Clinical Guideline

MANAGEMENT OF ACUTE AND CHRONIC HYPOCALCAEMIA SECONDARY TO PARATHYROID INSUFFICIENCY

SETTING	Trustwide
FOR STAFF	Part 1 – Medical staff who identify a possible case
	Part 2 - Specialist medical staff within the Endocrine Team Specialist surgical staff performing thyroid/neck surgery
	Part 3 - Specialist medical staff within the Endocrine Team Specialist surgical staff performing parathyroid surgery
	Part 4 – Specialist medical staff within the Endocrine Team
PATIENTS	Patients with hypocalcaemia and parathyroid insufficiency
	Patients undergoing thyroidectomy, parathyroidectomy or other neck surgery which may result in intentional or unintentional removal/damage of parathyroid glands

BACKGROUND

- Hypocalcaemia varies from asymptomatic to life-threatening.
- Acute hypocalcaemia causes increased neuromuscular irritability. Symptoms include peri-oral and fingertip paresthesia and numbness; positive Chvostek's (twitching of face muscles when tapping over CN VII) and Trousseau's (carpal spasm induced by inflation of BP cuff) signs and muscle cramps. Tetany and seizures are seen in severe hypocalcaemia.
- One of the most common causes of hypocalcaemia is hypoparathyroidism following thyroidectomy. In this group the reported incidence of transient hypocalcaemia ranges from 0.3% to 49% of patients, and that of permanent hypocalcaemia ranges from 0% to 13%.[1]
- Chronic hypocalcaemia is commonly due to inadequate levels of parathyroid hormone or vitamin D, or due to resistance to these hormones.[2]
- Parathyroid (PTH) hormone deficiency impairs conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. In patients with mild hypoparathyroidism it may be possible to achieve acceptable calcium levels by calcium supplementation alone, if given in large doses (1g elemental calcium three times daily). However, the majority of patients with parathyroid insufficiency will instead require treatment with the more potent hydroxylated derivatives of vitamin D; alfacalcidol or calcitriol. An adequate dietary intake of calcium is also required for such treatment to be effective.
- In hypoparathyroidism, normal renal retention of calcium is lost, thus attempting to raise the calcium level well into the normal range will result in unacceptable hypercalciuria with a risk of developing nephrocalcinosis and renal stones. Treatment targets are: a) relieve patient symptoms and b) raise calcium levels to around the lower limit of the reference range, without c) causing hypercalciuria.

Part 1
REFERRAL TO ENDOCRINE TEAM

Medical staff who identify a patient at risk of, or suffering from, post-operative or chronic hypocalcaemia should refer to the Endocrine Team for ongoing management.

Referral details should include

- Hospital Registration Number
- Surname
- Forename
- Date of Birth
- Diagnosis and treatment already received/date of surgery
- Corrected calcium levels, PTH, $PO4^-$, total Vitamin D and creatinine levels

Part 2
ENDOCRINE TEAM AND SURGICAL TEAM PERFORMING THYROID/NECK SURGERY
(see part 3 for additional guidance in intentional parathyroidectomy)

Management of acute hypocalcaemia

- Risk factors for post-operative hypocalcaemia to be considered pre-operatively include planned total thyroidectomy, hyperthyroidism, large goitres, pre-operative low serum total vitamin D (low sunlight, alcoholism etc), planned level 6 neck dissection and extensive cancer.
- Serum calcium concentration and PTH level should be checked immediately post-operatively. The half-life of PTH is short, therefore if the post-operative PTH level is normal on this sample usually patients do not require calcium supplementation. Occasionally a short term drop in calcium may be seen, which usually corrects by the following day and does not require treatment.
- Serum calcium concentration and PTH level should be repeated on the morning following surgery. If the calcium and PTH level are normal, and stable on this sample then monitoring can discontinue. If hypocalcaemia is present, or serum calcium levels are declining, monitoring should continue daily until hypocalcaemia improves and the serum calcium stabilises.[3] A decline in serum calcium concentration in the first 24 hours after surgery is predictive of the need for calcium supplementation.[3]
- Serum calcium should also be checked in the days following surgery if the patient develops symptoms of hypocalcaemia.
- Checking the serum PTH whilst the patient is hypocalcaemic, before commencing treatment, is advisable as it may help to predict those patients who will require long term treatment for hypoparathyroidism and those who will be able to discontinue treatment in the long term.
- Initial treatment for acute hypocalcaemia is shown in the table on page 3.

Corrected calcium level immediately after surgery, or if symptomatic patient	Initial treatment
> 2.4 mmol/L	No treatment, repeat calcium levels following morning and if stable can discontinue monitoring. In case of declining calcium levels continue daily monitoring until levels stabilise.
2.0 – 2.4 mmol/L	*Asymptomatic:* no treatment. Repeat calcium levels following morning and if stable can discontinue monitoring. In case of declining calcium levels consider calcium supplementation, as detailed for symptomatic patients, and continue daily monitoring until levels stabilise. *Symptomatic:* start elemental calcium 500milligrams TDS[3] for 3-4 days. Monitor calcium daily and adjust dose as indicated by response.[3] If hypocalcaemia worsens despite calcium supplementation, or the patient has a low PTH level, also commence alfacalcidol (or calcitriol).[3]
< 2.0 mmol/L	Commence alfacalcidol (or calcitriol) and calcium supplements, as detailed below. Consider commencing alfacalcidol at 1microgram BD in this situation (0.5micrograms BD in the elderly), initially monitoring calcium levels twice daily. 10mls 10% calcium gluconate solution IV may be used for acute calcium correction in symptomatic patients or when calcium levels continue to fall despite oral supplementation administered as above, given over 10 minutes via a large vein* with ECG monitoring.** Follow with an IV infusion 1.7 ml/kg 10% calcium gluconate in 250-1000mls 5% glucose over 4-6 hours* until calcium > 2.0 mmol/L.*** *calcium is irritating, risk of extravasation and tissue necrosis ** note risk of serious arrhymias if patient is on digoxin ***rebound hypocalcaemia can occur on stopping IV infusion

- An oral regime consisting of alfacalcidol (or calcitriol) and oral calcium should be commenced if the patient has had a total clearance of the parathyroid glands, or has a corrected calcium <2.0 mmol/L on day 3 following a partial clearance of the parathyroid glands. High dose calcium supplementation may be required initially, e.g. elemental calcium 1gram TDS.
    - Close monitoring of serum calcium is needed to prevent hypercalcaemia.[3] Rebound hypercalcaemia may occur as alfacalcidol takes a few days to stimulate increased calcium uptake form the gut.
    - The starting dose of alfacalcidol is usually 1 microgram/day (0.5 micrograms/day in the elderly).[2] Dose escalation to 1 microgram BD (0.5 microgram BD in the elderly) usually occurs if the corrected calcium remains < 2.0 mmol/L after 5-7 days. Upward dose titration should then occur every 5-7 days, with monitoring of calcium levels, until a low normal calcium (2.0-2.12 mmol/L) has been achieved.
    - If calcitriol is to be used the starting dose is 0.5 micrograms/day. Calcitriol is more potent than alfacalcidol[2], and close monitoring of serum calcium is essential during dose titration. Special care, and reduced dosing, should be used in the elderly.
    - Oral elemental calcium supplementation 500mg-1g qds should continue until serum calcium has corrected to within the lower end of the normal range.
    - An adequate dietary calcium intake should be maintained.

Withdrawing treatment for hypocalcaemia

- After total thyroidectomy, approximately 30% of patients will need calcium supplementation with or without alfacalcidol.[3] Hypoparathyroidism is often transient. A predictor of recovery is an elevated (or upper normal range) serum PTH concentration at the time of hypocalcaemia.[3] By 3 months after total thyroidectomy less than 10% of patients will still require supplementation.[3] The majority of those on calcium/alfacalcidol or calcitriol supplements can therefore have the treatment withdrawn. Supplements should be slowly and gradually reduced and serum calcium monitored every few months whilst supplements are withdrawn and eucalcaemia is restored.[3] The combined effects of hypocalcaemia and hypothyroidism are poorly tolerated and patients should therefore be euthyroid when dose reduction occurs.[3]
- Patients who become hypocalcaemic on withdrawal of treatment will need to continue treatment long term and should be managed as per the guideline below for management of chronic hypocalcaemia secondary to hypoparathyroidism.

Part 3
ENDOCRINE TEAM AND SURGICAL TEAM PERFORMING PARATHYROID SURGERY

- Close monitoring of serum calcium and PTH levels is required, as for patients in part 2 of this guideline.
- Supplementation with alfacalcidol and elemental calcium is often needed, potentially in high doses initially.
- Symptoms of hypocalcaemia should be treated irrespective of the measured serum calcium level as these patients can become symptomatic, with seizures, due to sudden declines in serum calcium levels though the measured serum calcium may still be within (or above) normal laboratory reference ranges. The rate of decline in serum calcium level should be taken into account in these patients.
- Parathryroidectomy for hyperparathyroidism can be associated with the development of ‘hungry bone syndrome’. This relatively uncommon but serious adverse effect of parathyroidectomy for hyperparathyroidism refers to a rapid, profound and prolonged hypocalcaemia associated with hypophosphataemia and hypomagnesaemia. It is thought to be due to an increased influx of calcium into bone following the sudden removal of the effect of high PTH levels on osteoclastic bone resorption.[4] Vitamin D deficiency is believed to be a risk factor for its development and should be identified pre-operatively, and usually treated [see separate guidance on safe vitamin D replacement in primary hyperparathyroidism, ‘Vitamin D deficiency in adults’].
- In patients with secondary hyperparathyroidism undergoing total parathyroidectomy, alfacalcidol should be administered for four days pre-operatively, with careful monitoring of serum calcium levels, to pre-load prior to surgery.

Part 4
ENDOCRINE TEAM ONLY

Management of chronic hypocalcaemia

- In a patient with hypocalcaemia the presence of a low, or normal PTH concentration implies a failure of PTH secretion [in cases of mild hypocalcaemia with mild hypoparathyroidism a diagnosis of an autoimmune hypoparathyroidism (autoimmune polyendocrine syndrome type 1 – due to mutations or deletions in *AIRE* gene) and familial hypocalcaemic hypercalciuria should be considered].

- The goals of treatment in chronic hypoparathyroidism are as follows[2 & 5]
    - to control the patient's symptoms (if present)
    - to maintain the serum calcium in the low normal range (2.0-2.12 mmol/L)
    - to maintain the serum phosphate and serum magnesium in the normal range
    - to reduce the risk of hypercalciuria, renal stones & nephrocalcinosis
    - to monitor & reduce risk of CKD (chronic kidney disease)

- Hypomagnesaemia can result in a failure of PTH secretion and should be corrected if present.
- Commence alfacalcidol at a dose of 1mcg/day (or 0.5mcg/day in the elderly).
- Titrate the dose, guided by serum calcium monitoring, every 4 to 7 days until a low normal serum calcium (2.0-2.12 mmol/L) is achieved.[2]
- If calcitriol is to be used, the starting dose is 0.5mcg/day.[2] Calcitriol is more potent than alfacalcidol[2], making close monitoring of serum calcium essential during dose titration. Special care, and reduced dosing, should be used in the elderly.
- It is also routinely recommended that patients with permanent hypoparathyroidism are co-prescribed cholecalciferol Vitamin D maintenance (e.g. 400-800 IU/day) in addition to their activated Vitamin D analogues (target total Vitamin D >50nmol/l).[6]
- Serum calcium, phosphate and creatinine should be checked every week to month during initial dose titration.[2]
- Once the treatment dose is stable, calcium, phosphate, magnesium and creatinine should be monitored regularly (e.g. 3-6 monthly).[2,6]
- An adequate dietary intake of calcium should be maintained. Elemental calcium supplements may be required if dietary calcium intake is insufficient.
- If hypoparathyroidism is permanent the lowest dose of supplements should be used to maintain the serum calcium at the lower end of the normal range, while aiming to avoid hypercalciuria. In stable cases annual measurement of calcium, phosphate, magnesium and creatinine is recommended.[3]
- 24hr urinary calcium should be measured at intervals (e.g. 2 yearly) and should be within the reference range.[5] If hypercalciuria is present, then reducing calcium and sodium intake in the diet and/or a thiazide diuretic may be considered.[6]
- If there is a drop in eGFR then medications should be reviewed along with a renal ultrasound to exclude renal calculi.

REFERENCES

1. Randolph GW. Surgery of the thyroid and parathyroid glands. Philadelphia: Saunders; 2003.
2. Fong and Khan. Hypocalcaemia. *Can. Fam. Physician* 2012; 58:158-62.
3. British Thyroid Association, Royal College of Physicians. *Guidelines for the management of thyroid cancer* (Perros P, ed) 2nd edition. Report of the Thyroid Cancer Guidelines Update Group. London: Royal College of Physicians, 2007.
4. Witteveen JE, van Thiel S *et al*, Hungry bone syndrome: still a challenge in the post-operative management of primary hyperparathyroidism: a systematic review of the literature. *Eur J Endocrinol.* 2013;168(3):R45-53.
5. Gosmanova S.et al. Renal complications in patients with chronic hypoparathyroidism on conventional therapy: A systematic literature review. Reviews in endocrine/metabolic disorders 2021;22:297-316
6. Bollerslev S. *et al.* European Society of Endocrinology Clinical Practice Guidleine: Treatment of chronic hypoparathyroidism in adults. *Eur J Endocrinol.* 2015;173(2):G1-G20.

QUERIES

Endocrine Specialist Registrar (referrals)	bleep [redacted]
Endocrine Consultants	via switchboard

[redacted]

USER GROUPS CONSULTED

Surgical Head and Neck team (UHBW: [redacted] and NBT: [redacted])