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Predictors of post-thyroidectomy hypocalcaemia: a systematic and narrative review

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Abstract

Objective. Hypocalcaemia is the most common complication after total or completion thyroidectomy. This study assesses recent evidence on predictive factors for post-thyroidectomy hypocalcaemia in order to identify the patients affected and aid prevention.

Method. Two authors independently assessed articles and extracted data to provide a narrative synthesis. This study was an updated systematic search and narrative review regarding predictors of post-thyroidectomy hypocalcaemia using the Ovid Medline, Embase, Cochrane and Cinahl databases. Results were limited to papers published from January 2012 to August 2019.

Results. Sixty-three observational studies with a total of 210 401 patients met the inclusion criteria. The median incidence was 27.5 per cent for transient biochemical hypocalcaemia, 12.5 per cent for symptomatic hypocalcaemia and 2.2 per cent for permanent hypocalcaemia. The most frequent statistically significant predictor of hypocalcaemia was peri-operative parathyroid hormone level. Symptomatic hypocalcaemia and permanent hypocalcaemia were seen more frequently in patients undergoing concomitant neck dissection.

Conclusion. Many factors have been studied for their link to post-thyroidectomy hypocalcaemia, and this study assesses the recent evidence presented in each case.

Main Article

Ms A E L McMurran takes responsibility for the integrity of the content of the paper

The findings from an earlier version of this study were presented at the ENT Scotland Summer Meeting, 11 May 2018, Dunblane, Scotland, UK.

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Introduction

Hypocalcaemia is the most frequent complication seen after thyroid surgery.[1,2] The risk is related to parathyroid gland injury and is highest when there is intervention to both thyroid lobes. Patients therefore require routine monitoring after total or completion thyroidectomy and may require treatment with oral or intravenous calcium, which can prolong the in-patient stay. Furthermore, a proportion of those with initial post-operative hypocalcaemia will develop permanent hypocalcaemia, which requires lifelong monitoring and supplementation. Therefore, many researchers have sought to identify the predictors of post-thyroidectomy hypocalcaemia in order to prevent this complication and mitigate its effects.

The literature available on this topic has been the source of a previous comprehensive and high-quality systematic review by Edafe *et al.*[3] However, a considerable amount of research has been produced in the years since, and the importance of early identification and prevention of post-thyroidectomy hypocalcaemia has increased with the growth of thyroid cancer and surgery rates worldwide.[4,5] Furthermore, the group of patients receiving total thyroidectomy for thyroid cancer has changed since the publication of the British Thyroid Association Guidelines for the Management of Thyroid Cancer in 2014.[6] These guidelines advocated total thyroidectomy for patients with larger tumours (more than 4 cm) or with additional risk factors such as multifocal disease, bilateral disease, extrathyroidal spread or lymph node involvement. This group is likely to require more extensive and complex thyroid surgery and will therefore potentially experience a greater risk to the function of the parathyroid glands and an increased risk of post-operative hypocalcaemia.

The purpose of this review is not to challenge the previous findings published by Edafe *et al..*,[3] but to create a narrative synthesis of the updated evidence to augment the existing knowledge of the predictive factors of hypocalcaemia post-thyroidectomy. Furthermore, we intend to add new information regarding the specific issue of symptomatic hypocalcaemia, which was not covered separately in the previous review.

Materials and methods

A comprehensive literature search was conducted using the databases Medline, Embase (Ovid), Cinahl ('Cumulated Index to Nursing and Allied Health Care'; Ebsco collections) and the Cochrane Library, with results limited to papers published from January 2012 to August 2019. This was done in order to update the evidence presented previously in the systematic review by Edafe *et al.*,[3] where the literature was reviewed up to 30 July 2012, in

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Table 1. PICOS research question

PICOS category	Description
Participants	Patients with thyroid disease
Intervention	Total or completion thyroidectomy
Comparison	Post-operative normocalcaemia versus development of transient biochemical, symptomatic or permanent hypocalcaemia
Outcome	Predictive factors in the development of post-operative hypocalcaemia
Study design	Observational studies

PICOS = participant, intervention, comparison, outcome, study design

order to address our research question with reference to the participant, intervention, comparison, outcome, study design ('PICOS') system (Table 1).

The search terms used were 'low calcium' OR 'hypocalcaemia' AND 'thyroidectomy'. The final search was carried out on 31 August 2019. Inclusion and exclusion criteria were set to identify observational studies looking at predictive factors for the development of transient, symptomatic or permanent hypocalcaemia after total (including subtotal and near-total) or completion thyroidectomy. Full inclusion and exclusion criteria are shown in Table 2.

All titles and abstracts for the studies identified by the initial literature search were scrutinised for their relevance by two authors (AELM and RB). The full texts of all available relevant studies were reviewed independently by at least two authors (AELM, RB and VK). Data were independently extracted from papers that met the inclusion criteria using a piloted proforma. Any differences of opinion between authors regarding study eligibility or data extraction were discussed, and if dispute remained this was resolved by the primary author. Extracted data included study type, sample size, patient characteristics, definition(s) of hypocalcaemia (including transient biochemical hypocalcaemia, symptomatic hypocalcaemia and permanent hypocalcaemia) and evidence regarding predictive factors for post-thyroidectomy hypocalcaemia. Specifically, a record was made of every association between a predictive factor and any type of hypocalcaemia and the corresponding *p*-value, in order to identify which predictive factors had been studied and where the evidence was statistically significant. This information was then combined to produce a narrative review of the effects of different predictors across the recent literature.

The papers were assessed for methodological quality during data collection. They were rated according to a modified version of the Newcastle–Ottawa Scale score,[7] which is a validated assessment tool for quality features in non-randomised studies. This version was modified to assess these papers specifically, including the requirement for a specific definition for separate types of hypocalcaemia and information on the incidence of permanent hypocalcaemia, as was previously used in the systematic review by Edafe *et al.*[3] Studies of poor methodological quality, signified by a modified Newcastle–Ottawa Scale score of less than six stars[8] out of a total of nine were excluded from the analysis.

This systematic review was registered with International Prospective Register of Systematic Reviews ('PROSPERO'; registration number: CRD42018099510) and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') guidelines.[9]

Table 2. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Observational studies presented as full journal articles	Non-observational studies and studies presented as abstracts, conference proceedings and letters
Studies assessing factors associated with transient, symptomatic or permanent hypocalcaemia after total or completion thyroidectomy including subtotal or near-total thyroidectomy	Studies assessing other elements of calcium homeostasis post-thyroidectomy, including patients with pre-operative calcium abnormalities, patients with hypoparathyroidism and the use of calcium supplementation as prophylaxis or treatment. Studies including patients undergoing hemi-thyroidectomy
Published from January 2012 to August 2019	Published before January 2012
Published in English	Not published in English
Newcastle–Ottawa Scale score of ≥6	Newcastle–Ottawa Scale score of <6

Results

Literature search

An initial keyword search of the listed databases yielded 3888 articles in total. Duplicates were removed, and titles and abstracts were assessed for relevance, excluding 3743 articles. Of the remaining 145 relevant articles, 121 were available as full texts. The 24 literature search results excluded at this time included published abstracts, editorials or letters, rather than full article texts. As shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram (Figure 1), 63 of the full-text studies met inclusion and exclusion criteria and were analysed in full. A full list of included studies and their characteristics is found in Table 3.

The reasons for exclusion of the other 58 articles were: 18 included hemi-thyroidectomy, 12 studied post-thyroidectomy hypocalcaemia but made no assessment of predictive factors, 10 assessed management options for post-thyroidectomy hypocalcaemia, 7 were of poor methodological quality with a modified Newcastle–Ottawa Scale score of less than 6 stars, 6 looked at pre-operative calcium supplementation regimes and 5 were not in English.

Included study characteristics

The 63 included observational studies comprised 30 prospective and 33 retrospective studies with a total of 210 401 subjects. The sample size ranged from 34 patients to 192 333 patients. Study participants were predominantly female (173 690 female participants: 82.6 per cent). The mean age of study participants was 49.2 years, although the overall range in participants' ages was broad (range, 10–90 years). The majority of patients underwent total thyroidectomy (99.4%) with neck dissection in 67.3 per cent. Thyroid malignancy was the indication for surgery in 94.2 per cent of cases.

Quality features of included studies

There was a variety of methodological quality seen in this review, with a mean Newcastle–Ottawa Scale score of 7.3 stars (out of a total of 9 stars) across all 63 studies. Many studies received lower scores because they did not include

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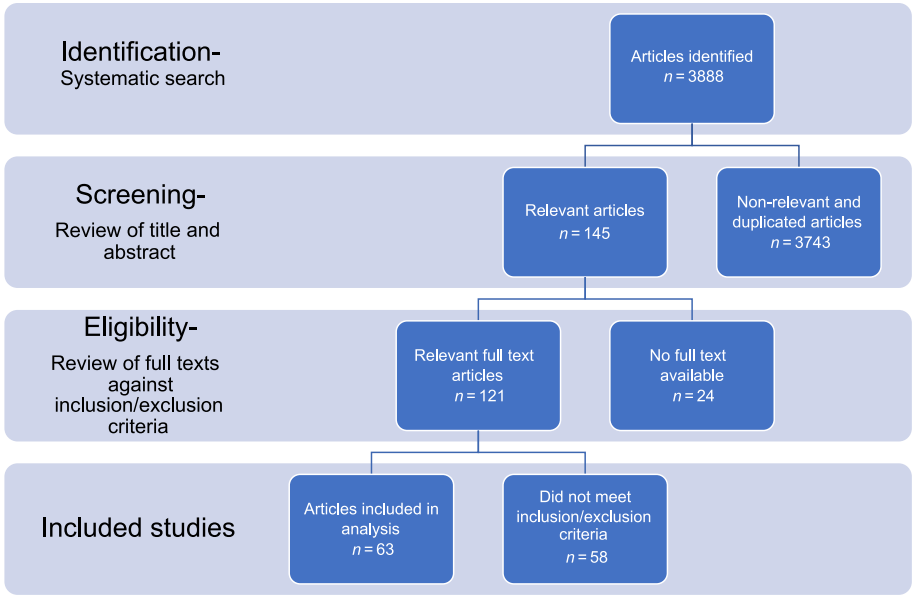


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') flow chart showing the literature search strategy for this study.

assessment of the incidence of permanent hypocalcaemia post-thyroidectomy or because there was no attempt to control for confounding factors such as the extent of thyroidectomy or concomitant neck dissection.

Definition and incidence of hypocalcaemia

Three separate types of post-thyroidectomy hypocalcaemia were described across the studies: these were transient biochemical hypocalcaemia, symptomatic hypocalcaemia and permanent hypocalcaemia. There was considerable variation in the definitions given for these subtypes of hypocalcaemia, particularly with the laboratory values considered to represent biochemical hypocalcaemia and the timing applied to the definition of permanent hypocalcaemia. The diagnosis of symptomatic hypocalcaemia was either based on the presence of symptoms alone or diagnosed in patients who had both symptoms and biochemical evidence of hypocalcaemia.

In the UK, the British Association of Endocrine and Thyroid Surgeons define post-thyroidectomy biochemical hypocalcaemia as a corrected calcium level of less than 2.10 mmol/l or ionised calcium of 1.2 mmol/l on day 1 post-operatively[2] to give a standard for comparison to use in their national audit report. In comparison, the studies included in this review defined biochemical hypocalcaemia variably as: serum total calcium of less than 7.5–8.5 mg/dl or less than 1.0–2.15 mmol/l; corrected calcium of less than 8.0–8.6 mg/dl or less than 1.90–2.10 mmol/l; or ionised calcium levels of less than 4.4 mg/dl or less than 1.0–1.18 mmol/l. In order to diagnose biochemical hypocalcaemia these measurements could be taken at a range of points from immediately post-operatively to 2 days post-operatively. However, the most frequently used definition was a corrected calcium level of less than 2.0 mmol/l or less than 8.0 mg/dl on day 1 post-operatively, which differs from the above definition given by the British Association of Endocrine and Thyroid Surgeons.

Generally, in this study we have accepted the definitions of hypocalcaemia given in each paper as valid in those populations, rather than trying to apply the British Association of Endocrine and Thyroid Surgeons definition retrospectively. Although we do recognise that these variations in hypocalcaemia definitions will have an effect on the reported incidence of post-thyroidectomy hypocalcaemia and therefore also the validity of any assessment of predictive factors, the standards given are roughly similar across the 57 studies. If anything, these standards represent stricter criteria for serum total, corrected or ionised calcium than those described in the definition from the British Association of Endocrine and Thyroid Surgeons.

There is a similar issue with the given definitions for permanent hypocalcaemia. Although some studies relate permanent hypocalcaemia to the need for ongoing calcium with or without vitamin D supplementation at six months as described by British Association of Endocrine and Thyroid Surgeons,[2] others have set three months or one year as the time limit. We acknowledge that this too will affect the reliability of the results, but in general the definitions used do all give an impression of longer term post-operative hypocalcaemia, and we have therefore compared these across the board according to the local standards set.

A wide range was also seen in the incidence of each subtype of hypocalcaemia described across the studies. Transient biochemical hypocalcaemia was found in a median of 27.5 per cent of 16 410 patients across 52 studies, but there is a range of incidence from 3.2 to 82.6 per cent. Symptomatic hypocalcaemia is found in a median of 12.5 per cent of 4706 patients across 26 studies, with a range of incidence from 0 to 50 per cent. Permanent hypocalcaemia was seen in a median of 2.2 per cent of 199 165 patients over 27 studies, with a range of 0 to 14.5 per cent (Figure 2).

Predictors of post-thyroidectomy hypocalcaemia

In total, the 63 studies included in the analysis assessed the association between transient biochemical, symptomatic and permanent post-thyroidectomy hypocalcaemia and 45 separate predictors. These predictors may be grouped as follows: biochemical factors (e.g. post-operative parathyroid hormone (PTH) level); surgical factors (e.g. total thyroidectomy versus completion thyroidectomy); patient factors (e.g. sex); and miscellaneous factors (e.g. season). Overall, 30 of these predictors showed a statistically significant association with post-thyroidectomy and hypocalcaemia in at least one study. Table 4 lists the studies where the association between a predictive factor and hypocalcaemia was studied, based on type of predictive factor.

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Table 3. Characteristics of included studies

Author & Year	Prospective or retrospective	Sample size (*n*)	Newcastle–Ottawa Scale score
Abdel-Halim *et al.* 2015[63]	Retrospective	69	8
Abdollahi *et al.* 2017[10]	Retrospective	57	6
Al-Khatib *et al.* 2014[11]	Retrospective	213	6
Alparslan Yumun *et al.* 2016[12]	Prospective	49	7
Al-Qahtani *et al.* 2014[13]	Retrospective	149	6
Ambe *et al.* 2014[66]	Retrospective	305	7
Aqtashi *et al.* 2017[39]	Retrospective	34	6
Blanchard *et al.* 2017[67]	Prospective	1350	9
Blanchard *et al.* 2019[68]	Prospective	1310	8
Bove *et al.* 2014[14]	Prospective	96	6
Chapman *et al.* 2012[15]	Retrospective	52	7
Chereau *et al.* 2017[58]	Prospective	48	9
Cherian *et al.* 2015[16]	Retrospective	150	7
Cherian *et al.* 2016[17]	Prospective	50	7
Chen *et al.* 2018[53]	Retrospective	469	7
Chisthi *et al.* 2017[18]	Prospective	100	6
Christou *et al.* 2019[59]	Prospective	1329	9
Danan & Shonka 2017[34]	Retrospective	67	6
De Palma *et al.* 2015[60]	Prospective	1846	6
Docimo *et al.* 2017[46]	Prospective	328	9
Edafe *et al.* 2014[19]	Retrospective	238	9
Falch *et al.* 2018[52]	Retrospective	702	9
Falcone *et al.* 2015[54]	Retrospective	264	7
Garrahy *et al.* 2016[20]	Retrospective	201	8
Godazandeh *et al.* 2015[69]	Prospective	125	7
Griffin *et al.* 2014[55]	Retrospective	121	7
Hammerstad *et al.* 2013[35]	Prospective	40	8
Inversini *et al.* 2016[21]	Retrospective	260	7
Islam *et al.* 2012[37]	Prospective	65	6
Kala *et al.* 2015[22]	Prospective	100	6
Kaleva *et al.* 2015[47]	Retrospective	64	7
Kalyonou *et al.* 2013[56]	Retrospective	190	9
Karatzanis *et al.* 2018[23]	Prospective	100	7
Kim *et al.* 2013[64]	Prospective	108	6
Kobayashi *et al.* 2014[44]	Retrospective	109	6
Lang *et al.* 2012[24]	Prospective	117	8
Lang *et al.* 2013[25]	Prospective	281	6
Lecerf *et al.* 2012[40]	Prospective	137	7
Lee *et al.* 2014[70]	Retrospective	205	7
Lee *et al.* 2015[42]	Prospective	134	7
Luo *et al.* 2017[43]	Retrospective	304	7
Mascarella *et al.* 2015[62]	Retrospective	810	8
Mehrvarz *et al.* 2014[36]	Prospective	99	7
Merchavy *et al.* 2015[57]	Retrospective	214	8
Miah *et al.* 2015[71]	Retrospective	225	8
Nair *et al.* 2013[38]	Prospective	806	9

(*Continued*)

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Table 3. (*Continued.*)

Author & Year	Prospective or retrospective	Sample size (*n*)	Newcastle–Ottawa Scale score
Nhan *et al.* 2012[72]	Retrospective	139	7
Noureldine *et al.* 2014[26]	Retrospective	304	8
Ozogul *et al.* 2014[61]	Retrospective	196	8
Paliogiannis *et al.* 2014[48]	Retrospective	102	6
Pisanu *et al.* 2013[27]	Prospective	112	8
Pradeep *et al.* 2013[28]	Prospective	145	8
Puzzielo *et al.* 2015[41]	Retrospective	75	7
Raffaelli *et al.* 2015[29]	Retrospective	1504	6
Reddy *et al.* 2016[45]	Prospective	100	8
Salinger & Moore 2013[30]	Prospective	111	6
Seo *et al.* 2015[31]	Retrospective	349	9
Seo *et al.* 2016[65]	Retrospective	192 333	9
Sheahan *et al.* 2013[50]	Prospective	126	8
Sung *et al.* 2016[32]	Prospective	237	8
Tongol & Mirasol 2016[49]	Retrospective	242	6
Vanderlei *et al.* 2012[51]	Prospective	40	6
White *et al.* 2015[33]	Prospective	196	6

Predictors of transient biochemical hypocalcaemia

Transient biochemical hypocalcaemia was the most frequently studied outcome in the included studies. The most frequently reported predictive factors were biochemical, with most specifically relating to PTH levels. Low post-operative PTH was found to have a statistically significant association with transient biochemical hypocalcaemia in 24 studies,[10–33] compared with 3 studies where there was not a statistically significant result[34–36]. Low intra-operative PTH levels and a larger differential PTH from the pre-operative to post-operative stage were also seen to have statistically significant associations in 2 studies[37,38] and 13 studies[10,12,14,15,22,23,27,29,31,36,39–41], respectively. Pre-operative PTH showed a non-significant association with transient biochemical hypocalcaemia in the majority of studies.[10,12,15,19,22,23,29,31,34–37,39,40,42,43]

Low post-operative calcium was the only other commonly assessed biochemical factor that showed a statistically significant positive association with transient biochemical hypocalcaemia in the majority of studies.[12,13,22–24,27,28,31,32,36,37,39,44,45] Positive associations were shown with post-operative calcitonin and post-operative albumin but in only one study.[18] Pre-operative vitamin D, magnesium, phosphate, creatinine, calcitonin and thyroid-stimulating hormone levels showed non-significant associations in the majority of studies where investigated. Alkaline phosphatase, albumin and T3 and T4 levels showed equivocal results from a limited number of studies.

Two surgical factors related to the parathyroid glands showed repeated significant associations with transient biochemical hypocalcaemia. These included an increasing

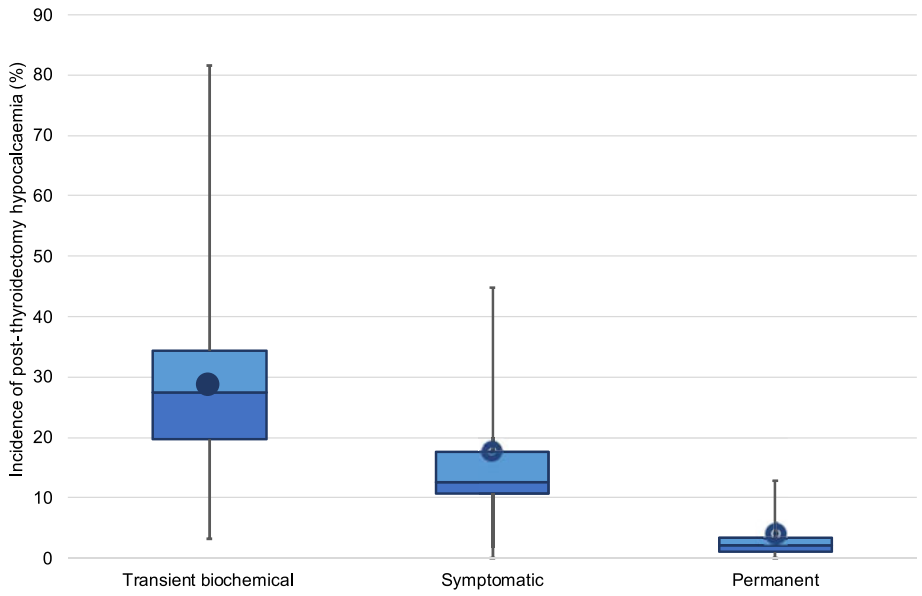


Fig. 2. A box and whisker chart showing incidence of hypocalcaemia post-thyroidectomy. This demonstrates the values for minimum and maximum (whiskers), interquartile ranges (boxes), median (line dividing boxes) and mean (circular data marker) regarding the incidence of post-thyroidectomy hypocalcaemia for each subtype of hypocalcaemia, across the included studies.

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number of parathyroid glands left in situ at the time of surgery (significant results in four of four studies[18,28,32,34]), and evidence of parathyroid glands in the pathology specimen (8 significant results from 12 studies)[20,33,38,42,46–49]. However, other surgical factors related to the parathyroid glands do not demonstrate the same connection; a higher number of parathyroid glands identified during the procedure was more frequently not statistically significant (six of nine results were not significant[31,34,40,43,50,51]) and equivocal results were seen when parathyroid glands are auto-transplanted (nine results significant[19,20,33,38,42,47–49,52], eight non-significant[19,30,50,53–57]). Similarly, the majority of studies which addressed the connection between transient biochemical hypocalcaemia and the extent of thyroidectomy and with neck dissection did not find a statistically significant association.

Patient factors including sex, age and indication for surgery showed generally non-significant results across the board. Age specifically gave a number of conflicting results. In six studies, age was found to have a statistically significant association with transient biochemical hypocalcaemia,[12,26,30,33,46,47] with four papers reporting this only in younger patients[12,26,30,33] and two papers reporting significance in older patients.[46,47] This is in comparison to 26 studies[11,16–19,24,25,27–29,31,32,38–40,42–44,49,52,54,56,58–61] that found no significant association to age.

Interestingly, several patient factors that were not frequently studied showed significant results, including one study highlighting the association between transient biochemical hypocalcaemia post-thyroidectomy and previous bariatric surgery, particularly Roux-en-Y surgery.[58] However, it should be noted that five studies[18,30,39,42,46] showed no significant relationship between having a higher body mass index and post-thyroidectomy hypocalcaemia. Another single paper assessed the connection with season and found that patients who underwent thyroidectomy in winter developed biochemical hypocalcaemia more frequently than those who had their operation in the summer months.[62]

Post-thyroidectomy symptomatic hypocalcaemia predictors

Symptomatic hypocalcaemia was investigated in 13 of the 63 studies. Biochemical predictors most frequently showed a statistically significant association, though in comparison with transient biochemical hypocalcaemia, there was now an association seen at pre-operative[30,43], intra-operative[18,45], post-operative[11,30,33,45,51,63,64] stages and differential PTH levels.[36,43,51] Post-operative calcium also presented a significant association in the majority of studies.[28,51,63] The majority of studies assessing other biochemical factors (vitamin D, pre-operative magnesium and pre-operative phosphate) showed non-significant results.

Total thyroidectomy is seen to have an equivocal association with symptomatic hypocalcaemia. However, neck dissection demonstrates a significant association in three studies.[20,33,46] Parathyroid gland factors are not seen to be as closely associated with symptomatic hypocalcaemia as with transient biochemical hypocalcaemia. Parathyroid gland auto-transplantation and parathyroid tissue found in the specimen were more frequently associated with non-significant results, and the issue of how many parathyroid glands are left in situ was not studied in relation to symptomatic hypocalcaemia. Patient factors including age, sex and indication for surgery continue to show a majority of non-significant results.

Permanent hypocalcaemia predictors

Out of the 63 studies, 9 included assessed predictors of permanent hypocalcaemia. Biochemical factors showed the most frequent significant associations, including intra-operative factors, post-operative factors and differential PTH. Pre-operative PTH levels and post-operative calcium levels did not follow this pattern.[35]

Neck dissection was the only clear statistically significant surgical predictor of permanent hypocalcaemia.[20,55,65] Parathyroid gland factors were generally not studied in relation to permanent hypocalcaemia. Furthermore, there remains no evidence for a statistically significant association with either age or sex.

Discussion

Summary of main results

This systematic review highlights the large number of factors that have been studied in relation to the development of post-thyroidectomy hypocalcaemia in the recent literature. Specifically, it corroborates the evidence presented by the previous review by Edafe *et al.*, which shows biochemical factors represent the most reliable predictors for both transient biochemical and permanent post-thyroidectomy hypocalcaemia.[3] However, this review also presents the evidence on symptomatic hypocalcaemia, which has more clinical relevance for patients and clinicians.

Narrative review of biochemical factors

Parathyroid hormone levels were the most frequently examined biochemical factors in the development of post-thyroidectomy hypocalcaemia. A significant association was shown between PTH and transient biochemical hypocalcaemia in 38 studies, between PTH and symptomatic hypocalcaemia in 14 studies, and between PTH and permanent hypocalcaemia in 4 studies. Generally, the intra-operative, post-operative and differential measures of PTH, but not pre-operative PTH levels, were frequently shown to have this association to all forms of post-operative hypocalcaemia.

It is difficult to comment on the most useful predictive cut-off point for post-operative PTH levels because these were expressed in several different measurements at different time points including PTH levels less than 17 ng/ml at skin closure,[24] less than 1.15 pmol/l at 1 hour post-operatively[13] or less than 12.1 pg/ml at 6 hours post-operatively.[27] However, measurement of PTH levels at skin closure or immediately post-operatively creates logistical issues in many settings, and it is valuable to note that generally any low post-operative PTH result is associated with post-thyroidectomy hypocalcaemia. For example, where post-operative PTH levels are less than 8 pg/ml, a patient is 5.08 times more likely to develop transient biochemical hypocalcaemia than if the levels are more than 8 pg/ml.[16] To overcome the issues with measurement differences across studies, one can look at the ratio of pre-operative to post-operative PTH levels, where there is evidence showing that a ratio of less than 0.253[12] or a reduction in PTH of more than 44 per cent[15] or more than 61 per cent[36] is predictive of transient biochemical hypocalcaemia. Furthermore, a reduction in PTH levels by more than 62 per cent can give a sensitivity and specificity of 100 per cent for the development of transient biochemical hypocalcaemia at day 2.[41]

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Pre-operative calcium levels have not been shown to accurately predict post-operative hypocalcaemia in the majority of these reviewed studies, in contrast to the findings of Edafe *et al*.[3] In comparison, low post-operative calcium levels are shown to have a significant association with transient biochemical and symptomatic hypocalcaemia but not permanent hypocalcaemia. It may be difficult to see how low post-operative calcium levels may be used to predict low post-operative calcium levels, though generally the studies analysed showed how an early fall in the post-operative calcium (i.e. the first 12 hours[28]) predicted ongoing hypocalcaemia in the post-operative period[12,13,22,24,27,28,31,32,36,37,49] and the severity of hypocalcaemia, in terms of the need for treatment.[28,51,63]

This review presents further evidence that other biochemical factors including vitamin D, peri-operative magnesium, post-operative phosphate, alkaline phosphatase, creatinine, calcitonin, albumin and thyroid hormone levels do not show statistically significant associations with post-operative hypocalcaemia in the majority of studies reviewed. These predictive factors are less frequently studied and therefore it is difficult to draw firm conclusions from the scant evidence available. Meta-analysis techniques could have been applied to make these conclusions, but as a result of the great heterogeneity of definitions for hypocalcaemia and each predictive factor examined in these non-randomised studies, it would be hard to interpret the validity of the result.

Narrative review of surgical factors

One might assume that total thyroidectomy would have an association with post-operative hypocalcaemia because any temporary damage to parathyroid glands happens in the same operation, in comparison to damage caused by an initial hemithyroidectomy and a later completion thyroidectomy. However, this review presents evidence that the extent of thyroid surgery has only an equivocal effect on the incidence of symptomatic hypocalcaemia, with little evidence for an association with either transient or permanent hypocalcaemia.

Similarly, neck dissection could reasonably be assumed to affect the parathyroid glands more than no dissection. However, in the studies analysed the addition of neck dissection to thyroid surgery shows an association with symptomatic and permanent hypocalcaemia only and not with transient biochemical hypocalcaemia.

This then leads to the complex information presented in relation to parathyroid gland surgical factors. Although there is clear evidence that parathyroid gland tissue found in the pathology specimen confers a higher risk of post-operative transient hypocalcaemia, the risk is also increased when a larger number of parathyroid glands are left in situ. This situation may be explained by noting that parathyroid glands left in situ potentially have a compromised blood supply as a result of their dissection. However, when the number of parathyroid glands identified was considered separately there were more non-significant associations with transient biochemical hypocalcaemia. Therefore, we can see that parathyroid gland factors are clearly closely associated with transient biochemical hypocalcaemia post-thyroidectomy, but not in an easily understood, or preventable way.

Parathyroid gland factors were studied less frequently in relation to symptomatic hypocalcaemia and permanent hypocalcaemia. Equivocal results are seen linking symptomatic hypocalcaemia to the number of parathyroid glands identified and also linking permanent hypocalcaemia to cases where parathyroid tissue was present in the specimen. This is surprising given the weight of evidence that links these factors to transient biochemical hypocalcaemia and because parathyroid gland damage or hypofunction is considered to be the main underlying pathogenesis of post-thyroidectomy hypocalcaemia as a whole.

Further surgical factors offer little to explain the difference, with prolonged operating times (more than 120 minutes)[12,24,25,40,44,46,49,52,61,66], the experience of the surgeon[19,51,61] and the surgical devices used[46,60,67] showing no overall association with post-thyroidectomy hypocalcaemia.

Narrative review of patient factors

Throughout the studies analysed, there is repeated evidence that patient age and sex are not reliably associated with post-thyroidectomy hypocalcaemia. Similarly, there are mostly non-significant associations with the indication for thyroidectomy, including malignancy, hyperthyroidism and Graves' disease. These indications may be more predictive of permanent hypocalcaemia.

Narrative review of miscellaneous factors

This review highlights several areas of novel research regarding the predictive factors for post-thyroidectomy hypocalcaemia. This includes the statistically significant associations between patients who have their surgery in the winter months, and those with a past medical history of bariatric surgery, which allows clinicians to recognise the potential increased risk in their patient population.

Evidence quality and potential biases

This review is based solely on non-randomised studies published in the English language; however, their Newcastle–Ottawa Scale scores of more than six stars show that these studies are of good methodological quality and therefore the evidence presented has reasonable quality and reliability. Literature in other languages was excluded due to the practical issues of managing the large number of results generated by the research question. This does introduce bias in the results, though we believe this is limited by the large number of included studies, combining results from over 200 000 patients. Publication bias may also play a role; however, the evidence from Table 4 would suggest that most studies reported information on predictors with no statistically significant association, meaning that this evidence was not lost.

The issues associated with the definition of hypocalcaemia have been discussed, and this limited the assessment of specific predictive factors by preventing useful application of meta-analysis techniques. Furthermore, although the inclusion criteria allow for data from all patients undergoing total or completion thyroidectomy, the indication for the majority of surgical procedures was malignancy. Specifically, this leads to an increased number of patients undergoing concurrent neck dissection, which is an important predictor of symptomatic and permanent hypocalcaemia. However, thyroid malignancy is the most frequent indication for total and completion thyroidectomy generally, and this bias applies to the population as a whole.

The quality of information presented is also poorer where very few papers assess a specific predictive factor. Here the difference of a few patients developing non-clinically relevant

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Table 4. Predictive factors in the development of post-thyroidectomy hypocalcaemia

	Transient biochemical hypocalcaemia				Symptomatic hypocalcaemia				Permanent hypocalcaemia			
	Significant	Total	Non-significant	Total	Significant	Total	Non-significant	Total	Significant	Total	Non-significant	Total
Biochemical predictive factors												
Calcium												
– Pre-operative calcium	10,19,24,29,31,39,45,58	8	11,12,22,23,25,32,34,35,36,42,44,46,47,58	14	28,45	2	11,46,51,63	4	–	0	31,35	2
– Post-operative calcium	12,13,22,23,24,27,28,31,32,36,37,39,44,49	14	33,35,46,47	4	28,51,63	3	33,46	2	35	1	31	1
PTH												
– Pre-operative PTH	11,18,26,30	4	10,12,15,19,22,23,29,31,34,35,36,37,39,40,42,43	16	30,43	2	51	1	–	0	35	1
– Intra-operative PTH	37,38	2	43	1	18,45	2	–	0	38	1	–	0
– Post-operative PTH	10,11,12,13,14,15,16,17,18,19,20,21,22,23,24, 25,26,27,28,29,30,31,32,33	24	34,35,36	3	13,30,45,51,63,64,72	7	20,28	2	31,35	2	12	1
– Differential PTH	10,12,14,15,22,23,27,29,31,36,39,40,41,52	13	34,43	2	36,43,51	3	–	0	31	1	–	0
Vitamin D												
– Pre-operative vitamin D	11,28,61	3	16,20,25,26,29,30,34,35,42,54,55,58,63,69,72	15	11,28	2	20,30,51	3	–	0	35,55	2
Magnesium												
– Pre-operative magnesium	20,43	2	17,29,35	3	43	1	11,20	2	–	0	35	1
– Post-operative magnesium	20	1	17,29,35	3	64	1	–	0	20	1	35	1
– Differential magnesium	–	0	35	1	–	0	–	0	–	0	35	1
Phosphate												
– Pre-operative phosphate	–	0	29,35,43,44,46	5	–	0	43,46	2	–	0	35	1
– Post-operative phosphate	–	0	29,35,46	3	35	1	46	1	–	0	35	1
Alkaline phosphatase	71	1	47	1	–	0	–	0	–	0	–	0
Creatinine	–	0	47	1	–	0	–	0	–	0	–	0
Calcitonin												
– Pre-operative calcitonin	–	0	18	1	–	0	–	0	–	0	–	0
– Post-operative calcitonin	18	1	–	0	–	0	–	0	–	0	–	0
Albumin												
– Pre-operative albumin	18	1	25	1	–	0	–	0	–	0	–	0
– Post-operative albumin	18	1	–	0	–	0	–	0	–	0	–	0
Thyroid hormones												
– Pre-operative TSH	–	0	12,18,24,25,28,35,44	7	–	0	–	0	–	0	35	1
– Post-operative TSH	–	0	35	1	–	0	–	0	–	0	35	1
– Pre-operative T3	44	1	18	1	–	0	–	0	–	0	–	0
– Pre-operative T4	44	1	18	1	–	0	–	0	–	0	–	0
Surgical predictive factors												
Total versus completion thyroidectomy	31,56,57,60	4	17,19,43,47,49,54,55	7	45,64	2	43,63	2	–	0	31,56	2
Neck dissection	20,31,33,34,46,60	6	16,19,26,32,39,40,42,43,47,49,54,55,56	13	20,33,46	3	43,45	2	20,55,65	3	31	1
Parathyroid gland factors												

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– Number of parathyroid glands identified	24,25,61	3	31,34,40,43,50,51	6	45,50	2	43,63	2	–	0	–	0
– Number of parathyroid glands left in situ	18,28,32,34	4	–	0	–	0	–	0	–	0	–	0
– Number of parathyroid glands auto-transplanted	19,20,33,38,42,47,48,49,52	9	19,30,50,53,54,55,56,57	8	–	0	43,51	2	–	0	20,52	2
– Parathyroid tissue in pathology specimen	20,33,38,42,46,47,48,49	8	34,43,50,57	4	46	1	20,30,50,63	4	38	1	20	1
Intra-operative factors												
– Surgical devices used	–	0	46,60,67	2	–	0	–	0	–	0	67	1
– Division of the inferior thyroid vein	70	1	–	0	70	1	–	0	–	0	–	0
– Blood loss	–	0	12,24,25,44,52,61	6	–	0	–	0	–	0	52	1
– Operative time >120 minutes	24,25,46,52	4	12,40,44,49,61,66	6	46	1	66	1	52	1	12,66	2
Thyroid specimen weight	32	1	12,19,20,24,25,44,49,52,58	9	–	0	20	1	–	0	20,52	2
Surgical experience	–	0	19,37,49	3	–	0	–	0	–	0	–	0
Patient predictive factors												
Age	12,26,30,33,46,47	6	11,16,17,18,19,24,25,27,28,29,31,32,38, 39,40,42,43,44,49,52,54,56,58,59,60,61	26	30,46	2	11,28,33,43,45,51,63,64	8	–	0	38,52,59	3
Sex	26,43,46,52,60,61	6	11,12,15,16,17,19,20,24,25,27,28,29,30,31, 32,33,38,39,40,42,44,47,49,54,56,58	26	30,46	2	11,28,33,43,45,51,63,64	8	–	0	20,38,52	3
Ethnicity	26	1	19	1	–	0	–	0	–	0	–	0
Body mass index	–	0	18,30,42,46,52	5	63	1	30	1	–	0	–	0
Previous bariatric surgery	58	1	–	0	–	0	–	0	–	0	58	1
Indication for thyroidectomy												
– Malignant versus benign	20,26,46,47,58,60	6	11,12,19,24,29,30,33,40,43,50,55,56,57	13	20,46	2	11,30,43,45,63,65	6	20	1	52	1
– Hyperthyroidism	38,56	2	16,17,20,29,43,50,55,61	8	–	0	20,43,45,50	50	38	1	20	1
– Graves' disease	24,72	2	20,55,47,71	4	–	0	20	1	38	1	20	1
– Goitre	–	0	20,29,38	3	–	0	–	0	–	0	–	0
– Thyroiditis	25	1	24,38,43,47	4	–	0	43,45	2	–	0	–	0
– Extra-thyroid extension	–	0	32	1	–	0	–	0	–	0	–	0
Miscellaneous predictive factors												
Season	62	1	–	0	–	0	62	1	–	0	–	0

This table lists the reference number of each paper where the association between the named predictive factor and hypocalcaemia is studied, according to whether the result was statistically significant or not statistically significant. For ease of understanding, the total number of either significant or non-significant associations among the included studies is listed for each predictive factor. PTH = parathyroid hormone; TSH = thyroid stimulating hormone

biochemical hypocalcaemia may be considered as important as factors that are shown to have significant associations in multiple studies. However, to prevent such misunderstandings we have presented the information on all the predictors assessed in the reviewed studies in Table 4. The information in Table 3 details each study's sample size and Newcastle–Ottawa Scale rating, so that readers can understand where the evidence is strongest.

Implications for clinical practice

This review highlights several factors clearly linked to post-thyroidectomy hypocalcaemia; however, it is disappointing that although these factors may be assessed to predict hypocalcaemia they cannot necessarily be manipulated in order to prevent it. However, it is hoped that this evidence will highlight the issue of post-thyroidectomy hypocalcaemia and its effect on patients in both the short and long term therefore reinforcing the importance of routine monitoring of calcium levels after total and completion thyroidectomy. The authors also note the growing practice of pre-operative vitamin D administration to patients considered to be at high risk of post-thyroidectomy hypocalcaemia and hope that this review may offer further evidence about the patients most likely to be affected. This study also offers further evidence that PTH levels are perhaps one of the most reliable predictors of all forms of post-thyroidectomy hypocalcaemia. The authors recommend that PTH levels are evaluated in the routine blood tests after total and completion thyroidectomy in order to identify patients who are likely to have an ongoing issue with hypocalcaemia.

Implications for research

This systematic review demonstrates the large amount of evidence available on transient biochemical hypocalcaemia post-thyroidectomy, but it is not able to show the same level of research into symptomatic or permanent hypocalcaemia, which are arguably more important to patients and clinicians alike. We would therefore suggest that further research should focus more on the reasons why patients develop symptomatic or permanent hypocalcaemia post-thyroidectomy.

- Many factors have been studied in the evaluation of post-thyroidectomy hypocalcaemia
- This review summarises the evidence published in the literature from 2012 to 2019
- Biochemical factors, such as post-operative parathyroid hormones, offer the best means of predicting transient biochemical hypocalcaemia, symptomatic hypocalcaemia and permanent hypocalcaemia
- Surgical factors involving the identification and preservation of the parathyroid glands also demonstrate a relationship to transient biochemical post-thyroidectomy hypocalcaemia, but in a less predictable manner
- Concomitant neck dissection is found to be a repeated predictor for symptomatic and permanent hypocalcaemia

Conclusion

This updated systematic and narrative review offers further evidence on the incidence and predictors of post-thyroidectomy hypocalcaemia. It shows a large variety in the incidence of hypocalcaemia in the international literature. In keeping with the previous review, it shows that the measurement of biochemical factors such as PTH offers the best means of identifying patients who will develop transient biochemical hypocalcaemia. Issues surrounding the identification and preservation of parathyroid glands intra-operatively also affect the development of this post-operative complication, but in a less predictable way.

This review has also separately assessed the evidence available on symptomatic hypocalcaemia, showing that this too may be predicted by biochemical factors like PTH and post-operative calcium level, but that there is a closer relationship to surgical factors including neck dissection and parathyroid gland factors than is seen with transient biochemical hypocalcaemia.

The evidence relating to the development of permanent hypocalcaemia post-thyroidectomy has shown fewer clear predictors. PTH again is seen to have a close connection, but otherwise only neck dissection shows a statistically significant association in the majority of studies.

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