NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Guideline

Hyperparathyroidism (primary): diagnosis, assessment and initial management

Draft for consultation, November 2018

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

This draft guideline contains:

- the draft recommendations
- recommendations for research
- rationale and impact sections that explain why the committee made the recommendations and how they might affect practice
- the guideline context.

Information about how the guideline was developed is on the guideline's page on the NICE website. This includes the evidence reviews, the scope, and details of the committee and any declarations of interest.

Contents

Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in 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 Diagnosis and assessment

Diagnostic testing

Albumin-adjusted serum calcium measurement

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[1]
- an incidental finding of elevated albumin-adjusted serum calcium (2.6 mmol/litre or above).

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

1.1.3 If the person's albumin-adjusted serum calcium level is 2.6 mmol/litre or above, or 2.5 mmol/litre or above with features of primary hyperparathyroidism, repeat the albumin-adjusted serum calcium measurement at least once. Base the decision to carry out further repeat

[1] See the NICE guideline on renal and ureteric stones: assessment and management (publication expected December 2018).

measurements on the level of albumin-adjusted serum calcium and the person's symptoms.

1.1.4 Be aware that chronic non-differentiated symptoms, such as fatigue or depression, might indicate primary hyperparathyroidism and consider measuring albumin-adjusted serum calcium.

Parathyroid hormone measurement

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

- 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 specialist advice if:

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

1.1.9 Do not offer further investigations for primary hyperparathyroidism if:

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

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

Vitamin D measurement

1.1.11 For people with a probable diagnosis of primary hyperparathyroidism, measure vitamin D and correct any deficiency.

Excluding familial hypocalciuric hypercalcaemia

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

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

Assessment after diagnosis

1.1.13 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.

To find out why the committee made the recommendations on diagnosis and assessment and how they might affect practice, see rationale and impact.

1.2 Referral for surgery

1.2.1 Refer people with 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.

1.2.2 Consider referral to a surgeon with expertise in parathyroid surgery for people with primary hyperparathyroidism irrespective of the features listed in recommendation 1.2.1.

To find out why the committee made the recommendations on referral for surgery and how they might affect practice, see rationale and impact.

1.3 Surgical management

Preoperative imaging

1.3.1 Be aware that surgery should proceed regardless of preoperative imaging results.

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

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

1.3.4 Do not offer more preoperative imaging if the first-modality and second-modality scans do not identify an adenoma or are discordant.

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

Type of surgery

1.3.6 Offer a choice of focused parathyroidectomy or 4-gland exploration to people who have had preoperative imaging that shows a single adenoma in the neck.

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

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

Intraoperative parathyroid hormone monitoring

1.3.9 Do not use intraoperative parathyroid hormone monitoring in first-time parathyroid surgery.

Follow-up after surgery

1.3.10 Measure albumin-adjusted serum calcium and parathyroid hormone before discharge after surgery for primary hyperparathyroidism.

1.3.11 Measure albumin-adjusted serum calcium 3 to 6 months after surgery for primary hyperparathyroidism.

1.3.12 If albumin-adjusted serum calcium is within the reference range 3 to 6 months after surgery for primary hyperparathyroidism, do not routinely monitor it. See table 1 for recommendations on monitoring.

Repeat surgery

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

- conduct a multidisciplinary team 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 table 1.

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

To find out why the committee made the recommendations on surgical management and how they might affect practice, see rationale and impact.

1.4 Non-surgical management

Calcimimetics

1.4.1 Consider cinacalcet[2] 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:

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

1.4.2 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[2] on how well it reduces symptoms.

1.4.3 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[2] on how well it reduces either symptoms or albumin-adjusted serum calcium level.

Bisphosphonates

1.4.4 Do not offer people with primary hyperparathyroidism a bisphosphonate for long-term management of hypercalcaemia.

1.4.5 Consider a bisphosphonate to reduce fracture risk for people with primary hyperparathyroidism, in line with the NICE technology appraisal guidance on bisphosphonates for treating osteoporosis.

To find out why the committee made the recommendations on non-surgical management and how they might affect practice, see rationale and impact.

[2] At the time of consultation (November 2018) cinacalcet did not have a UK marketing authorisation for use after unsuccessful surgery for primary hyperparathyroidism. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

1.5 Monitoring

1.5.1 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[1]	**People who have not had parathyroid surgery, or for whom parathyroid surgery has not been successful**[1]	**People who have had parathyroid surgery for multigland disease, or have disease that recurs after successful surgery**[1]
Consider opportunistic monitoring of albumin-adjusted serum calcium if the person has a routine blood test, no more than once a year	Measure albumin-adjusted serum calcium and eGFR (estimated glomerular filtration rate) or serum creatinine annually, or every 2 to 3 months if the person is taking cinacalcet[2,3]	Seek specialist endocrine opinion on monitoring
Seek specialist opinion according to local pathways on monitoring for people who have osteoporosis	Consider a DXA (dual-energy X-ray absorptiometry) scan at diagnosis and every 2 to 3 years	
Seek specialist opinion according to local pathways on monitoring for people who have renal stones	Offer ultrasound of the renal tract at diagnosis and when presenting or if a renal stone is suspected [4]	
Assess fracture risk in line with the NICE guideline on osteoporosis		
Assess cardiovascular risk in line with the NICE guideline on cardiovascular disease		

[1] For women who are pregnant see pregnancy in this guideline

[2] As set out in the BNF

[3] At the time of consultation (November 2018) cinacalcet did not have a UK marketing authorisation for use after unsuccessful surgery for primary hyperparathyroidism. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[4] See the NICE guideline on renal and ureteric stones: assessment and management (publication expected December 2018)

To find out why the committee made the recommendations on monitoring and how they might affect practice, see rationale and impact.

1.6 Pregnancy

Care before pregnancy

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

Care during pregnancy

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

- an obstetrician
- a physician
- a surgeon
- a midwife
- an anaesthetist.

1.6.3 Do not offer a calcimimetic to pregnant women with primary hyperparathyroidism.

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

1.6.5 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.

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

Information and support before and during pregnancy

1.6.7 For women with primary hyperparathyroidism who are pregnant or planning a pregnancy:

- follow the recommendations in information and support
- tell them that there is no evidence that primary hyperparathyroidism affects the baby either before or after birth.

To find out why the committee made the recommendations on pregnancy and how they might affect practice, see rationale and impact.

1.7 Information and support

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

1.7.2 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 parathyroid hormone levels are normal
- prognosis
- possible effects on daily life
- possible long-term effects.

1.7.3 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.

1.7.4 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.

1.7.5 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 recommendations for monitoring in this guideline.

To find out why the committee made the recommendations on information and support and how they might affect practice, see rationale and impact.

Recommendations for research

The guideline committee has made the following recommendations for research.

Key recommendations for research

1 Bone turnover markers

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

To find out why the committee made the research recommendation on bone turnover markers see the rationale sections on assessment after diagnosis, referral for surgery and follow-up after surgery.

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?

To find out why the committee made the research recommendation on unsuccessful first surgery see the rationale section on repeat 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?

To find out why the committee made the research recommendation on the long-term outcomes of different management strategies see the rationale section on all people with primary hyperparathyroidism.

4 Managing primary hyperparathyroidism during pregnancy

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

To find out why the committee made the research recommendation on managing primary hyperparathyroidism during pregnancy see the rationale section on care during 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.

Diagnosis and assessment

Recommendations 1.1.1 to 1.1.13

Why the committee made the recommendations

Albumin-adjusted serum calcium measurement

Limited evidence, and the committee's clinical experience, suggest that primary hyperparathyroidism is more common in people who have symptoms of hypercalcaemia or have had a fragility fracture or a renal stone. In addition, the committee noted that primary hyperparathyroidism is most often discovered after a routine blood test that shows a raised serum calcium level.

Although no evidence was available on the type of serum calcium measurement, the committee agreed that an albumin-adjusted sample will ensure that the amount of free calcium is measured. They did not think that ionised calcium should 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.

The committee noted that a person's serum calcium levels can vary. They therefore thought it important to measure albumin-adjusted serum calcium level more than once before moving on to more expensive measurement of parathyroid hormone. The cost of measuring serum calcium level is relatively low. Repeating this measurement provides reassurance of consistent serum calcium levels and can be expected to reduce the number of unnecessary tests to measure parathyroid hormone.

The committee also wanted to raise awareness of the possibility of primary hyperparathyroidism in people with undifferentiated symptoms such as fatigue or depression. They agreed that albumin-adjusted serum calcium testing could be considered for people with these symptoms. They noted that there is uncertainty about the relationship between these symptoms and primary hyperparathyroidism.

Parathyroid hormone measurement

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

experience. They noted that most people with primary hyperparathyroidism have a serum calcium level above 2.6 mmol/litre. However, they recognised that there is a small group of people with primary hyperparathyroidism whose calcium level is within the normal reference range (normocalcaemia). They therefore agreed that setting a threshold for PTH measurement of albumin-adjusted serum calcium level repeatedly 2.6 mmol/litre or above, or 2.5 mmol/litre or above if there is clinical suspicion of hyperparathyroidism, would identify most people with primary hyperparathyroidism.

Based on their clinical experience, the committee recommended performing a PTH test for people with an albumin-adjusted serum calcium level repeatedly 2.6 mmol/litre or above, because they are most likely to have hypercalcaemia, which is a strong indicator of primary hyperparathyroidism. The committee agreed that PTH testing 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 albumin-adjusted serum calcium should be re-measured at the same time PTH is measured, because the PTH result 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 before referral.

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 varies between laboratories so the committee were unable to specify numerical PTH thresholds.

The committee agreed that if someone has had an incidental finding of elevated albumin-adjusted serum calcium, the albumin-adjusted serum calcium test should be repeated and if it remains elevated PTH testing should be offered. The committee recognised that repeat calcium testing will reduce the number of unnecessary PTH tests. The committee felt that repeating the calcium test is necessary due to random error or changes in the level of physiologically active calcium because of alterations in blood pH or serum albumin. In addition, the committee noted that primary hyperparathyroidism is most often discovered after a routine blood test that shows a raised serum calcium level. The committee agreed that specialist advice should be sought for people with raised albumin-adjusted serum calcium and whose PTH is above the midpoint of the reference range. If PTH is below the midpoint but albumin-

adjusted serum calcium is raised, specialist advice should be sought because there are a small number of people who have primary hyperparathyroidism with a low PTH. If PTH is below the midpoint and albumin-adjusted serum calcium is not raised, primary hyperparathyroidism is unlikely.

Vitamin D measurement

No evidence was available on measuring vitamin D to assess primary hyperparathyroidism, so the recommendation is based on the committee's knowledge and experience. Vitamin D deficiency can lead to a rise in the amount of parathyroid hormone that is secreted, exacerbate bone disease and increase postoperative risk. The committee therefore agreed that vitamin D deficiency should be ruled out or corrected before diagnosing or treating primary hyperparathyroidism.

Excluding familial hypocalciuric hypercalcaemia

The committee agreed that it is important to exclude familial hypocalciuric hypercalcaemia (FHH) because it needs no treatment. In FHH the urinary calcium creatinine level is low. Based on the evidence, they agreed that any one of 3 tests to measure urine calcium excretion could be used. They were not able to recommend thresholds for these measurements because the evidence is inconsistent.

Assessment after diagnosis

The committee agreed that baseline assessment of symptoms and comorbidities, measurement of eGFR or serum creatinine, a DXA scan to assess bone mineral density and an ultrasound scan of the renal tract are needed to help determine the optimal management pathway. They agreed not to recommend phosphate measurement because improvements in parathyroid hormone assays have reduced its usefulness. They also agreed not to recommend alkaline phosphatase measurement because it is not helpful in the diagnosis of primary hyperparathyroidism.

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

recommendation for research on the clinical utility of bone markers in the diagnosis and management of primary hyperparathyroidism.

How the recommendations might affect practice

The committee considered that the recommendations on indications for diagnostic testing reflect good practice, but acknowledged that they could lead to a change in practice for some NHS providers. The committee also noted that there may be an increase in demand for primary care services (such as appointments or blood tests) as a result of the increased awareness of the symptoms such as thirst, frequent or excessive urination, or constipation. Although there is a low cost of testing for serum calcium, these recommendations apply to a large population. However, the committee considered that if such testing helps to diagnose and treat primary hyperparathyroidism sooner then this could reduce the number of fractures or renal stones due to primary hyperparathyroidism, and therefore it could lead to savings.

The committee thought that implementing a standardised sequence of tests for albumin-adjusted serum calcium and parathyroid hormone will reduce variations in practice for diagnostic testing and may be cost saving.

Overall, the impact on resources is uncertain, but not expected to be substantial.

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

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Referral for surgery

Recommendations 1.2.1 and 1.2.2

Why the committee made the recommendations

There was no evidence available on surgery compared with non-surgical treatment for people who have 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 and should be offered. The committee also agreed that surgery would be more 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. Non-surgical treatment, such as calcimimetics, is an ongoing cost with no curative benefit.

For people with 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 in 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 recommendation for research on the clinical utility of bone turnover markers in the diagnosis and management of primary hyperparathyroidism.

How the recommendations might affect practice

The committee noted that the indications for surgery are in line with current practice and are not expected to have a substantial resource impact. However, it is uncertain how many additional surgeries will be performed as a result of the recommendation to consider surgery for people with primary hyperparathyroidism who do not have symptoms or signs. If widely implemented there is potential for a substantial resource impact.

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

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Surgical management

Recommendations 1.3.1 to 1.3.14

Why the committee made the recommendations

Preoperative imaging

The committee agreed that the purpose of preoperative imaging is to help guide the surgical approach, and not to decide whether to proceed with surgery.

There was limited evidence on preoperative imaging so the committee also used their clinical knowledge and experience to make the recommendations. They agreed that preoperative imaging to localise suspected abnormal parathyroid tissue is desirable but not essential in all circumstances (for example, if a decision has already been made to perform 4-gland exploration). Some surgeons proceed to focused surgery on the basis of a single imaging modality, either ultrasound or sestamibi. Evidence suggested that ultrasound scanning is accurate in localising abnormal parathyroid tissue. The committee agreed that ultrasound scanning is widely available, safe and does not involve any exposure to radiation. However, they noted that the accuracy of ultrasound depends on the expertise of the person performing it and ideally should be performed by a head and neck radiologist. They therefore allowed for sestamibi to be used if the expertise is not available to perform ultrasound.

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. There was no evidence available for 4DCT scanning.

The committee agreed that if dual scanning fails to identify an adenoma or is discordant, further imaging should not be offered because it will not add useful information and will expose the person to unnecessary radiation.

Type of surgery

There was a small amount of evidence showing that for people with a single adenoma, both focused parathyroidectomy and 4-gland exploration are safe and effective. The committee acknowledged that focused parathyroidectomy offers the potential advantages of lower temporary hypocalcaemia, a shorter surgery time and

marginal cosmetic benefit. However, it also carries a slightly higher chance of recurrence or persistent disease. They therefore agreed that people should be offered a choice of focused parathyroidectomy or 4-gland exploration if preoperative imaging shows a single adenoma in the neck.

The committee agreed that, based on their experience, people whose preoperative imaging (first imaging modality with or without a second-modality scan) is negative or 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, the committee agreed that 4-gland exploration should be considered. This is because the specific anatomical location of the adenoma cannot be assured.

Intraoperative parathyroid hormone monitoring

There was limited evidence on intraoperative parathyroid hormone (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 parathyroid hormone 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 recommendation for research on the clinical utility of bone turnover markers in the diagnosis and management of primary hyperparathyroidism.

Repeat surgery

There was no evidence on further surgical management for people who have had unsuccessful primary 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 primary surgery and it carries a higher risk. They also made a recommendation for research on management after unsuccessful primary surgery.

How the recommendations might affect practice

The committee observed that the recommendations for preoperative imaging largely reflect current practice. However, they noted that there is variation in the number and type of preoperative tests carried out and the resulting course of action. They thought that the recommendations will necessitate changes in practice for some providers. They noted that using a maximum of 2 imaging modalities before surgery could lead to cost savings 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 that IOPTH testing should not be carried out is likely to lead to cost savings because the expensive reagents used in IOPTH testing will no longer be needed.

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. The committee considered that this is not best practice and probably reflects imaging sensitivity rather than misdiagnosis. 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, and hence no substantial resource impact.

The recommendations on repeat surgery are current practice in many areas, and are not expected to have a substantial resource impact.

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

- evidence review B: diagnostic tests (for the recommendation for research on the clinical utility of bone turnover markers)
- 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 repeat surgery)
- evidence review I: monitoring (for the recommendations on follow-up after surgery).

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Non-surgical management

Recommendations 1.4.1 to 1.4.5

Why the committee made the recommendations

Calcimimetics

Cinacalcet is the only calcimimetic for which evidence was available. 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 had unsuccessful surgery, those for whom surgery is unsuitable and those who have declined surgery. The committee noted that cinacalcet does not directly stop kidney problems or bone loss caused by primary hyperparathyroidism, and that parathyroidectomy is the only definitive treatment for primary hyperparathyroidism.

Based on their clinical experience, the committee agreed that cinacalcet could improve quality of life for people with symptoms of hypercalcaemia and an albumin-adjusted serum calcium level above 2.85 mmol/litre, or an albumin-adjusted serum

calcium level of 3.0 mmol/litre with or without symptoms. Therefore, the cut-off was set at 2.85 mmol/litre for people with symptoms of hypercalcaemia. For the cut-off to define hypercalcaemia in the presence or absence of symptoms, the committee agreed from clinical experience that this should be set at above 3.0 mmol/litre, largely due to the increased risk of hypercalcaemic crises that may be seen with this degree of hypercalcaemia. They 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

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

There was evidence showing that bisphosphonate treatment improves lumbar spine bone mineral density for people with primary hyperparathyroidism. Based on the evidence and their experience, the committee agreed that bisphosphonate treatment could be considered as a means of reducing fracture risk. The committee based the recommendation on the NICE technology appraisal guidance on bisphosphonates for treating osteoporosis. .

How the recommendations might affect practice

These recommendations are considered to be current practice in many areas, and are not expected to have a substantial resource impact.

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.

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Monitoring

Recommendation 1.5.1

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 consider checking albumin-adjusted serum calcium levels as part of routine blood testing.

For people who have osteoporosis, although bone density improves after surgery, skeletal recovery can take some time and need 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 for whom parathyroid surgery has not been successful

The committee noted the increased risk of renal stones and fractures in people who have not had parathyroid surgery and in people who have had unsuccessful 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 long-term monitoring for these people is essential so that surgery can be offered when needed.

Based on their clinical experience the committee agreed that monitoring for people who have had unsuccessful surgery should be the same as that for people who have had no previous surgery. This monitoring is to bridge the gap between first surgery and MDT review and reassessment in a specialist centre.

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

The committee, based on their experience, agreed that individualised monitoring and specialist advice is needed for some groups of people such as those with multigland disease. They noted that for people with multigland disease there is a higher risk of

recurrence than for people who had a single adenoma, but the risk is still very low. The committee agreed that those with multigland disease will benefit from a specialist with knowledge of associated syndromes.

All people with primary hyperparathyroidism

Based on their experience, 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 recommendation for research to look at the long-term outcomes of different management strategies for primary hyperparathyroidism.

How the recommendations might affect practice

The recommendations reflect current practice in most NHS centres, so the committee considered that there would be little change in practice, and hence no substantial impact on resource use.

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.

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Pregnancy

Recommendations 1.6.1 to 1.6.7

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.

Care during pregnancy

Based on their experience, the committee agreed that management of primary hyperparathyroidism in pregnant women should be discussed with a multidisciplinary team (MDT) because of the high risk of maternal and neonatal complications. The MDT should discuss preoperative imaging and type of parathyroid surgery, taking into consideration the benefits and risks of various imaging techniques on a case-by-case basis. The committee agreed that pregnant women should be referred for specialist care if needed.

The safety and efficacy of calcimimetics for pregnant women is largely unknown so the committee agreed that calcimimetics 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 multidisciplinary team 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 on managing primary hyperparathyroidism during pregnancy so the committee made a research recommendation to explore the use of different management strategies for primary hyperparathyroidism during pregnancy.

Information and support before and during pregnancy

There was no evidence available on information and support before and during pregnancy. The committee agreed that women should be reassured that there is no evidence to associate primary hyperparathyroidism with congenital abnormalities or developmental delay.

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 resource impact.

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

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Information and support

Recommendations 1.7.1 to 1.7.5

Why the committee made the recommendations

No evidence was found so the committee based the recommendations on their own experience and the experiences of the lay members and their patient networks. 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 have a resource impact.

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

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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 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, gastro-intestinal 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 and referral to secondary care. 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 resources

To find out what NICE has said on topics related to this guideline, see our web page on thyroid disorders.