve (AUC_{24}) for serum calcium that was significant for 100IU intramuscularly, but not for the intranasal doses. The second study[50] (table II) showed a decrease in serum calcium levels after 5 days. Initially, on day 2–3, the decrease was larger but this tended to decrease with time, i.e. the response was not sustained.[50] The fact that it was not

possible to sustain the decline in serum calcium levels with calcitonin limits the use of calcitonin to an acute decrease in serum calcium levels in patients with hypercalcaemic crisis.

5.2.2 Effects in Patients without Primary Hyperparathyroidism

From studies in patients with osteoporosis, calcitonin has been shown in a meta-analysis to decrease the risk of vertebral fractures (RR = 0.46; 95% CI 0.25, 0.87; $p < 0.01$), but not the risk of non-vertebral fractures (RR = 0.52; 95% CI 0.22, 1.23; $p = 0.14$).[56] However, the meta-analysis revealed signs of publication bias, as the largest trial did not show consistent reductions in the risk of vertebral fractures.[57]

5.2.3 Adverse Effects

With nasal application of calcitonin, the adverse effect is local irritation. With systemic administration, dyspepsia and flushing may be seen.[50,55]

5.2.4 Conclusions

Studies with calcitonin have only shown a temporary decrease in serum calcium levels, and the evidence for an effect on hard endpoints is limited. Thus, the use of calcitonin should be limited to emergency use in hypercalcaemic crisis.

5.3 Bisphosphonates

Table III and table IV contain details of studies with bisphosphonates in patients with primary hyperparathyroidism. Most studies on the medical management of primary hyperparathyroidism have been carried out using bisphosphonates and the general quality of studies is higher that with other agents, especially for alendronate (table III). The studies of alendronate were randomised placebo-controlled trials and not just simple before-and-after studies. Trials have included both sustained oral use of bisphosphonates and intermittent intravenous infusions.

5.3.1 Alendronate

Alendronate seems to be the most widely studied bisphosphonate (table III). The decrease in serum calcium was on average 0.11 mmol/L. Several studies reported a trend towards an increase in serum PTH levels.[58,59,61,62] There was a non-significant trend towards the decrease in serum calcium levels being smaller with increasing study duration and thus treatment duration (Spearman's correlation coefficient: $r = 0.67$, $2p = 0.14$).

The effect of alendronate was mediated through a decrease in bone turnover and, thus, in urine calcium excretion (table III).

The available studies reported an increase in spine and hip BMD, and an unchanged to increasing forearm BMD. In addition, a trend towards an increase in total body BMD was seen (table III). Upon termination of alendronate, serum calcium levels increased and BMD decreased.[60]

Effects in Patients without Primary Hyperparathyroidism

From studies in patients with osteoporosis in general, alendronate has been shown at a meta-analysis level and in large RCTs to be effective in preventing vertebral (RR = 0.52; 95% CI 0.43, 0.65),[70] non-vertebral (RR = 0.51; 95% CI 0.38, 0.69),[70] hip (RR = 0.49; 95% CI 0.23, 0.99),[71] and forearm (RR = 0.52; 95% CI 0.31, 0.87) fractures.[71]

5.3.2 Clodronate

Table IV lists several studies on clodronate in patients with primary hyperparathyroidism. The mean decrease in serum calcium level was 0.19 mmol/L. In addition to the studies mentioned in table IV, two small studies have been performed. In the first study conducted in four patients with hyperparathyroidism, there was a decrease in serum calcium levels in three of four patients with the use of oral clodronate 0.8–3.2 g/day (three of the patients subsequently underwent parathyroidectomy).[72] In the second study,[73] four patients received intravenous clodronate 500mg for 6 days and

Table III. Effects of alendronate on serum calcium levels, bone turnover markers, bone mineral density (BMD) and hard endpoints in primary hyperparathyroidism (mean ± SEM)

Regimen	Patient characteristics	Baseline albumin-adjusted calcium (mmol/L)	Study duration	Decrease in serum calcium (mmol/L)	PTH changes	Change in urine calcium excretion	Change in turnover markers	Change in BMD	Effect on hard endpoints	Ref.
10 mg/day PO	26 elderly patients, 13 alendronate, 13 placebo	Alendronate: 2.75 ± 0.10 Placebo: 2.73 ± 0.08	2y	Alendronate: increased 0.02 Placebo: increased 0.01	Alendronate: PTH increased 13 ± 8%, NS Placebo: PTH increased 5.4 ± 4.7%, NS	Fasting urine calcium creatinine unchanged	↓ ALP, ↓ BGP, ↓ urine desoxypyridinoline	↑ lumbar spine, ↑ hip, ↑ total body	NA	58
10 mg/day PO for 1y	44 patients, 22 alendronate, 22 placebo, RCT	Alendronate: 2.68 ± 0.03 Placebo: 2.64 ± 0.03	1y	Alendronate: 0.04 ± 0.04, NS Placebo: increased 0.02 ± 0.04, NS	Alendronate: 17.2 ± 3.8 to 21.1 ± 6.0, NS Placebo: 15.6 ± 1.2 to 15.1 ± 2.4, NS	24h urine calcium from 4.97 ± 0.7 to 3.6 ± 0.9 mmol/day in the alendronate group*	↓ ALP, ↓ urine NTX	↑ lumbar spine (4.7%)*, ↑ hip (3.2%)*, ↑ forearm (1.6%)*	No serious adverse events	59
10 mg/day PO for 48wk	40 patients, 20 alendronate, 20 placebo, RCT	Alendronate: 2.82 ± 0.18 Placebo: 2.81 ± 0.16	48wk	Alendronate: 0.09 Placebo: increased 0.01, significant difference between alendronate and placebo	PTH unchanged in both groups	24h urine calcium unchanged at 4.91 for alendronate and 4.73 with placebo	↓ ALP, ↓ BGP, ↓ urine NTX	↑ lumbar spine (3.6%)*, ↑ hip (4.4%)*, ↔ forearm (0.9%)	NA	60
10 mg/day PO for 24mo	32 patients with T-score <–1 and non-vertebral fracture or T-score <–2.5 (n = 14) were treated, the rest (n = 18) were untreated	Treated: 2.84 ± 0.03 Untreated: 2.82 ± 0.04	24mo	Alendronate: 0.15 ± 0.03* Untreated: increased 0.07 ± 0.04[a]	After 6wk PTH increased from 104 ± 15 to 117 ± 16 ng/L, after 3mo PTH reverted to initial values and remained stable	No significant changes in 24h urine calcium	↓ ALP, ↓ BGP, ↓ urine hydroxyproline	Alendronate: ↑ lumbar spine (7.3%)*, ↑ hip (2.6%, NS), ↔ radius (0.7%, NS), Untreated:↑ lumbar spine (4%)*, ↔ hip, ↓ radius (–1.5%, NS)	4 of 14 on alendronate developed dyspepsia vs 1 of 18 untreated	61

Continued next page

Table III. Contd

Regimen	Patient characteristics	Baseline albumin-adjusted calcium (mmol/L)	Study duration	Decrease in serum calcium (mmol/L)	PTH changes	Change in urine calcium excretion	Change in turnover markers	Change in BMD	Effect on hard endpoints	Ref.
2.5mg IV daily for 5d	12 patients	2.90 ± 0.06	5d	0.30 ± 0.08	PTH from 17.5 ± 6.38 to 22.8 ± 8.8*	Spot urine calcium/ creatinine from 0.27 ± 0.11 to 0.20 ± 0.08, NS	↔ ALP, ↓ urine hydroxyproline	NA	NA	62
5mg IV once	6 patients	2.80	56d	1wk: 0.17 ± 0.05* 4wk: 0.01 ± 0.04	No change in PTH, initial level 122 pg/mL (range 90–225)	NA	↓ ALP, ↓ urine hydroxyproline (initial decrease, increased after 4wk)	NA	NA	63

a Figures unreliable because of dropouts according to authors.

ALP = alkaline phosphatase; **BGP** = bone Gla protein (osteocalcin); **IV** = intravenous; **NA** = not available; **NS** = not statistically significantly different; **NTX** = N-terminal cross links of collagen; **PO** = oral; **PTH** = parathyroid hormone; **RCT** = randomised controlled trial; ↓ indicates decrease; ↑ indicates increase; ↔ indicates unchanged; * 2p < 0.05 for change over time.

the typical course was a decline in serum calcium levels. The studies in table IV were small, but showed a decrease in serum calcium levels mediated through a decrease in bone turnover that also led to a decrease in urinary calcium excretion. None of the studies had hard endpoints or reported BMD results. PTH levels increased non-significantly in two trials and remained stable in one trial (table IV).

Effects in Patients without Primary Hyperparathyroidism

In patients without primary hyperparathyroidism only one randomised controlled trial has reported a decrease in vertebral fractures with the use of clodronate.[74] The study failed to show a reduction in non-vertebral fractures, but the study size was a limiting factor.[74]

5.3.3 Other Bisphosphonates

Only one study was available for each of the bisphosphonates etidronate, risedronate and pamidronate in patients with primary hyperparathyroidism. In the study that included pamidronate, results were combined for pamidronate and clodronate recipients and it is no possible to differentiate the effects of the individual drugs.[68]

In addition to the studies mentioned in table IV, one case report reported a decrease in serum calcium and alkaline phosphatase levels, and an increase in serum phosphate levels with etidronate 400 mg/day in varying periods of ≈6 months over >3 years in a 75-year-old woman with skeletal pain due to primary hyperparathyroidism.[75] The patient reported diminishing skeletal pain after etidronate treatment.[75] One small study in seven patients of whom five had primary hyperparathyroidism showed a decrease in serum calcium levels with etidronate 20 mg/kg for 6 months (one patient only 5 weeks).[76] In a group of elderly patients with primary hyperparathyroidism, surgery was more effective in lowering serum calcium levels and increasing BMD than etidronate.[64]

Table IV. Effects of other bisphosphonates (etidronate, clodronate, risedronate, pamidronate) on serum calcium levels, bone turnover markers, bone mineral density (BMD) and hard endpoints in primary hyperparathyroidism (mean ± SEM)

Regimen	Patient characteristics	Baseline albumin-adjusted calcium (mmol/L)	Study duration	Decrease in serum calcium (mmol/L)	PTH changes	Change in urine calcium excretion	Change in turnover markers	Change in BMD	Effect on hard endpoints	Ref.
Etidronate 200mg for 14d, 10wk pause	22 patients, 9 etidronate, 13 surgery, RCT	Etidronate: 2.70 ± 0.04 Surgery: 2.75 ± 0.05	1y	Etidronate: 0.10 ± 0.05 Surgery: 0.40 ± 0.05	Etidronate: 90.5 ± 15.9 to 113.6 ± 18.7 Surgery: 97.6 ± 12.1 to 19.1 ± 5.0*	Morning urine calcium/creatinine Etidronate from 0.38 ± 0.05 to 0.34 ± 0.05 Surgery from 0.25 ± 0.06 to 0.25 ± 0.07	↓ urine desoxypyridinolone*	Etidronate: ↑ lumbar spine (10%), ↑ total body (8%%) Surgery: ↑ lumbar spine (20%), NS, ↑ total body (3%), NS	NA	64
Clodronate 0.8–1.6g PO daily for 2–3mo	12 patients, all treated	3.01 ± 0.07	12wk	0.17 ± 0.09*	From 303 ± 177 to 357 ± 277 pmol/L, NS	Morning 2h urine calcium/creatinine from 0.49 ± 0.06 to 0.34 ± 0.06*	↓ urine hydroxyproline*	NA	NA	65
Clodronate 1600 mg/day	14 patients, RCT	2.88 ± 0.03	12wk	0.18 ± 0.06*	From 106 ± 13 to 123 ± 15μL Eq/mL, NS	Urine 24h calcium/ creatinine from 185 ± 29 to 113 ± 23 mg/g creatinine	↓ urine hydroxyproline*	NA	NA	66
Clodronate 1.0–3.2 g/day	9 patients	2.88 ± 0.09	6wk	0.25 ± 0.10*	From 1.28 ± 0.48 to 1.13 ± 0.42, NS	Morning 2h urine calcium/creatinine from 0.058 ± 0.0006 to 0.018 ± 0.002*	↔ ALP, ↓ urine hydroxyproline	NA	NA	67
Pamidronate 60–90mg IV once (n = 23), clodronate 600mg IV once (n = 2)	25 patients, all treated	2.73 ± 0.03	Median 15d	0.24 ± 0.04	From 13.9 ± 2.8 to 27.1 ± 10.1*	NA	NA	NA	NA	68
Risedronate 20–40 mg/day for 2 × 1wk during 65d	19 patients, all treated	2.76 ± 0.04	65d	0.16 ± 0.06*	PTH increased from 165 ± 25 to 200 ± 25*	↓ Fasting 2h urine calcium/creatinine	↓ ALP	NA	NA	69

ALP = alkaline phosphatase; **IV** = intravenous; **NA** = not available; **NS** = not statistically significantly different; **PO** = oral; **PTH** = parathyroid hormone; **RCT** = randomised controlled trial; ↓ indicates decrease; ↑ indicates increase; ↔ indicates unchanged; * 2p < 0.05 for change over time.

Effects in Patients without Primary Hyperparathyroidism

In patients without primary hyperparathyroidism, a meta-analysis on etidronate for the treatment and prevention of osteoporosis showed a reduction in vertebral fractures (RR = 0.63; 95% CI 0.44, 0.92; $p < 0.01$), while no reduction in non-vertebral fracture risk (RR = 0.99; 95% CI 0.69, 1.42; $p < 0.01$) could be demonstrated.[77] Among patients without primary hyperparathyroidism, there is also evidence from meta-analyses in patients with osteoporosis that alendronate and risedronate are effective in preventing vertebral (RR = 0.64; 95% CI 0.54, 0.77; $p < 0.01$),[77,78] non-vertebral (RR = 0.73; 95% CI 0.61, 0.87; $p < 0.01$),[77,78] and hip fractures (RR = 0.62; 95% CI 0.50, 0.79; $p < 0.01$).[79] There are only small RCTs for pamidronate, which show a reduction in the risk of vertebral fractures, while no reduction could be demonstrated for non-vertebral fractures.[80,81]

5.3.4 Adverse Effects of Bisphosphonates

The adverse effects associated with bisphosphonate use are gastrointestinal discomfort with pain, diarrhoea and nausea. Observational evidence suggests that oral alendronate is associated with oesophageal erosions and ulcerative oesophagitis.[82] This may be of concern in patients with primary hyperparathyroidism, who may present with an increased risk of gastric and duodenal ulcers. One systematic review[70] found that there was no significant difference between alendronate ≥5mg and placebo in the proportion of women with osteoporosis discontinuing alendronate because of any adverse effect or because of gastrointestinal effects (nine RCTs, discontinuing alendronate because of adverse effects: RR 1.15; 95% CI 0.93, 1.42; seven RCTs, discontinuing alendronate because of gastrointestinal adverse effects: RR 1.03; 95% CI 0.80, 1.30; $p = 0.83$). There was no significant difference between alendronate and placebo in the proportion of gastrointestinal adverse effects in those who continued treatment (ten RCTs; RR 1.03; 95% CI 0.98, 1.07; $p = 0.23$). In many of the RCTs that were included in the meta-analysis, women with a history of peptic ulcer disease or oesophageal disease were excluded. This would have removed the population most likely to develop gastrointestinal adverse effects.

Bisphosphonates administered intravenously may be associated with flu-like symptoms.[79]

5.3.5 Conclusions

Bisphosphonates seem able to decrease serum calcium levels, and increase spine and hip BMD. However, the effect wears off after termination of therapy and a decrease in effect on serum calcium levels may perhaps be seen with time. This potential decreasing effect with time needs further evaluation, as it was not seen in all trials. The trend towards an increase in PTH during bisphosphonate treatment is troubling because it may signal a worsening of the underlying condition. However, this observation also needs further evaluation, as the PTH increase was only temporary in some of the trials. Whether it is possible to prevent the increase in PTH with, for example, vitamin D supplementation remains to be tested, as the increase may perhaps signal insufficiency in vitamin D status (see section 8.3). However, this needs thorough investigation because hypercalcaemia in primary hyperparathyroidism is attenuated by vitamin D deficiency and the addition of vitamin D would risk increasing serum calcium levels.

Bisphosphonates may be used to lower serum calcium levels, and as a particularly interesting feature to increase BMD and thus prevent osteoporosis in patients with primary hyperparathyroidism. The only available randomised controlled comparison with surgery suggested that surgery in elderly subjects was more effective in lowering serum calcium levels and increasing BMD than etidronate.[64]

6. Calcimimetics

Calcimimetics act by stimulating the CaSR[83] and thus decreasing PTH secretion,[2] resulting in a decrease in serum calcium levels in hyperparathyroidism (primary[84,85] and secondary hyperparathyroidism,[86-88] and in patients with parathyroid cancer[89]).[90,91] These drugs represent a very interesting new concept in the treatment of primary hyperparathyroidism, as they directly interact with the cause of the disease (the increased PTH secretion despite elevated serum calcium levels).[2] The only currently marketed compound is cinacalcet (table V).

6.1 Cinacalcet

6.1.1 Effects

Cinacalcet is a phenylalkylamine compound that acts as a positive allosteric modulator of the CaSR.[2] In primary hyperparathyroidism it has been used in dose of 30–50mg twice a day.[84,85] The initial dose is 30mg twice daily and may be increased to 50mg twice daily over an interval of 2–4 weeks. Serum calcium levels decreased rapidly after the second dose to normal levels[85] and the decrease was maintained for up to 1 year,[84] which is the longest treatment duration reported. After discontinuation, serum calcium levels increased to pretreatment levels.[85] In contrast to the studies with antiresorptive drugs, serum calcium levels were only marginally elevated in the available studies.[84,85] PTH levels decreased to a nadir 4 hours after cinacalcet administration and returned to pretreatment levels after 12 hours.[85] The urine calcium/creatinine ratio decreased,[85] but bone turnover markers increased. The reason for this increase in bone turnover remains unclear. BMD remained unchanged after 1 year of cinacalcet therapy.[84] The reason for the unchanged BMD in contrast to the trials with alendronate may be the increased bone turnover, but it remains to be further studied whether BMD is unaf-

Table V. Effects of calcimimetics serum calcium, bone turnover markers, bone mineral density (BMD) and hard endpoints in primary hyperparathyroidism (mean ± SEM)

Drug	Patient characteristics	Baseline albumin-adjusted calcium (mmol/L)	Study duration	Decrease in serum calcium (mmol/L)	PTH changes	Change in urine calcium excretion	Change in turnover markers	Change in BMD	Effect on hard endpoints	Ref.
Cinacalcet 30–50mg bid	78 patients, RCT	Cinacalcet: 2.68 ± 0.13 Placebo: 2.68 ± 0.10	52wk	Cinacalcet: 0.25 ± 0.18* Placebo: increased 0.05 ± 0.21	Cinacalcet: 105 ± 36 to 91 ± 34 pg/mL, NS Placebo: 120 ± 54 to 112 ± 49 pg/mL, NS	Fasting urine calcium : creatinine: Cinacalcet: 0.26 ± 0.14 to 0.16 ± 0.07* Placebo: 0.22 ± 0.10 to 0.25 ± 0.12, NS	↑ ALP, ↑ urine and serum NTX	Lumbar spine, femur and radius unchanged	Overall similar adverse effects, nausea (28% vs 16%) more frequent with cinacalcet. Headache (23% vs 41%) less frequent with cinacalcet	84
Cinacalcet 30–50mg bid	22 patients, RCT	Cinacalcet: 2.65 ± 0.21 Placebo: 2.60 ± 0.15	15d	Cinacalcet: 0.42 ± 0.28 Placebo: no change	↓ PTH with cinacalcet, unchanged with placebo	↓ urine 24h calcium : creatinine	NA	NA	No difference in overall adverse effects	85

ALP = alkaline phosphatase; **bid** = twice daily; **NA** = not available; **NS** = not statistically significantly different; **NTX** = N-terminal cross links of collagen; **PTH** = parathyroid hormone; **RCT** = randomised controlled trial; ↓ indicates decrease; ↑ indicates increase; * 2p < 0.05 for change over time.

fected by cinacalcet over longer time periods. In the actual study, BMD of the spine was within the normal range at study start and this may explain why no increase was seen.[84] However, hip and forearm BMD were in the osteopaenic range,[84] and it remains unexplained why these were not affected by cinacalcet, given that cinacalcet indeed does possess effects on BMD besides its effects on serum calcium levels.

6.1.2 Adverse Effects

Nausea was more frequent with cinacalcet than with placebo in patients with primary hyperparathyroidism.[84] In general, controlled clinical trials have reported nausea and vomiting in >10% of patients, and in 1–10% of patients asthenia, anorexia, hypocalcaemia, low testosterone levels, myalgias, dizziness, paraesthesias and rashes have been reported. In rare instances, convulsions have been reported (<1%). However, these observations stem from trials in patients with secondary hyperparathyroidism due to kidney failure.[86-88,92]

6.1.3 Conclusions

Cinacalcet represents an interesting new drug for lowering serum calcium levels in patients with primary hyperparathyroidism. However, no data at present support an effect on BMD or other hard endpoints.

One of the interesting applications of cinacalcet and other calcimimetics is the possibility to reversibly test whether lowering serum calcium levels would improve the patient's symptoms (equivalent to a medical 'parathyroidectomy'). This could be used to advocate surgery in patients with atypical or mild symptoms, who improve during treatment with cinacalcet. However, this needs further investigation, as a 'placebo effect' of drug treatment needs to be assessed. One way of testing this could be to randomise patients to cinacalcet or not, and subsequently randomise to parathyroidectomy or not, to test whether patients responding to drug also responded to surgery, and whether the adverse effects of the surgery would justify such a procedure.

7. General Considerations

Figure 1 shows the correlation between treatment duration (study duration) and change in serum calcium levels using data from all of the studies featured in tables I–V. There was a trend towards a smaller decrease with increasing treatment duration (2p = 0.08). This may be the result of the trend towards an increase in PTH levels seen in some trials with antiresorptive drugs. This observation needs further investigation. With cinacalcet, serum calcium levels seemed to remain stable after the initial decrease, and no rebound effect was seen. An increase in BMD was seen with bisphosphonates but not with cinacalcet. No reports on other hard endpoints other than BMD (e.g. cardiovascular events such as MI, fractures etc.) are available. However, these may be difficult to address, as even surgical treatment has not shown a convincing reduction in cardiovascular endpoints and occurrence of kidney stones.[19] On the other hand, drug treatment may perhaps be better than surgery in modifying certain risk factors and organ damage induced by the high calcium levels.

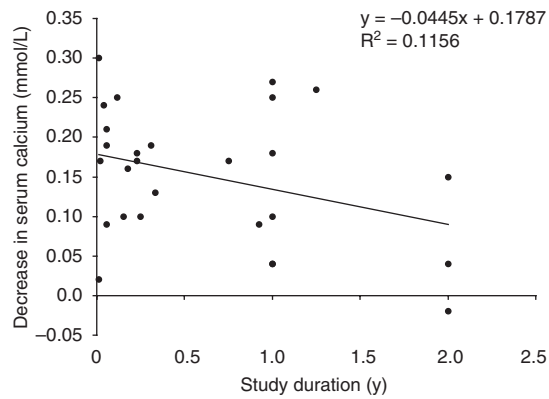

Fig. 1. Correlation between study duration and decrease in serum calcium levels. There was a borderline significant trend towards a smaller decrease in serum calcium with increasing study duration (2p = 0.08, Spearman correlation coefficient). The figure is based on the results on changes in serum calcium from all studies in tables I–V. The analysis represents a meta-regression

8. Other Approaches for Treating Primary Hyperparathyroidism

8.1 Regimens for Treating Hypercalcaemia

Drugs and the principles used for treating hypercalcaemia in general may also be applied in hypercalcaemia of primary hyperparathyroidism. These principles include: (i) rehydration and high fluid intake to increase urinary calcium excretion; (ii) loop diuretics in selected non-dehydrated patients to increase urine calcium output (avoid thiazide diuretics as these increase calcium reabsorption and thus may induce hypercalcaemia); (iii) calcitonin infusions in severe hypercalcaemia, especially if kidney function is impaired; and (iv) intravenous bisphosphonates.

The treatment of severe hypercalcaemia should be based on the presence of symptoms and findings linked to hypercalcaemia such as dehydration and dysequilibrium hypercalcaemia (rapidly increasing serum calcium levels). Usually patients with primary hyperparathyroidism present with equilibrium hypercalcaemia, i.e. serum calcium level is stable over time. Patients with primary hyperparathyroidism may be asymptomatic despite significantly elevated serum calcium levels. Acute treatment of hypercalcaemia must thus be based on symptoms and findings and not just on serum calcium levels. Many studies have been performed in intensive care settings.

In dehydrated patients, fluid intake is vital to correct dehydration. If administered intravenously, saline solution is the fluid of choice as it both corrects the dehydration and increases urinary calcium excretion. Usually around 3 L/day of oral or intravenous fluids is recommended, although this evidence stems from studies in hypercalcaemia of malignancy.[93] If the patient is overhydrated or has heart failure, care should be taken not to overload the patient with fluid.

Use of diuretics should be limited to well hydrated patients and patients who – for example for reasons of cardiac failure – cannot tolerate large amounts of fluid and who are not dehydrated. A dose of frusemide (furosemide) 40 mg/day is recommended,[93] but should be titrated in individual patients. Again the evidence comes from hypercalcaemia of malignancy.

There are many different regimens for treating hypercalcaemia with calcitonin and bisphosphonates.[94] Again the evidence mainly stems from studies of hypercalcaemia of malignancy. In general, calcitonin lowers serum calcium levels within hours,[95] whereas intravenous bisphosphonates take 1–2 days to have a marked effect on serum calcium levels.[96] Thus, calcitonin may have a place where an acute lowering of serum calcium is needed before the effect of a bisphosphonate sets in (usually at albumin-adjusted serum calcium levels >4 mmol/L, or >3.5 mmol/L if kidney function is impaired). One should be aware that rapid infusion of bisphosphonates in severely dehydrated patients[97] may induce kidney failure, and adequate hydration should thus be ensured and infusion rates kept within recommended guidelines. Cinacalcet may also find a place in the acute lowering of calcium levels.

8.2 Drugs for Treating Complications of Hypercalcaemia

If complications of hypercalcaemia are present (e.g. an ulcer of the stomach), specific drugs can be used in the same way as in patients without primary hyperparathyroidism. However, coexistence of ulcers should raise suspicion of multiple endocrine neoplasia type 1, and severe hypertension should raise suspicion of phaeochromocytoma (multiple endocrine neoplasia type 2A). Specific drugs or surgery for the treatment of complications include: (i) proton pump inhibitors, such as omeprazole, or histamine H_2-receptor antagonists, such as cimetidine, for the treatment of stomach or duodenal

ulcers; (ii) antihypertensive treatment in patients with hypertension; (iii) HMG-CoA reductase inhibitor (statin) therapy in patients with arteriosclerosis; (iv) percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) in patients with angina pectoris or MI; (v) β-adrenoceptor antagonists (β-blockers), ACE inhibitors, aspirin (acetylsalicylic acid) etc. in patients after an MI; and (vi) insulin or oral antidiabetics in patients with diabetes mellitus, etc.

As in sections 5.1.5 and 5.3.3, osteoporosis may be treated using raloxifene or bisphosphonates as in patients with idiopathic or corticosteroid-induced osteoporosis. Calcium and vitamin D supplementation may be used with little risk of inducing hypercalcaemia.[98]

8.3 Vitamin D

In patients with primary hyperparathyroidism, serum 25-hydroxy-vitamin D levels may be low.[8] It has been debated whether vitamin D deficiency may be a risk factor for primary hyperparathyroidism because low vitamin D levels may increase PTH levels (secondary hyperparathyroidism), which may turn into autonomous PTH secretion (primary hyperparathyroidism), or whether the increased PTH level may stimulate the 1-α-hydroxylase activity and thus increase 1,25-dihydroxy-vitamin D at the cost of decreased 25-hydroxy vitamin D levels.[8] Vitamin D may be used safely in patients with very low 25-hydroxy-vitamin D levels without inducing hypercalcaemia.[98,99] However, there may be differences in the effects of vitamin D supplementation in patients with marginally decreased and in patients with very low vitamin D levels. In patients with primary hyperparathyroidism and very low vitamin D levels, osteomalacia may be present and serum calcium levels will not increase until the bone is fully mineralised.

BMD has been reported to increase in patients with primary hyperparathyroidism and low serum vitamin D levels upon correction of the vitamin D deficiency, but this may reflect correction of osteomalacia.[98] In patients with marginally decreased serum vitamin D levels, the effects of vitamin D supplementation may be different and perhaps lead to hypercalcaemia as osteomalacia is not present.

Some of the newer vitamin D analogues with low hypercalcaemic potential such as paricalcitol, doxercalciferol, maxacalcitol and falecalcitriol may perhaps also find a place in the treatment and prevention of primary hyperparathyroidism.

8.4 Other Drugs

Other drugs that have been tested for the treatment of primary hyperparathyroidism include phosphorus,[100] but this is now obsolete for lowering serum calcium levels. β-Blockers have been tested and found ineffective in primary hyperparathyroidism with regard to lowering serum calcium levels.[101] Cimetidine has also been tested and found to have little efficacy in lowering serum calcium levels.[102,103]

9. Perspectives and Conclusions

Several pharmacological treatment options exist for primary hyperparathyroidism. Antiresorptive drugs (bisphosphonates and raloxifene) lower serum calcium levels and prevent bone loss; however, PTH levels may increase during bisphosphonate treatment. Cinacalcet lowers serum calcium and PTH levels, but no effect on BMD has been demonstrated. Further research into these treatment modalities and combinations is needed.

Future development of drugs to manage primary hyperparathyroidism may focus on drugs interfering with PTH synthesis or secretion, PTH receptor agonists (or perhaps receptor blockers), and PTH-specific antibodies. Combination therapy with, for example, cinacalcet and a bisphosphonate may also be a possibility. Further studies are needed to evaluate

the best way of managing patients with mild asymptomatic primary hyperparathyroidism.

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