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ORIGINAL ARTICLE

Huge variations in definition and reported incidence of postsurgical hypoparathyroidism: a systematic review

Torben Harsløf[1] · Lars Rolighed[2] · Lars Rejnmark[1]

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Abstract

Purpose The reported incidence of post surgical hypoparathyroidism (HypoPT) varies greatly. Previous research suggests that the definition of HypoPT is not consistent in the literature. We therefore conducted a systematic review to investigate how HypoPT is defined and whether this definition, as well as the selected threshold for hypocalcemia affects the incidence.

Methods Using a predefined search string we identified all articles in PubMed reporting on the incidence of postsurgical HypoPT from 1st January 2010 to January 2017.

Results We identified 89 articles that employed 20 different definition of HypoPT. The incidence of HypoPT varied from 0.0% to 20.2%. The definitions were not associated with incidence of HypoPT. Use of prophylactic post-operative calcium supplements, however decreased the risk of HypoPT ($p = 0.03$), and there was a trend towards a lower risk of HypoPT when using a definition of hypocalcemia below lower limit of the reference range ($p = 0.09$).

Conclusion The large number of definitions of HypoPT, as well as the huge variation in incidence point to a problem suggests that the awareness of HypoPT should be raised. Use of prophylactic post-operative calcium supplements may decrease risk of HypoPT. This, however, may be due to reverse causality as awareness of the risk of HypoPT may promote the use of calcium supplementation.

Keywords Hypoparathyroidism · Permanent · Definition · Incidence

Background

Hypoparathyroidism is most commonly a consequence of surgery on the neck—in particular total thyroidectomy [1]. Postsurgical hypoparathyroidism is either transient or permanent depending on whether the hypocalcemia subsides within a given period. At present, permanent hypoparathyroidism is defined by both American and European experts as a disease in which the production of parathyroid hormone (PTH) is inadequate to maintain a normal plasma calcium level more than six months after surgery [2, 3].

The reported frequency of permanent hypoparathyroidism (HypoPT) and hypocalcemia varies greatly in the literature from 0.0% to 17.4% [4, 5] and appears to depend on factors such as surgeon's experience [6], reason for surgery (e.g., goiter, thyroid cancer, Graves' disease) [7], and surgical technique [8]. In a recent paper, however, Mehanna et al. showed, that the definition of hypoparathyroidism is of major importance to the reported incidence of the disease. In the paper the authors employed 10 different definitions of permanent hypoparathyroidism described in the literature and found that the incidence subsequently varied from 0.9% to 4.4% [9]. None of the definitions complied with the one from the endocrine societies. Given this, as well as the large number of definitions used and the great variability in the reported incidence, we conducted a systematic literature search in order to analyze the definitions used and their impact on the reported frequency of permanent hypoparathyroidism as a complication to neck surgery.

Methods

We conducted a systematic literature search using Pubmed in January 2017. We first used the search terms

✉ Torben Harsløf
torbhars@rm.dk

[1] Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark

[2] Department of Otorhinolaryngology, Aarhus University Hospital, Aarhus, Denmark

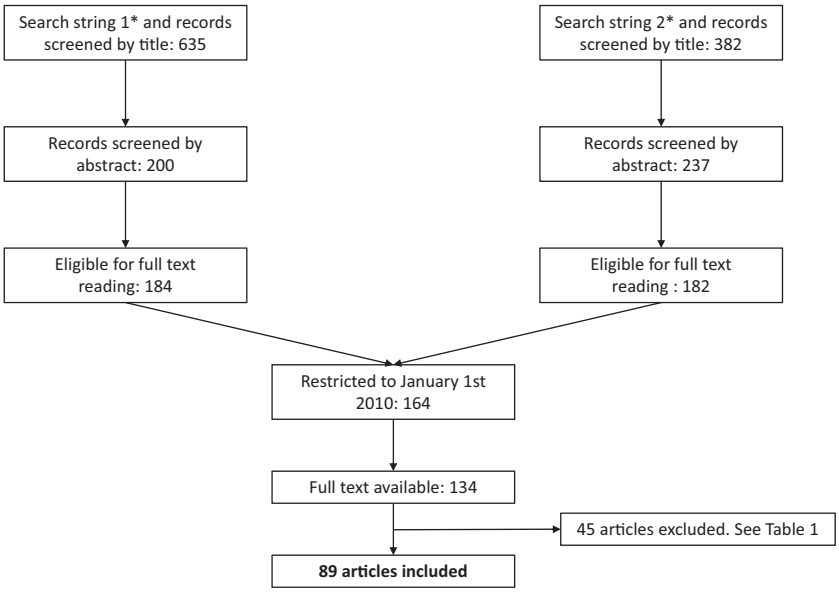

Fig. 1 Flowchart depicting the selection proces for inclusion of manuscripts in the article

"hypoparathyroidism AND surgery AND thyroid* AND persistent", "hypoparathyroidism AND surgery AND thyroid* AND chronic", "hypoparathyroidism AND surgery AND thyroid* AND permanent", and "hypoparathyroidism AND surgery AND thyroid* AND incidence". The asterisk (*) denotes that the term was truncated and that all endings of the word were included in the search. We then combined the results of these searches using the operator "OR" and the limits "human" and "English" and retrieved 635 papers. Next, we screened the titles and abstracts and ended up with 184 papers (Fig. 1).

Then we conducted a new search with the terms "hypocalcemia AND surgery AND thyroid* AND persistent", "hypocalcemia AND surgery AND thyroid* AND chronic", "hypocalcemia AND surgery AND thyroid* AND permanent", and "hypocalcemia AND surgery AND thyroid* AND incidence" and combined the results as described above. We retrieved another 382 titles that were reduced to 237 after having read the titles and again to 182 after having read the abstracts. In total, we then had 366 papers and included only those from 1st January 2010. This gave us 164 articles of which we could get a full manuscript from 134 articles. We finally excluded case series with fewer than 20 patients and articles in selected groups of patients as shown in Table 1. We excluded these articles to secure validity of data (exclusion of questionnaire-based papers and multiple publications from same cohort) and to make data across studies most comparable and thereby minimize bias. The inclusion of papers concerning complicated patients (e.g., obese patients or substernal goiter) might introduce bias if certain definitions pertained to certain complicated groups of patients. After this, we had a final sample of 89 articles [4–8, 10–93]. Author T.H. performed the literature search and retrieved data from all 89 articles and either author L.Ro. or L.Re. adjudicated the findings.

Table 1 List of types of papers that were excluded from the study

Types of excluded papers
Papers concerning children only
Papers concerning multiple endocrine neoplasia only
Papers concerning obese patients only
Papers concerning substernal goiter only
Papers concerning endoscopic surgery only
Reviews and meta-analyses
Papers concerning reoperations
If total thyroidectomies could not be clearly distinguished form other types of thyroidectomy
Articles based on questionnaires
Multiple papers from same cohort

For the data analysis we considered only patients who had undergone total thyroidectomy. Accordingly, in papers reporting different types of thyroidectomy only data on total thyroidectomy was extracted. If necessary, we calculated the prevalence of HypoPT ourselves (see Table 1).

Evidently, different investigators have used a large number of different definitions of HypoPT. For data analysis we therefore clustered these many definitions by constructing a hierarchical definition and accommodated each of the different definitions we found into this Table 2.

Statistics

To evaluate the effect of certain parameters on the prevalence of HypoPT we used ANOVA. As the incidence of

Table 2 Hierarchic definition of permanent hypoparathyroidism

Hierarchic definition of permanent hypoparathyroidism			No. of papers
1	The correct definition	Most accurate definition	0
2	Hypocalcemia		33
3	Symptomatic hypocalcemia or marked (asymptomatic) hypocalcemia (>10% below lower reference level)		11
4	Low PTH (with or without need for treatment)		27
5	ICD diagnosis code		2
6	No definition	Least accurate definition	16

The hierarchical order was defined so that one is the most correct definition and six the least correct definition. All included papers in the study were accomodated into one of the hierarchic definitions based on authors´ judgment.

HypoPT was not normally distributed, data was log-transformed. To subsequently display the data we calculated the exponential value and obtained medians with 95% confidence intervals (CI). Level of significance was 0.05 and we performed all calculations using SPSS version 24.

Results

In the 89 papers included, we found no less than 20 different definitions of permanent HypoPT (Table 3). The most prevalent finding was "no definition" (16 papers) meaning that about one in six papers reporting on HypoPT as a complication to total thyroidectomy did not specifically define this complication. Moreover, five definitions were only used in one study and another five in only two. None of the included papers employed the correct definition.

In total, the studies comprised 109,991 patients. The median number of patients was 186 (range from 25 to 42911) and the median prevalence of HypoPT in the studies was 2.0% (range from 0 to 20.2). Characteristics of the included studies, as well as the effect of these characteristics on the incidence of HypoPT are shown in Table 4. Regarding the definition of hypocalcemia, 41.6% of the studies used a threshold value of serum calcium levels below the lower limit of the reference range, 22.5% used the lower limit of the reference interval as cut-off value, whereas 36.0% did not report how hypocalcemia was defined. To reassure a diagnosis of permanent HypoPT follow-up, measurements of serum calcium levels are needed. This was the case in 67.4% of papers, not the case in 7.9% of papers and not described in 24.7% of the papers. Length of follow up was <6 months in 10.1% of the studies, ≥6 months in 65.2% of the studies, whereas 24.7% of the studies did not report length of follow up.

Use of systematic prophylactic calcium supplementation following surgery was reported in nine (10.1%) of the papers, whereas 58.4% of the papers reported no use of supplementation and 31.5% of the papers did not report on this matter. The median incidence of HypoPT in studies where prophylactic calcium supplementation was given was 0.65; CI 0.04–1.44%, whereas it was 2.81; CI 2.00–3.80% in studies not supplying systematic supplementation, and 2.10; CI 1.30–3.09% in studies not describing this ($p = 0.03$). Among the nine studies reporting prophylactic calcium supplementation, two used a definition of hypocalcemia based on the lower level of the reference range but three used a definition *below* lower limit of the reference range and four of the studies did not report the applied level. The incidence of HypoPT was 1.63 (CI 0.98–2.42)% in studies using a definition of hypocalcemia below lower limit, 2.71; CI 1.48–4.37% in studies using the lower limit, and 2.97; CI 1.95–4.26% in studies not defining hypocalcemia ($p = 0.09$). Length of follow-up or systematic follow-up on calcium levels did not affect the reported incidence of HypoPT ($p > 0.20$ for both). Likewise, the hierarchic definition of HypoPT was not associated with the incidence ($p = 0.24$, data not shown) and the incidence did not differ between studies stating any definition of HypoPT and those not stating a definition ($p = 0.81$, data not shown).

Discussion

In the present study, we conducted a systematic literature search on the risk of permanent HypoPT after thyroid surgery in order to analyze the definitions used, as well as their impact on the frequency of this complication. Most notably, we identified 20 different definitions in 89 papers of which none of the definitions complied with the official definition [2, 3]. The median incidence of HypoPT in the studies was 2.0% but varied greatly from 0% to 20.2%. Importantly, different cut-off levels for hypocalcemia were used in the studies and there was a trend towards a lower incidence of

Table 3 List of definitions of permanent hypoparathyroidism found during the literature search. The definitions are in random order

Study specific definitions of hypoparathyroidism		No. of papers	Hierarchic definition	References
1	No definition	16	6	[26, 29, 34, 44, 48, 49, 58, 61, 66, 69, 74, 75, 82, 84, 86, 88]
2	Asymptomatic and symptomatic (symptoms of hypocalcemia relieved by calcium and vitamin D) hypocalcemia	2	2	[18, 72]
3	Low calcium level *and* symptoms of hypocalcemia *or* calcium level >10% below lower reference level	2	3	[4, 93]
4	Low calcium level *and* symptoms of hypocalcemia	5	3	[12, 71, 77, 83, 87]
5	ICD diagnosis codes	2	5	[13, 54]
6	Low PTH level or calcium <2.00 mmol/L for 12 months or Calcium and/or vitamin D supplementation necessary to relieve symptoms for >12 months	1	3	[14]
7	Low PTH-level *and* need for treatment with calcium and vitamin D for >12 months	3	4	[16, 40, 78]
8	Low PTH level *and* need for treatment with calcitriol or > 2 g calcium daily for >12 months	2	4	[17, 22]
9	Hypocalcemia that regardless of PTH level requires treatment with calcium and/or vitamin D for >1 year after surgery	11	2	[6, 19, 35, 39, 43, 46, 56, 60, 65, 68, 92]
10	Low calcium and PTH level	7	4	[5, 15, 37, 42, 53, 55, 62]
11	Low PTH level	6	4	[21, 24, 38, 63, 64, 73]
12	Hypocalcemia with or without symptoms	10	2	[7, 11, 20, 27, 30, 31, 41, 52, 57, 81]
13	Hypocalcemia that regardless of PTH level requires treatment with calcium and/or vitamin D for >6 months	8	2	[8, 23, 25, 32, 45, 47, 51, 79]
14	Calcium levels >10% below lower reference level	1	3	[28]
15	Patients taking calcium or vitamin D >6 months after surgery	7	4	[10, 33, 36, 50, 59, 70, 80]
16	Patients that despite taking calcium and vitamin D have hypocalcemia after 6 months	1	4	[67]
17	Low PTH level without high calcium level	1	4	[76]
18	Hypocalcemia that regardless of PTH level requires calcium and vitamin D for >3 months	1	2	[85]
19	Symptoms or low calcium level	2	2	[89, 91]
20	Hypocalcemia that is not relieved by treatment	1	4	[90]

Table 4 Association between risk of hypoparathyroidism (HypoPT) and predefined clinical variables found in the included studies

	Number of studies, *n* (%)	Incidence of HypoPT in percentages, median (95% CI)	*P*-value
Definition of hypocalcemia			
Below lower limit	37 (41.6)	1.63 (0.98–2.42)	0.09
Lower limit	20 (22.5)	2.71 (1.48–4.37)	
N/A	32 (36.0)	2.97 (1.95–4.26)	
Systematic follow-up calcium measurements			
Yes	60 (67.4)	2.40 (1.76–3.16)	0.51
No	7 (7.9)	1.30 (0.25–4.23)	
N/A	22 (24.7)	2.42 (1.29–3.97)	
Prophylactic calcium supplementation			
Yes	9 (10.1)	0.65 (0.04–1.44)	**0.03**
No	52 (58.4)	2.81 (2.00–3.80)	
N/A	28 (31.5)	2.10 (1.30–3.09)	
Length of follow-up			
<6 months	9 (10.1)	2.62 (0.73–5.81)	0.30
≥6 months	58 (65.2)	2.57 (1.94–3.30)	
N/A	22 (24.7)	1.59 (0.71–2.77)	

Significant *p*-values are shown in boldface

HypoPT with lower threshold levels ($p = 0.09$). Finally, systematic calcium supplementation post operatively appeared to decrease the risk of HypoPT ($p = 0.03$). Because of the many definitions of HypoPT we could not assess the risk with every definition. In an attempt to increase power and cluster the many definitions we therefore constructed a hierarchic definition and analyzed the association between the hierarchical definition and the incidence of HypoPT. We failed, however, to find an association between this and reported incidences of HypoPT. Our analysis therefore cannot directly explain the great variation in the incidence of HypoPT between studies.

The fact that we found so many definitions, nonetheless, points to a problem. In addition, the fact that many of the definitions were only used in one or two studies shows that these definitions are private to a few studies and may suggest that awareness of HypoPT should be raised.

Our data seemingly suggests that prophylactic calcium supplementation decreases the risk of HypoPT. Of the included studies, only nine provided this and of these, seven studies used either a definition of hypocalcemia below the lower level of the reference interval or did not provide a definition (data not shown). Therefore, the result may be biased by the definitions used in those particular studies. This highlights a problem with the many definitions of HypoPT; if the definitions vary across studies and these many definitions are linked to other factors that also differ (e.g., the use of calcium supplements) this may lead to biased overall conclusions.

In addition, the finding that systematic calcium supplements decreases the risk of HypoPT may also be an example of reverse causality meaning that an awareness of the risk of HypoPT promotes the use of calcium supplementation, which is also part of the treatment of HypoPT and thereby normalizes a patient's biochemistry resulting in a lower prevalence.

Finally, there was a trend in our data towards an impact of the calcium threshold levels used to define HypoPT and reported incidence estimates of the disease i.e., risk decreased with lower level applied. This is not surprising but again suggests that the different definitions may have an impact. Obviously, using a definition relying on the lower limit of the reference interval seems practical and could be employed by all. Unfortunately, this is currently not the case as some use a definition that is intendedly below the lower limit of the reference interval.

Our findings corroborates the finding in the study by Mehanna et al. (REF) in which the authors identified 10 different definitions of hypocalcemia and permanent HypoPT in the literature and applied them to their own cohort of 202 patients. The incidence of temporary hypocalcemia thus varied from 0 to 46% and that of permanent HypoPT varied from 0.9% to 4.4% [9]. The lowest incidence was found using a total plasma calcium cut-off level of 1.7 mmol/L and the highest using one of 2.1 mmol/L. Most investigators use total plasma calcium without accounting for the influence of plasma albumin levels. Measurements of plasma ionized calcium is recommended since it is independent of albumin.

Strengths of the present study includes the systematic literature search with a well-characterized pre-defined search string leading to a considerable number of studies being included. A limitation, however, is that we only searched PubMed and no other databases. We think it is unlikely, though, that the inclusion of a few additional studies would have altered the main conclusions. Furthermore, our intent was not to uncover any definition ever used to identify patients with HypoPT, but to review how HypoPT in general is defined within a representative sample of scientific publications, which we believe can be done by searching PubMed. Also, we have restricted our search to 1st January 2010 and onwards. The study by Mehanna et al. [9] was published in August 2009 and stressed the problem with too many definitions. Our study thus demonstrates that this problem remains unsolved. In conclusion, we have documented, that the definition of HypoPT varies greatly between studies and that numerous definitions are used. This does not immediately explain the great variability in the incidence of HypoPT between studies. The finding that calcium supplements seemingly protect against HypoPT, as

well as the fact that these supplements are provided in studies with a poor definition of hypocalcemia calls for concern and suggests that inconsistent definitions may be linked to confounding factors that affect the reported incidence of HypoPT.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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References

1. J.P. Bilezikian, A. Khan, J.T. Potts et al. Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research. J. Bone Miner. Res **26**, 2317–2337 (2011)
2. J.P. Bilezikian, M.L. Brandi, N.E. Cusano et al. Management of hypoparathyroidism: present and future. J. Clin. Endocrinol. Metab. **101**, 2313–2324 (2016)
3. J. Bollerslev, L. Rejnmark, C. Marcocci et al. European society of endocrinology clinical guideline: treatment of chronic hypoparathyroidism in adults. Eur. J. Endocrinol. **173**, G1–G20 (2015)
4. P.V.F. Jensen, S.M. Jelstrup, P. Homøe, Long-term outcomes after total thyroidectomy. Dan. Med J. **62**, A5156 (2015)
5. S. Merchavy, T. Marom, V.-I. Forest et al. Comparison of the incidence of postoperative hypocalcemia following total thyroidectomy vs completion thyroidectomy. Otolaryngol. Head Neck Surg. **152**, 53–56 (2015)
6. S.H. Paek, Y.M. Lee, S.Y. Min et al. Risk factors of hypoparathyroidism following total thyroidectomy for thyroid cancer. World J. Surg. **37**, 94–101 (2013)
7. A. Puzziello, L. Rosato, N. Innaro et al. Hypocalcemia following thyroid surgery: incidence and risk factors. A longitudinal multicenter study comprising 2,631 patients. Endocrine **47**, 537–542 (2014)
8. O. Edafe, P. Prasad, B.J. Harrison, S.P. Balasubramanian, Incidence and predictors of post-thyroidectomy hypocalcaemia in a tertiary endocrine surgical unit. Ann. R. Coll. Surg. Engl. **96**, 219–223 (2014)
9. H.M. Mehanna, A. Jain, H. Randeva et al. Postoperative hypocalcemia–the difference a definition makes. Head Neck **32**, 279–283 (2010)
10. H. Kwon, J.W. Yi, R.-Y. Song et al. Comparison of bilateral axillo-breast approach robotic thyroidectomy with open thyroidectomy for graves' disease. World J. Surg. **40**, 498–504 (2016)
11. A.J. Cherian, S. Ponraj, S.M. Gowri et al. The role of vitamin D in post-thyroidectomy hypocalcemia: still an enigma. Surgery **159**, 532–538 (2016)
12. P.C. Ambe, D.R. Wassenberg, Is sutureless thyroid surgery safe in the hands of surgical trainees. A single centre retrospective study. BMC Res Notes **9**, 118 (2016)
13. A. Weiss, R.P. Parina, J.A. Tang et al. Outcomes of thyroidectomy from a large California state database. Am. J. Surg. **210**, 1170–1176 (2015). discussion 1176-7
14. J.-B. Wang, H.-L. Sun, C.-Y. Song, L. Gao, Association between decreased serum parathyroid hormone after total thyroidectomy and persistent hypoparathyroidism. Med Sci. Monit. **21**, 1223–1231 (2015)
15. A. Selberherr, C. Scheuba, P. Riss, B. Niederle, Postoperative hypoparathyroidism after thyroidectomy: efficient and cost-effective diagnosis and treatment. Surgery **157**, 349–353 (2015)
16. S.T. Seo, J.W. Chang, J. Jin et al. Transient and permanent hypocalcemia after total thyroidectomy: early predictive factors and long-term follow-up results. Surgery **158**, 1492–1499 (2015)
17. K. Ritter, D. Elfenbein, D.F. Schneider et al. Hypoparathyroidism after total thyroidectomy: incidence and resolution. J. Surg. Res **197**, 348–353 (2015)
18. A. Puzziello, R. Gervasi, G. Orlando et al. Hypocalcaemia after total thyroidectomy: could intact parathyroid hormone be a predictive factor for transient postoperative hypocalcemia? Surgery **157**, 344–348 (2015)
19. P. Praženica, L. O'Keeffe, R. Holý, Dissection and identification of parathyroid glands during thyroidectomy: association with hypocalcemia. Head Neck **37**, 393–399 (2015)
20. G.H. Lee, Y.H. Ku, H.Il Kim et al. Vitamin D level is not a predictor of hypocalcemia after total thyroidectomy. Langenbeck's Arch. Surg. **400**, 617–622 (2015)
21. S. Gupta, P. Chaudhary, C.K. Durga, D. Naskar, Validation of intra-operative parathyroid hormone and its decline as early predictors of hypoparathyroidism after total thyroidectomy: a prospective cohort study. Int J. Surg. **18**, 150–153 (2015)
22. L. De Pasquale, P.V. Sartori, L. Vicentini et al. Necessity of therapy for post-thyroidectomy hypocalcaemia: a multi-centre experience. Langenbeck's Arch. Surg. **400**, 319–324 (2015)
23. S. Coiro, F.M. Frattaroli, F. De Lucia et al. A comparison of the outcome using Ligasure^{TM} small jaw and clamp-and-tie technique in thyroidectomy: a randomized single center study. Langenbeck's Arch. Surg. **400**, 247–252 (2015)
24. T. Bojic, I. Paunovic, A. Diklic et al. Total thyroidectomy as a method of choice in the treatment of Graves' disease - analysis of 1432 patients. BMC Surg. **15**, 39 (2015)
25. C.N. Abdel-Halim, L. Rejnmark, V.E. Nielsen, Post-operative parathyroid hormone can be used as a predictor of normocalcaemia after total thyroidectomy. Dan. Med J. **62**, A5157 (2015)
26. F. Tartaglia, G. Russo, M. Sgueglia et al. Total thyroidectomy in geriatric patients: a retrospective study. Int J. Surg. **12**(Suppl 2), S33–S36 (2014)
27. P. Sperlongano, S. Sperlongano, F. Foroni et al. Postoperative hypocalcemia: assessment timing. Int J. Surg. **12**(Suppl 1), S95–S97 (2014)
28. S.M. Shiryazdi, S. Kargar, M. Afkhami-Ardekani, H. Neamatzadeh, Risk of postoperative hypocalcemia in patients underwent total thyroidectomy, subtotal thyroidectomy and lobectomy surgeries. Acta Med. Iran. **52**, 206–209 (2014)
29. P. Rajeev, R. Sutaria, T. Ezzat et al. Changing trends in thyroid and parathyroid surgery over the decade: is same-day discharge feasible in the United Kingdom? World J. Surg. **38**, 2825–2830 (2014)
30. P. Praženica, K. O'Driscoll, R. Holy, Incidental parathyroidectomy during thyroid surgery using capsular dissection technique. Otolaryngol. Head Neck Surg. **150**, 754–761 (2014)
31. A. Pergel, A.F. Yucel, I. Aydin et al. A safety-based comparison of pure LigaSure use and LigaSure-tie technique in total thyroidectomy. Chirurgia **109**, 60–65 (2014)
32. S.I. Noureldine, D.J. Genther, M. Lopez et al. Early predictors of hypocalcemia after total thyroidectomy: an analysis of 304 patients using a short-stay monitoring protocol. JAMA Otolaryngol. Head Neck Surg. **140**, 1006–1013 (2014)
33. I. Nawrot, A. Pragacz, K. Pragacz et al. Total thyroidectomy is associated with increased prevalence of permanent hypoparathyroidism. Med. Sci. Monit. **20**, 1675–1681 (2014)
34. M. Monacelli, R. Lucchini, A. Polistena et al. Total thyroidectomy and central lymph node dissection. Experience of a referral centre for endocrine surgery. G Chir. **35**, 117–121 (2014)

35. Y. Ito, M. Kihara, K. Kobayashi et al. Permanent hypoparathyroidism after completion total thyroidectomy as a second surgery: how do we avoid it? Endocr. J. **61**, 403–408 (2014)
36. T.P. Griffin, M.S. Murphy, P. Sheahan, Vitamin D and risk of postoperative hypocalcemia after total thyroidectomy. JAMA Otolaryngol. Head Neck Surg. **140**, 346–351 (2014)
37. T.-L. Chow, C.-Y. Choi, A.N.-K. Chiu, Postoperative PTH monitoring of hypocalcemia expedites discharge after thyroidectomy. Am. J. Otolaryngol. **35**, 736–740 (2014)
38. P.G. Calò, F. Medas, G. Loi et al. Differentiated thyroid cancer in the elderly: our experience. Int J. Surg. **12**(Suppl 2), S140–S143 (2014)
39. M. Almquist, P. Hallgrimsson, E. Nordenström, A. Bergenfelz, Prediction of permanent hypoparathyroidism after total thyroidectomy. World J. Surg. **38**, 2613–2620 (2014)
40. M.T. Julián, J.M. Balibrea, M.L. Granada et al. Intact parathyroid hormone measurement at 24h after thyroid surgery as predictor of parathyroid function at long term. Am. J. Surg. **206**, 783–789 (2013)
41. S. Tolone, R. Roberto, G. del Genio et al. The impact of age and oral calcium and vitamin D supplements on postoperative hypocalcemia after total thyroidectomy. A prospective study. BMC Surg. **13**(Suppl 2), S11 (2013)
42. S.S. Hammerstad, I. Norheim, T. Paulsen et al. Excessive decrease in serum magnesium after total thyroidectomy for Graves' disease is related to development of permanent hypocalcemia. World J. Surg. **37**, 369–375 (2013)
43. J. Herranz González-Botas, D. Lourido Piedrahita, Hypocalcaemia after total thyroidectomy: incidence, control and treatment. Acta Otorrinolaringol. Esp. **64**, 102–107 (2013)
44. A. Prasai, P.A. Nix, M. Aye et al. Total thyroidectomy for safe and definitive management of Graves' disease. J. Laryngol. Otol. **127**, 681–684 (2013)
45. G. Dionigi, S. Van Slycke, S. Rausei et al. Parathyroid function after open thyroidectomy: a prospective randomized study for ligasure precise versus harmonic FOCUS. Head Neck **35**, 562–567 (2013)
46. M.C. Shinall, J.T. Broome, R. Nookala et al. Total thyroidectomy for Graves' disease: compliance with American Thyroid Association guidelines may not always be necessary. Surgery **154**, 1009–1015 (2013)
47. P. Sheahan, R. Mehanna, N. Basheeth, M.S. Murphy, Is systematic identification of all four parathyroid glands necessary during total thyroidectomy?: a prospective study. Laryngoscope **123**, 2324–2328 (2013)
48. S.H. Woo, J.P. Kim, J.J. Park et al. Comparison of natural drainage group and negative drainage groups after total thyroidectomy: prospective randomized controlled study. Yonsei Med. J. **54**, 204–208 (2013)
49. A. Al-Adhami, A.C. Snaith, W.L. Craig, Z.H. Krukowski, Changing trends in surgery for Graves' disease: a cohort comparison of those having surgery intended to preserve thyroid function with those having ablative surgery. J. Otolaryngol. Head Neck Surg. **42**, 37 (2013)
50. T.-Y. Sung, Y. Lee, J.H. Yoon et al. Importance of the intraoperative appearance of preserved parathyroid glands after total thyroidectomy. Surg. Today **46**, 356–362 (2016)
51. A. Pisanu, A. Saba, F. Coghe, A. Uccheddu, Early prediction of hypocalcemia following total thyroidectomy using combined intact parathyroid hormone and serum calcium measurement. Langenbeck's Arch. Surg. **398**, 423–430 (2013)
52. M. Raffaelli, C. De Crea, L. Sessa et al. Prospective evaluation of total thyroidectomy versus ipsilateral versus bilateral central neck dissection in patients with clinically node-negative papillary thyroid carcinoma. Surgery **152**, 957–964 (2012)
53. A. Sousa, A. de, J.M.P. Salles, J.M.A. Soares et al. Predictors factors for post-thyroidectomy hypocalcaemia. Rev. Col. Bras. Cir. **39**, 476–482 (2012)
54. R. Vashishta, A. Mahalingam-Dhingra, L. Lander et al. Thyroidectomy outcomes: a national perspective. Otolaryngol. Head Neck Surg. **147**, 1027–1034 (2012)
55. M. Barczyński, A. Konturek, A. Hubalewska-Dydejczyk et al. Randomized clinical trial of bilateral subtotal thyroidectomy versus total thyroidectomy for Graves' disease with a 5-year follow-up. Br. J. Surg. **99**, 515–522 (2012)
56. J. Järhult, P.-O. Andersson, L. Duncker, Alternating from subtotal thyroid resection to total thyroidectomy in the treatment of Graves' disease prevents recurrences but increases the frequency of permanent hypoparathyroidism. Langenbeck's Arch. Surg. **397**, 407–412 (2012)
57. G. Docimo, S. Tolone, D. Pasquali et al. Role of pre and postoperative oral calcium and vitamin D supplements in prevention of hypocalcemia after total thyroidectomy. G Chir. **33**, 374–378 (2012)
58. R. Cirocchi, C. Boselli, S. Guarino et al. Total thyroidectomy with ultrasonic dissector for cancer: multicentric experience. World J. Surg. Oncol. **10**, 70 (2012). https://doi.org/10.1186/1477-7819-10-70
59. P. Hallgrimsson, E. Nordenström, M. Almquist, A.O.J. Bergenfelz, Risk factors for medically treated hypocalcemia after surgery for Graves' disease: a Swedish multicenter study of 1,157 patients. World J. Surg. **36**, 1933–1942 (2012). https://doi.org/10.1007/s00268-012-1574-4
60. M. Annerbo, P. Stålberg, P. Hellman, Management of Grave's disease is improved by total thyroidectomy. World J. Surg. **36**, 1943–1946 (2012). https://doi.org/10.1007/s00268-012-1617-x
61. J.M. Segel, W.S. Duke, J.R. White et al. Outpatient thyroid surgery: safety of an optimized protocol in more than 1,000 patients. Surgery **159**, 518–23 (2016). https://doi.org/10.1016/j.surg.2015.08.007
62. M. Barczyński, A. Konturek, M. Stopa et al. Total thyroidectomy for benign thyroid disease: is it really worthwhile? Ann. Surg. **254**, 724–729 (2011). discussion 729-30
63. W.F. Ezzat, H. Fathey, S. Fawaz et al. Intraoperative parathyroid hormone as an indicator for parathyroid gland preservation in thyroid surgery. Swiss Med Wkly **141**, w13299 (2011)
64. J.J. Houlton, W. Pechter, D.L. Steward, PACU PTH facilitates safe outpatient total thyroidectomy. Otolaryngol. Head Neck Surg. **144**, 43–47 (2011)
65. K.C. Welch, C.R. McHenry, Total thyroidectomy: is morbidity higher for Graves' disease than nontoxic goiter? J. Surg. Res **170**, 96–99 (2011)
66. P. Accetta, I. Accetta, A.C. Accetta et al. Total thyroidectomy for benign thyroid diseases. Rev. Col. Bras. Cir. **38**, 223–226 (2011)
67. M. Testini, A. Gurrado, N. Avenia et al. Does mediastinal extension of the goiter increase morbidity of total thyroidectomy? A multicenter study of 19,662 patients. Ann. Surg. Oncol. **18**, 2251–2259 (2011)
68. N.B. Sands, R.J. Payne, V. Côté et al. Female gender as a risk factor for transient post-thyroidectomy hypocalcemia. Otolaryngol. Head Neck Surg. **145**, 561–564 (2011)
69. A.J. Kim, J.C. Liu, I. Ganly, D.H. Kraus, Minimally invasive video-assisted thyroidectomy 2.0: expanded indications in a tertiary care cancer center. Head Neck **33**, 1557–1560 (2011)
70. J. Kirkby-Bott, H. Markogiannakis, A. Skandarajah et al. Preoperative vitamin D deficiency predicts postoperative hypocalcemia after total thyroidectomy. World J. Surg. **35**, 324–330 (2011)
71. J. Liu, A. Bargren, S. Schaefer et al. Total thyroidectomy: a safe and effective treatment for Graves' disease. J. Surg. Res **168**, 1–4 (2011)

72. A. Reinisch, P. Malkomes, J. Liese et al. Education in thyroid surgery: a matched-pair analysis comparing residents and board-certified surgeons. Langenbeck's Arch. Surg. **401**, 239–247 (2016)
73. G.R. Qasaimeh, S. Al Nemri, A.K. Al Omari, Incidental extirpation of the parathyroid glands at thyroid surgery: risk factors and post-operative hypocalcemia. Eur. Arch. Otorhinolaryngol. **268**, 1047–1051 (2011)
74. L. Dogan, N. Karaman, K.B. Yilmaz et al. Total thyroidectomy for the surgical treatment of multinodular goiter. Surg. Today **41**, 323–327 (2011)
75. B. Zarebczan, D. Mohanty, H. Chen, A comparison of the LigaSure and harmonic scalpel in thyroid surgery: a single institution review. Ann. Surg. Oncol. **18**, 214–218 (2011)
76. A. Sitges-Serra, S. Ruiz, M. Girvent et al. Outcome of protracted hypoparathyroidism after total thyroidectomy. Br. J. Surg. **97**, 1687–1695 (2010)
77. G. Cocchiara, M. Cajozzo, G. Amato et al. Terminal ligature of inferior thyroid artery branches during total thyroidectomy for multinodular goiter is associated with higher postoperative calcium and PTH levels. J. Visc. Surg. **147**, e329–e332 (2010)
78. L. Youngwirth, J. Benavidez, R. Sippel, H. Chen, Parathyroid hormone deficiency after total thyroidectomy: incidence and time. J. Surg. Res **163**, 69–71 (2010)
79. S.N. Karamanakos, K.B. Markou, K. Panagopoulos et al. Complications and risk factors related to the extent of surgery in thyroidectomy. Results from 2,043 procedures. Hormones **9**, 318–325 (2010)
80. Y.S. Lee, K.-H. Nam, W.Y. Chung et al. Postoperative complications of thyroid cancer in a single center experience. J. Korean Med Sci. **25**, 541–545 (2010)
81. M. Barczyński, A. Konturek, A. Hubalewska-Dydejczyk et al. Five-year follow-up of a randomized clinical trial of total thyroidectomy versus Dunhill operation versus bilateral subtotal thyroidectomy for multinodular nontoxic goiter. World J. Surg. **34**, 1203–1213 (2010)
82. M. Vaiman, A. Nagibin, J. Olevson, Complications in primary and completed thyroidectomy. Surg. Today **40**, 114–118 (2010)
83. S. Narayanan, D. Arumugam, S. Mennona et al. An evaluation of postoperative complications and cost after short-stay thyroid operations. Ann. Surg. Oncol. **23**, 1440–1445 (2016)
84. R.A. Dedivitis, E.G. Pfuetzenreiter Jr, C.E.M. Nardi, E.C.Dde Barbara, Prospective study of clinical and laboratorial hypocalcemia after thyroid surgery. Braz. J. Otorhinolaryngol. **76**, 71–77 (2010)
85. M. Shindo, A. Stern, Total thyroidectomy with and without selective central compartment dissection: a comparison of complication rates. Arch. Otolaryngol. Head Neck Surg. **136**, 584–587 (2010)
86. E. Kamer, H. Unalp, H. Derici et al. Flapless conventional thyroidectomy: a prospective, randomized study. Surg. Today **40**, 1018–1022 (2010)
87. M.W. Seybt, D.J. Terris, Outpatient thyroidectomy: experience in over 200 patients. Laryngoscope **120**, 959–963 (2010)
88. M. Hassanain, M. Wexler, Conservative management of well-differentiated thyroid cancer. Can. J. Surg. **53**, 109–118 (2010)
89. Y.K. So, Y.-I. Son, S.D. Hong et al. Subclinical lymph node metastasis in papillary thyroid microcarcinoma: a study of 551 resections. Surgery **148**, 526–531 (2010)
90. T. Youssef, G. Gaballah, E. Abd-Elaal, E. El-Dosoky, Assessment of risk factors of incidental parathyroidectomy during thyroid surgery: a prospective study. Int J. Surg. **8**, 207–211 (2010)
91. T.-A. Moo, J. McGill, J. Allendorf et al. Impact of prophylactic central neck lymph node dissection on early recurrence in papillary thyroid carcinoma. World J. Surg. **34**, 1187–1191 (2010)
92. Z. El Khatib, J. Lamblin, S. Aubert et al. Is thymectomy worthwhile in central lymph node dissection for differentiated thyroid cancer? World J. Surg. **34**, 1181–1186 (2010)
93. M.A. Mascarella, V.-I. Forest, C. Nhan et al. Seasonal difference in postthyroidectomy hypocalcemia: a montreal-based study. Otolaryngol. Head Neck Surg. **154**, 263–267 (2016)