NICE National Institute for Health and Care Excellence

NICE guideline

Hyperparathyroidism (primary): diagnosis, assessment and initial management

NICE guideline
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Your responsibility

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

Overview

This guideline covers diagnosing, assessing and managing primary hyperparathyroidism. It aims to improve recognition and treatment of this condition, reducing long-term complications and improving quality of life.

Who is it for?

- Healthcare professionals
- People with suspected or confirmed primary hyperparathyroidism, their families and carers

Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in NICE's information on making decisions about your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity) and safeguarding.

1.1 Diagnostic testing in primary care

Measuring albumin-adjusted serum calcium

1.1.1 Measure albumin-adjusted serum calcium for people with any of the following features, which might indicate primary hyperparathyroidism:

- symptoms of hypercalcaemia, such as thirst, frequent or excessive urination, or constipation
- osteoporosis or a previous fragility fracture (for recommendations on assessing the risk of fragility fracture in people with osteoporosis, see the NICE guideline on osteoporosis)
- a renal stone (for recommendations on assessing and managing renal stones, see the NICE guideline on renal and ureteric stones)
- an incidental finding of elevated albumin-adjusted serum calcium (2.6 mmol/litre or above).

1.1.2 Consider measuring albumin-adjusted serum calcium for people with chronic non-differentiated symptoms.

1.1.3 Do not measure ionised calcium when testing for primary hyperparathyroidism.

1.1.4 Repeat the albumin-adjusted serum calcium measurement at least once if the first measurement is either:

- 2.6 mmol/litre or above **or**
- 2.5 mmol/litre or above and features of primary hyperparathyroidism are present.

  Base the decision to carry out further repeat measurements on the level of albumin-adjusted serum calcium and the person's symptoms.

Measuring parathyroid hormone

1.1.5 Measure parathyroid hormone (PTH) for people whose albumin-adjusted serum calcium level is either:

- 2.6 mmol/litre or above on at least 2 separate occasions **or**
- 2.5 mmol/litre or above on at least 2 separate occasions and primary hyperparathyroidism is suspected.

1.1.6 When measuring PTH, use a random sample and do a concurrent measurement of the albumin-adjusted serum calcium level.

1.1.7 Do not routinely repeat PTH measurement in primary care.

1.1.8 Seek advice from a specialist with expertise in primary hyperparathyroidism if the person's PTH measurement is either:

- above the midpoint of the reference range and primary hyperparathyroidism is suspected **or**
- below the midpoint of the reference range with a concurrent albumin-adjusted serum calcium level of 2.6 mmol/litre or above.

1.1.9 Do not offer further investigations for primary hyperparathyroidism if:

- the person's PTH is within the reference range but below the midpoint of the reference range **and**
- their concurrent albumin-adjusted serum calcium level is below 2.6 mmol/litre.

1.1.10 Look for alternative diagnoses, including malignancy, if the person's PTH is below the lower limit of the reference range.

For a short explanation of why the committee made the recommendations and how they might affect practice, see the rationale and impact section on diagnostic testing in primary care.

Full details of the evidence and the committee's discussion are in evidence review A: indications for diagnostic testing and evidence review B: diagnostic tests.

1.2 Testing and assessment in secondary care

Measuring vitamin D

1.2.1 For people with a probable diagnosis of primary hyperparathyroidism, measure vitamin D and offer vitamin D supplements if needed.

Excluding familial hypocalciuric hypercalcaemia

1.2.2 To differentiate primary hyperparathyroidism from familial hypocalciuric hypercalcaemia, measure urine calcium excretion using any one of the following tests:

- 24-hour urinary calcium excretion
- random renal calcium:creatinine excretion ratio
- random calcium:creatinine clearance ratio.

Assessment after diagnosis

1.2.3 For people with a confirmed diagnosis of primary hyperparathyroidism:

- assess symptoms and comorbidities
- measure eGFR (estimated glomerular filtration rate) or serum creatinine
- do a DXA (dual-energy X-ray absorptiometry) scan of the lumbar spine, distal radius and hip
- do an ultrasound scan of the renal tract.

For a short explanation of why the committee made the recommendations and how they might affect practice, see the rationale and impact section on testing and assessment in secondary care.

Full details of the evidence and the committee's discussion are in evidence review A: indications for diagnostic testing and evidence review B: diagnostic tests.

1.3 Referral for surgery

1.3.1 Refer people with a confirmed diagnosis of primary hyperparathyroidism to a surgeon with expertise in parathyroid surgery if they have:

- symptoms of hypercalcaemia such as thirst, frequent or excessive urination, or constipation **or**
- end-organ disease (renal stones, fragility fractures or osteoporosis) **or**
- an albumin-adjusted serum calcium level of 2.85 mmol/litre or above.

1.3.2 Consider referral to a surgeon with expertise in parathyroid surgery for people with a confirmed diagnosis of primary hyperparathyroidism even if they do not have the features listed in recommendation 1.3.1.

For a short explanation of why the committee made the recommendations and how they might affect practice, see the rationale and impact section on referral for surgery.

Full details of the evidence and the committee's discussion are in evidence review C: indications for surgery.

1.4 Surgical management

Preoperative imaging

1.4.1 Offer preoperative imaging (usually ultrasound) to people having surgery for primary hyperparathyroidism if it will inform the surgical approach.

1.4.2 Consider a second preoperative imaging modality (usually a sestamibi scan) if it will further guide the surgical approach.

1.4.3 Do not offer more preoperative imaging if the first-modality (usually ultrasound) and second-modality scans (usually a sestamibi scan) do not identify an adenoma or are discordant.

1.4.4 Proceed with surgery, performed by a surgeon with expertise in 4-gland exploration, even if preoperative imaging has not identified an adenoma.

1.4.5 If preoperative imaging shows an ectopic adenoma, refer the person to a centre with the relevant expertise.

Type of surgery

1.4.6 Offer a choice of either 4-gland exploration or focused parathyroidectomy to people whose preoperative imaging shows a single adenoma in the neck. Discuss the choice of surgery with the person, and explain:

- what happens during each type of surgery

- how well each type of surgery works
- what types of anaesthesia are used
- how long each type of surgery is likely to take
- how large the resulting scars are likely to be
- the risks of each type of surgery.

1.4.7 Offer 4-gland exploration to people who have had preoperative imaging that does not identify a single adenoma.

1.4.8 Consider 4-gland exploration for people having surgery for primary hyperparathyroidism whose first-modality and second-modality scans are discordant.

Intraoperative PTH monitoring

1.4.9 Do not use intraoperative PTH monitoring in first-time parathyroid surgery.

Follow-up after surgery

1.4.10 Measure albumin-adjusted serum calcium and PTH before discharge after surgery for primary hyperparathyroidism to provide baseline information for later follow-up.

1.4.11 Measure albumin-adjusted serum calcium 3 to 6 months after surgery for primary hyperparathyroidism to confirm whether surgery has been successful.

1.4.12 If albumin-adjusted serum calcium is within the reference range 3 to 6 months after surgery for primary hyperparathyroidism, regard the surgery as successful. Monitor albumin-adjusted serum calcium once a year. See the section on monitoring.

Unsuccessful surgery

1.4.13 For people who have had unsuccessful surgery for primary hyperparathyroidism:

- conduct a multidisciplinary team (MDT) review at a specialist centre that includes:
  - initial findings from surgery
  - previous imaging and histology
  - the clinical and biochemical indications for repeat surgery
- offer monitoring as set out in the section on monitoring.

1.4.14 If repeat surgery is performed for primary hyperparathyroidism, it should be done at a centre with expertise in reoperative parathyroid surgery.

For a short explanation of why the committee made the recommendations and how they might affect practice, see the rationale and impact section on surgical management.

- Full details of the evidence and the committee's discussion are in evidence review D: surgical localisation (for the recommendations on preoperative imaging)
- evidence review E: surgical interventions (for the recommendations on type of surgery)
- evidence review F: management options in failed primary surgery (for the recommendations on unsuccessful surgery)
- evidence review I: monitoring (for the recommendations on follow-up after surgery).

1.5 Non-surgical management

Calcimimetics

In May 2019, the use of cinacalcet after unsuccessful surgery for primary hyperparathyroidism was off label. See NICE's information on prescribing medicines.

1.5.1 Consider cinacalcet for people with primary hyperparathyroidism if surgery has been unsuccessful, is unsuitable or has been declined, and if their albumin-adjusted serum calcium level is either:

- 2.85 mmol/litre or above with symptoms of hypercalcaemia **or**
- 3.0 mmol/litre or above with or without symptoms of hypercalcaemia.

1.5.2 For people whose initial albumin-adjusted serum calcium level is 2.85 mmol/litre or above with symptoms of hypercalcaemia, base decisions on whether to continue treatment with cinacalcet on how well it reduces symptoms.

1.5.3 For people whose initial albumin-adjusted serum calcium level is 3.0 mmol/litre or above, base decisions on whether to continue treatment with cinacalcet on how well it reduces either symptoms or albumin-adjusted serum calcium level.

Bisphosphonates

1.5.4 Consider a bisphosphonate to reduce fracture risk for people with primary hyperparathyroidism and increased fracture risk.

1.5.5 Do not offer bisphosphonates for chronic hypercalcaemia of primary hyperparathyroidism.

For a short explanation of why the committee made the recommendations and how they might affect practice, see the rationale and impact section on non-surgical management.

Full details of the evidence and the committee's discussion are in:

- evidence review F: management options in failed primary surgery
- evidence review G: calcimimetics
- evidence review H: bisphosphonates.

1.6 Monitoring

1.6.1 Offer monitoring to all people diagnosed with primary hyperparathyroidism, as set out in table 1.

Table 1 Monitoring for people with primary hyperparathyroidism

People who have had successful parathyroid surgery	People who have not had parathyroid surgery, or whose surgery has not been successful
Measure albumin-adjusted serum calcium once a year.	Measure albumin-adjusted serum calcium and estimated glomerular filtration rate or serum creatinine once a year, unless the person is taking cinacalcet. (In May 2019, cinacalcet was off label for use after unsuccessful surgery for primary hyperparathyroidism. See NICE's information on prescribing medicines.) If the person is taking cinacalcet, offer monitoring as set out in the summary of product characteristics. If the results of monitoring raise concerns, follow the recommendation on repeating the measurement in the section on measuring albumin-adjusted serum calcium.

People who have had successful parathyroid surgery	People who have not had parathyroid surgery, or whose surgery has not been successful
If the person has osteoporosis, seek specialist opinion according to local pathways on monitoring.	Consider a dual-energy X-ray absorptiometry scan at diagnosis and every 2 to 3 years. If the results of monitoring raise concerns, follow the recommendation on referring people with features listed in the section on referral for surgery.
If the person has renal stones, seek specialist opinion according to local pathways on monitoring.	Offer ultrasound of the renal tract at diagnosis, when presenting and if a renal stone is suspected (for recommendations on assessing and managing renal stones, see the NICE guideline on renal and ureteric stones). If the results of monitoring raise concerns, follow the recommendation on referring people with features listed in the section on referral for surgery.

For people who have had parathyroid surgery for multigland disease, or have disease that recurs after successful surgery, seek specialist endocrine opinion on monitoring.

For women who are pregnant, see the section on pregnancy.

For all people with primary hyperparathyroidism, assess cardiovascular risk and fracture risk in line with the NICE guidelines on cardiovascular disease and osteoporosis.

For a short explanation of why the committee made the recommendations and how they might affect practice, see the rationale and impact section on monitoring.

Full details of the evidence and the committee's discussion are in evidence review F: management options in failed primary surgery and evidence review I: monitoring.

1.7 Pregnancy

Care before pregnancy

1.7.1 Offer parathyroid surgery to women who have primary hyperparathyroidism and are considering pregnancy.

Care during pregnancy

1.7.2 Discuss the management of primary hyperparathyroidism for pregnant women with a MDT in a specialist centre, and refer the woman for specialist care if needed. The MDT should include:

- an obstetrician
- a physician with expertise in primary hyperparathyroidism
- a surgeon
- a midwife
- an anaesthetist.

1.7.3 Do not offer cinacalcet to pregnant women with primary hyperparathyroidism.

1.7.4 Do not offer a bisphosphonate to pregnant women with primary hyperparathyroidism.

1.7.5 Be aware that women with primary hyperparathyroidism are at increased risk of hypertensive disease in pregnancy. For recommendations on diagnosing and managing hypertension in pregnant women, see the NICE guideline on hypertension in pregnancy.

1.7.6 Consult a specialist centre MDT for advice on monitoring for pregnant women with primary hyperparathyroidism.

For a short explanation of why the committee made the recommendations and how they might affect practice, see the rationale and impact section on pregnancy.

Full details of the evidence and the committee's discussion are in evidence review J: pregnancy.

1.8 Information and support

1.8.1 Follow the recommendations on enabling people to actively participate in their care in the NICE guideline on patient experience in adult NHS services.

1.8.2 Give people with primary hyperparathyroidism information about the condition, including:

- what primary hyperparathyroidism is
- what the parathyroid glands do
- causes of primary hyperparathyroidism
- symptoms
- diagnosis, including diagnosis if calcium or PTH levels are normal
- prognosis
- possible effects on daily life
- possible long-term effects.

1.8.3 Give people information about treatments for primary hyperparathyroidism that includes:

- the surgical and non-surgical treatments that are available
- how well the treatments are likely to work
- the advantages and disadvantages of each treatment, including possible complications and side effects

- why these particular treatments are being offered
- why other treatments are not advised.

1.8.4 Give advice on how to reduce the symptoms of primary hyperparathyroidism and prepare for surgery or other treatment, including:

- exercise
- diet
- hydration
- pain relief
- what to expect after treatment, recovery time and return to daily activities, including return to work.

1.8.5 Discuss ongoing care and monitoring for primary hyperparathyroidism, explaining the type and frequency of monitoring that will be offered and the purpose of each. See the section on monitoring.

For a short explanation of why the committee made the recommendations and how they might affect practice, see the rationale and impact section on information and support.

Full details of the evidence and the committee's discussion are in evidence review K: patient information.

Terms used in this guideline

Advice from a specialist

This may be a referral or a telephone call to a specialist.

Chronic non-differentiated symptoms

Long-term symptoms that could have a number of different causes. Some of these symptoms are experienced by people with primary hyperparathyroidism, but they can also be symptoms of other conditions. Examples include fatigue, mild confusion, bone, muscle or joint pain, anxiety, depression, irritability, low mood, apathy, insomnia, frequent urination, increased thirst and digestive problems.

Hypercalcaemia

A high level of calcium in the blood, defined as an albumin-adjusted serum calcium level of 2.6 mmol/litre or above. Although hypercalcaemia often causes few or no symptoms, some people feel unusually thirsty, need to urinate frequently or become constipated.

Recommendations for research

The guideline committee has made the following recommendations for research.

1 Bone turnover markers

What is the clinical utility of bone turnover markers in the diagnosis and management of primary hyperparathyroidism?

For a short explanation of why the committee made the recommendation for research, see the rationale on assessment after diagnosis.

Full details of the evidence and the committee's discussion are in evidence review B: diagnostic tests.

2 Management after unsuccessful first surgery

What is the best and most cost-effective management strategy for people whose first surgery for primary hyperparathyroidism is not successful?

For a short explanation of why the committee made the recommendation for research, see the rationale on unsuccessful surgery.

Full details of the evidence and the committee's discussion are in evidence review F: management options in failed primary surgery.

3 Long-term outcomes of different management strategies

What are the long-term outcomes of different management strategies for primary hyperparathyroidism? Which strategies are most cost effective?

For a short explanation of why the committee made the recommendation for research, see the rationale on all people with primary hyperparathyroidism.

Full details of the evidence and the committee's discussion are in evidence review I: monitoring.

4 Managing primary hyperparathyroidism during pregnancy

What are the optimal management strategies for primary hyperparathyroidism during pregnancy?

For a short explanation of why the committee made the recommendation for research, see the rationale on care during pregnancy.

Full details of the evidence and the committee's discussion are in evidence review J: pregnancy.

Rationale and impact

These sections briefly explain why the committee made the recommendations and how they might affect practice. They link to details of the evidence and a full description of the committee's discussion.

Diagnostic testing in primary care

Recommendations 1.1.1 to 1.1.10

Why the committee made the recommendations

Type of serum calcium measurement

Although no evidence was available, the committee are confident, based on their knowledge and experience, that albumin-adjusted serum calcium measurement produces an accurate indication of the amount of calcium that is active in the body. Calcium that is bound to albumin is not active and does not have clinical effects. Adjusting for albumin compensates for this, and allows better identification of the active calcium that may be causing symptoms or signs.

Indications for serum calcium measurement

Limited evidence, and the committee's experience, suggest that hypercalcaemia in primary hyperparathyroidism is associated with particular symptoms, notably thirst, frequent or excessive urination, or constipation, and with conditions such as osteoporosis, fragility fractures or renal stones. Diagnostic testing is therefore indicated for people with these symptoms or conditions. However, the committee noted that hypercalcaemia is often asymptomatic and agreed that an incidental finding of elevated albumin-adjusted serum calcium in a person without symptoms should also trigger diagnostic testing.

Noting that people with primary hyperparathyroidism sometimes have chronic non-differentiated symptoms, the committee agreed that diagnostic testing could be considered for people with these symptoms. Examples include fatigue, depression, mild confusion, anxiety, irritability, insomnia or digestive problems. The committee

acknowledged that there could be multiple causes for these symptoms and that their association with primary hyperparathyroidism is uncertain.

Ionised calcium measurement

The committee agreed that ionised calcium should not be measured because point-of-care testing is not subject to the stringency of laboratory testing and the sample has to be handled very quickly, making ionised calcium measurement unreliable.

Repeating albumin-adjusted serum calcium measurement

Because serum calcium levels can vary with changes in blood pH or serum albumin, and the cost of measurement is relatively low, the committee agreed that albumin-adjusted serum calcium should be measured at least twice before moving on to more expensive measurement of parathyroid hormone (PTH).

Type of PTH measurement

No evidence was available on measurement of PTH in the diagnosis or assessment of primary hyperparathyroidism. The committee based their recommendations on the normal reference range for albumin-adjusted serum calcium as defined by the Association of Clinical Biochemistry, which is 2.2 to 2.6 mmol/litre, and their own experience.

Indications for PTH measurement

The committee noted that most people with primary hyperparathyroidism have an albumin-adjusted serum calcium level above 2.6 mmol/litre. However, they also discussed a type of primary hyperparathyroidism that affects a smaller number of people, in which the albumin-adjusted serum calcium level is within the normal range. This is known as 'normocalcaemic primary hyperparathyroidism' and it often goes unrecognised. To address this, the committee added a lower criterion of 2.5 mmol/litre (with clinical suspicion of primary hyperparathyroidism) for PTH measurement.

Carrying out PTH measurement

The committee were in agreement that PTH measurement can be done at any time of day. Although there is a marginal diurnal difference, it is not enough to need adjusting for. They agreed that the PTH measurement needs to be interpreted in the context of a concurrent

albumin-adjusted serum calcium measurement. They also agreed that there is no benefit in repeating the PTH measurement in primary care.

Interpreting PTH measurement and seeking specialist advice

The committee noted that PTH levels can vary widely from one individual to another, and that there is uncertainty about the level of PTH at which primary hyperparathyroidism can be ruled out. The reference range for PTH differs between laboratories so the committee were unable to specify numerical PTH thresholds.

The committee agreed, based on their experience, that advice from a specialist with expertise in primary hyperparathyroidism should be sought if:

- PTH is above the midpoint of the reference range and primary hyperparathyroidism is suspected, because these features indicate that primary hyperparathyroidism is likely
- PTH is below the midpoint of the reference range but albumin-adjusted serum calcium is raised, because this indicates that primary hyperparathyroidism cannot be ruled out.

If PTH is below the midpoint of the reference range and albumin-adjusted serum calcium is not raised, the committee agreed that primary hyperparathyroidism is unlikely.

How the recommendations might affect practice

The committee expects that these recommendations could lead to a change in practice for some providers. There may be an increased demand for primary care services (such as appointments or blood tests) as a result of increased awareness of symptoms such as thirst, frequent or excessive urination, or constipation. Repeating albumin-adjusted serum calcium measurements will increase the number of such tests but can be expected to reduce the number of PTH tests.

Implementing a standardised sequence of diagnostic tests should lead to more rapid diagnosis, and reduce the need to manage complications of undiagnosed primary hyperparathyroidism such as fractures, renal stones and chronic long-term symptoms.

Return to recommendations

Testing and assessment in secondary care

Recommendations 1.2.1 to 1.2.3

Why the committee made the recommendations

Measuring vitamin D

No evidence was available on measuring vitamin D to assess primary hyperparathyroidism, so the recommendation is based on the committee's knowledge and experience.

The committee noted that vitamin D deficiency can lead to a rise in PTH level, exacerbate bone disease and increase postoperative risk. It is therefore important to assess and correct vitamin D for people with primary hyperparathyroidism. However, the committee were aware that vitamin D testing is not available to all primary care providers, and that waiting for vitamin D to be measured, and corrected if necessary, before seeking specialist advice could delay diagnosis. They therefore concluded that vitamin D measurement and correction are best carried out in secondary care.

Excluding familial hypocalciuric hypercalcaemia

The committee agreed that it is important to exclude familial hypocalciuric hypercalcaemia (FHH) because it needs no operative treatment. Evidence showed that the 3 tests recommended are equally accurate in the diagnosis of FHH. The committee were not able to recommend thresholds for these measurements because the evidence is inconsistent.

Assessment after diagnosis

The committee agreed that baseline assessment will help to determine optimal management in secondary care. They did not recommend phosphate measurement because improvements in PTH assays have reduced its usefulness.

The committee acknowledged the potential of bone turnover markers to enable earlier and more accurate diagnosis of primary hyperparathyroidism but were unable to make a recommendation because of a lack of evidence. They therefore made a research recommendation on bone turnover markers.

How the recommendations might affect practice

Measuring vitamin D in secondary care is expected to be a change in practice for some services. Current practice varies, partly because of the varying availability of vitamin D measurement in primary care. In primary care services where vitamin D measurement is available, vitamin D is being measured and deficiencies corrected before PTH is measured. By standardising practice and reducing delays in diagnostic testing, the committee expects improvements in the diagnosis of primary hyperparathyroidism and more prompt treatment for people with the condition.

Measuring urine calcium excretion in secondary care is current practice.

Return to recommendations

Referral for surgery

Recommendations 1.3.1 and 1.3.2

Why the committee made the recommendations

There was no evidence available on surgery compared with non-surgical treatment for people with a confirmed diagnosis of primary hyperparathyroidism and symptoms or other indications for surgery. However, the committee reasoned that the lack of evidence is likely to reflect the broad consensus that surgery is beneficial for these people. The committee also agreed that surgery is cost effective because, although the initial cost is high, it can be expected to result in a cure and eliminate the need for further treatment. It relieves symptoms of hypercalcaemia such as thirst, polyuria and constipation, and can prevent future adverse events such as renal stones and fragility fractures. Non-surgical treatment, such as calcimimetics, is an ongoing cost with no curative benefit.

For people with a confirmed diagnosis of primary hyperparathyroidism but no symptoms or indications for surgery, the committee based their recommendation on limited evidence together with their clinical experience. They noted that surgery has shown benefits for this group. Although specific symptoms of primary hyperparathyroidism are absent, people in this group can experience non-specific symptoms such as fatigue, depression or muscle weakness that affect their quality of life. Furthermore, future decrements in quality of life and events associated with end-organ damage may occur. Therefore surgery can be considered as a means of resolving non-specific symptoms and avoiding further

deterioration in health.

The committee acknowledged the potential of bone turnover markers to help identify people who could benefit from surgery but were unable to make a recommendation because of a lack of evidence. They therefore made a research recommendation on bone turnover markers.

How the recommendations might affect practice

The recommendations are broadly in line with current practice. It is uncertain how many additional surgeries will be performed as a result of the recommendation to consider surgery for people without symptoms or signs, but the committee do not anticipate a significant increase in the number of referrals for surgery.

Return to recommendations

Surgical management

Recommendations 1.4.1 to 1.4.14

Why the committee made the recommendations

Preoperative imaging

There was limited evidence on preoperative imaging so the committee also used their clinical knowledge and experience to make the recommendations. They agreed that the purpose of preoperative imaging is to help guide the surgical approach. It is not essential in all circumstances (for example, if a decision has already been made to perform 4-gland exploration).

Evidence suggested that ultrasound scanning is accurate in identifying abnormal parathyroid tissue. Ultrasound scanning is widely available, safe and does not involve any exposure to radiation. However, the committee noted that the accuracy of ultrasound depends on the expertise of the person performing it. They therefore recommended sestamibi as an alternative.

Although dual scanning using 2 different imaging modalities has the advantage of

providing both anatomical and functional information, the committee agreed that a second imaging modality is only needed if it will further inform the surgical approach. Evidence suggests that sestamibi scanning is accurate in detecting single-gland disease. The committee did not make a recommendation on 4D CT scanning because there was no evidence available.

The committee agreed that if dual scanning fails to identify an adenoma or is discordant, further imaging will not add useful information and will expose the person to unnecessary radiation. They acknowledged that preoperative imaging does not detect all adenomas, so 4-gland exploration should be offered if preoperative imaging does not identify an adenoma.

Type of surgery

The committee agreed that, based on their experience, people whose preoperative imaging does not identify a single adenoma will more frequently have multigland disease and will benefit from 4-gland exploration. If the first-modality and second-modality scans are discordant, 4-gland exploration can be considered because the specific anatomical location of the adenoma cannot be assured.

For people with a single adenoma, a small amount of evidence shows that both focused parathyroidectomy and 4-gland exploration are safe and effective. The committee agreed that focused parathyroidectomy offers the potential advantages of lower temporary hypocalcaemia, a shorter surgery time and minor cosmetic benefit. However, it also carries a marginally (around 5%) higher chance of recurrence or persistent disease. They therefore agreed that people with a single adenoma should be offered a choice of focused parathyroidectomy or 4-gland exploration, and that the possible benefits and risks of each type of surgery should be discussed with them.

Intraoperative PTH monitoring

There was limited evidence on intraoperative PTH (IOPTH) monitoring. The committee noted that in their experience, there is a marginal benefit with the use of IOPTH, but this could be partially attributed to surgical expertise.

IOPTH monitoring is costly and its effectiveness in improving surgical outcomes is uncertain. The committee agreed that their experience together with the limited evidence did not support IOPTH monitoring as part of standard practice.

Follow-up after surgery

Based on their knowledge and experience, the committee agreed that people who have had parathyroid surgery can be considered biochemically cured if their albumin-adjusted serum calcium and PTH levels are within the reference range before discharge after surgery and their albumin-adjusted serum calcium level is within the reference range 3 to 6 months after surgery.

The committee acknowledged the potential of bone turnover markers to check bone health after surgery for primary hyperparathyroidism but were unable to make a recommendation because of a lack of evidence. They therefore made a research recommendation on bone turnover markers.

Unsuccessful surgery

There was no evidence on further surgical management for people who have had unsuccessful first surgery, and very limited evidence on drug therapy with cinacalcet compared with placebo. The committee agreed that input from a multidisciplinary team at a specialist centre should be sought, noting that repeat parathyroid surgery is relatively uncommon, failure rates are higher than in first surgery and it carries a higher risk. They also made a research recommendation on management after unsuccessful first surgery.

How the recommendations might affect practice

The recommendations for preoperative imaging largely reflect current practice. However, there is variation in the number and type of preoperative tests carried out and the resulting course of action. The committee thought that the recommendations will necessitate changes in practice for some providers. They noted that using a maximum of 2 imaging modalities before surgery would change practice in centres that currently use more than 2 imaging modalities.

Although not widely used, IOPTH testing is most likely to be found in larger centres that are undertaking parathyroidectomies most frequently. The recommendation is expected to lead to changes in practice in these centres.

The recommendations on type of surgery are considered to generally reflect current practice. However, in some centres, current practice is not to offer surgery to people if no adenoma is identified on imaging. These recommendations will therefore necessitate

changes in practice for some providers.

The recommendations on follow-up after surgery reflect current practice in most NHS centres, so the committee thought that there would be little change in practice.

The recommendations on unsuccessful surgery are current practice in many areas.

Return to recommendations

Non-surgical management

Recommendations 1.5.1 to 1.5.5

Why the committee made the recommendations

Calcimimetics

Cinacalcet is the only calcimimetic for which evidence was available. The committee noted that cinacalcet does not directly stop kidney problems or bone loss caused by primary hyperparathyroidism, and that surgery is the only definitive treatment for primary hyperparathyroidism.

Based on the evidence and their experience, the committee agreed that treatment with cinacalcet could be considered for the purpose of reducing symptoms and lowering the risk of a hypercalcaemic crisis for people who have not had surgery and those for whom surgery has not been successful. The committee agreed that, in their experience, cinacalcet can improve quality of life for people with symptoms of hypercalcaemia and an albumin-adjusted serum calcium level of 2.85 mmol/litre or above. For people with an albumin-adjusted serum calcium level of 3.0 mmol/litre or above, who are more at risk of hypercalcaemic crises, cinacalcet can both improve quality of life and help to prevent hypercalcaemic crises.

The committee agreed that treatment-related changes in serum calcium should be managed by basing initiation and continuation of treatment on albumin-adjusted serum calcium level and symptoms. They also agreed that treatment with cinacalcet should be continued if it produces a decrease in albumin-adjusted serum calcium or an improvement in symptoms, because discontinuation is likely to reverse these improvements. The

committee noted that there is no evidence for and little likelihood of benefit from cinacalcet for people with normal calcium levels and no symptoms.

Bisphosphonates

There was evidence showing that bisphosphonate treatment improves lumbar spine bone mineral density for people with primary hyperparathyroidism. The committee based the recommendation on the NICE technology appraisal guidance on bisphosphonates for treating osteoporosis.

Based on the evidence and their clinical experience, the committee agreed that bisphosphonates should not be offered to reduce hypercalcaemia in the long term.

How the recommendations might affect practice

These recommendations are considered to be current practice in many areas, and are not expected to lead to major changes in practice.

Return to recommendations

Monitoring

Recommendation 1.6.1

Why the committee made the recommendations

People who have had successful parathyroid surgery

Based on their knowledge and experience, the committee agreed that the risk of recurrent disease after successful parathyroid surgery is very low and therefore it is sufficient to monitor albumin-adjusted serum calcium levels once a year.

For people who have osteoporosis, although bone density improves after surgery, skeletal recovery can take some time and needs specialist monitoring. The risk of renal stones decreases after successful surgery, but the residual risk persists and the committee agreed that specialist opinion on monitoring should be sought.

People who have not had parathyroid surgery, or whose surgery has not been successful

Based on their clinical experience, the committee agreed that monitoring for people who have had unsuccessful surgery should be the same as for people who have had no previous surgery. Monitoring bridges the gap between first surgery and multidisciplinary review and reassessment in a specialist centre.

The committee noted the increased risk of renal stones and fractures in people who have had unsuccessful or no parathyroid surgery. Evidence suggests that around one-third of people who do not have symptoms or indications for surgery will go on to develop these. The committee agreed that monitoring will ensure that surgery, including repeat surgery, can be offered when needed.

People who have had parathyroid surgery for multigland disease, or have disease that recurs after successful surgery

The committee agreed that people with multigland disease, or disease that has recurred after successful surgery, have a slightly increased risk of future recurrence and will benefit from specialist endocrine opinion on monitoring.

All people with primary hyperparathyroidism

For all people with primary hyperparathyroidism, the committee agreed that there was no evidence to suggest that surgery modifies cardiovascular disease risk or fracture risk, so these should be assessed in line with NICE guidance.

The committee noted the limited evidence on long-term outcomes and made a research recommendation on long-term outcomes of different management strategies.

How the recommendations might affect practice

The recommendations reflect current practice in most NHS centres, so the committee expects little change in practice.

Return to recommendations

Pregnancy

Recommendations 1.7.1 to 1.7.6

Why the committee made the recommendations

Care before pregnancy

The committee noted that having surgery for primary hyperparathyroidism before becoming pregnant allows women to start their pregnancy with a normal serum calcium level, which reduces their risk of pregnancy-associated complications of primary hyperparathyroidism. They noted that the risk of stillbirth and neonatal tetany increases with a serum calcium level above 2.85 mmol/litre.

Care during pregnancy

Based on their experience, the committee agreed that management of primary hyperparathyroidism during pregnancy should be discussed with a multidisciplinary team (MDT) because of the high risk of maternal and neonatal complications.

The safety and efficacy of cinacalcet for pregnant women is largely unknown, so the committee agreed that cinacalcet should not be offered during pregnancy. They also agreed that bisphosphonates are potentially harmful for the mother and the fetus.

There was no evidence on monitoring for pregnant women. The committee agreed that monitoring should be guided by a specialist centre MDT because of the risk of maternal or fetal complications. They also highlighted primary hyperparathyroidism as a risk factor for pre-eclampsia and hypertension.

There was little overall evidence so the committee made a research recommendation on managing primary hyperparathyroidism during pregnancy.

How the recommendations might affect practice

The recommendations made for women who are pregnant or considering pregnancy might change practice in some areas. However, this is a small population so they are not expected to have a substantial impact on practice.

Return to recommendations

Information and support

Recommendations 1.8.1 to 1.8.5

Why the committee made the recommendations

No evidence was found so the committee based the recommendations on their knowledge and experience. The committee agreed that primary hyperparathyroidism is an under-recognised condition among both the general population and healthcare professionals. They emphasised the importance of accurate, balanced and up-to-date information so that people with the condition can understand it and make informed choices, particularly with regard to surgery.

How the recommendations might affect practice

The recommendations broadly reflect current practice. They focus on the information and support that should be given rather than on specific interventions and therefore are not expected to change practice.

Return to recommendations

Context

Primary hyperparathyroidism is a disorder of one or more of the parathyroid glands. The parathyroid gland becomes overactive and secretes excess amounts of parathyroid hormone, causing hypercalcaemia, hypophosphataemia and hypercalciuria. The most common cause of primary hyperparathyroidism is a non-cancerous tumour (an adenoma) in one of the parathyroid glands.

Primary hyperparathyroidism is one of the leading causes of hypercalcaemia and one of the most common endocrine disorders. About 1 to 4 people per 1,000 are known to have the condition. Women are twice as likely to develop primary hyperparathyroidism as men. It can develop at any age, but in women in the UK, it is most often diagnosed between the ages of 50 and 60.

The signs and symptoms of primary hyperparathyroidism are predominantly brought about by hypercalcaemia and include thirst and increased urine output, gastrointestinal symptoms such as constipation, and effects on the central nervous system such as fatigue and memory impairment. Long-term effects include kidney stones, bone-related complications such as osteoporosis and fractures, and cardiovascular disease.

This guideline provides recommendations on recognition, diagnosis and management of primary hyperparathyroidism. It offers advice for primary care professionals on initial diagnostic testing. It also provides guidance for secondary care professionals on indications for surgery, preoperative imaging, types of surgery and follow-up care after surgery.

Finding more information and committee details

To find out what NICE has said on topics related to this guideline, see NICE's topic page on thyroid disorders.

For full details of the evidence and the guideline committee's discussions, see the evidence reviews. You can also find information about how the guideline was developed, including details of the committee.

NICE has produced tools and resources to help you put this guideline into practice. For general help and advice on putting our guidelines into practice, see resources to help you put NICE guidance into practice.

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