Post-operative parathyroid hormone can be used as a predictor of normocalcaemia after total thyroidectomy

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ABSTRACT

INTRODUCTION: Development of hypocalcaemia is a serious complication to total thyroidectomy (TT). The measurement of intact plasma parathyroid hormone (iPTH) has been internationally described as a good predictor of hypocalcaemia. Despite this, consensus in the field has yet to be reached among clinicians. We aimed to evaluate if measurement of iPTH 24 hours postoperatively (24-iPTH) can identify patients who *do not* subsequently develop clinically significant hypocalcaemia (CSH), thereby allowing for early discharge after TT.

METHODS: This was a historic cohort study of all patients who had a TT in the period from January 2013 to March 2014 at the Department of Oto-rhino-laryngology, Aarhus University Hospital, Denmark. Only patients with 24-iPTH measurements were included. Postoperative treatment with calcium or activated vitamin D analogue was defined as CSH. Data were collected from medical records.

RESULTS: A total of 69 patients were included, 80% were women, the median age was 47 and 83% had a malignant disease. A total of 35% developed CSH and the median hospitalisation period was four days. The sensitivity, specificity and positive predictive value of 24-iPTH ≥ 2.8 pmol/l to exclude CSH were 76%, 92% and 94%, respectively. In addition, we found that a body mass index > 25 kg/m^2 significantly increased the risk of developing CSH.

CONCLUSIONS: he measurement of 24-iPTH ≥ 2.8 pmol/l can be used to predict patients who will not develop CSH after TT and allow for early discharge of more than 50% of the patients.

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Post-operative hypocalcaemia is a common and serious complication following total thyroidectomy (TT) varying in incidence from 2% to 27% [1, 2]. Patients may have symptoms such as paresthesia, tingling and in the worst cases seizures. Most patients develop transient hypocalcaemia, whereas permanent hypocalcaemia is less frequent [3]. The main cause is damage to the parathyroid glands during surgery, including vascular injury and accidental removal of the glands.

In order to shorten the length of hospitalisation after TT and even make same-day surgery possible reliable and simple tests are needed to accurately identify patients who are eligible for early discharge. In many recent international studies [2-15], plasma intact parathyroid hormone (iPTH) has proven to be an effective predictor of hypocalcaemia. Despite the presence of many discharge strategies based on iPTH [5-8], consensus in the field has yet to be reached among clinicians in Denmark [5-8].

Traditionally, post-thyroidectomy hypocalcaemia is diagnosed by means of either total or ionized serum calcium assessments every 6-12 hours. National guidelines from the Danish Head and Neck Cancer Group (DAHANCA) suggest daily monitoring of serum calcium and recommend initiation of treatment upon onset of symptoms or if ionized serum calcium (i-Ca^{2+}) falls below 1.00 mmol/l [16]. Nevertheless, this strategy has its limitations in diagnosing hypocalcaemia at an early stage since serum calcium levels usually do not reach a nadir until at least 48 hours post-operatively and can be delayed for up to four days after surgery [9].

Using a historic cohort design, we aimed to evaluate if measurement of iPTH 24 hours post-operatively (24-iPTH) can identify patients who *do not* develop clinically significant hypocalcaemia (CSH), thereby allowing early discharge after TT.

METHODS

Through digital medical records, data were collected from all patients who underwent TT in the period from January 2013 to March 2014 at the Department of Oto-rhino-laryngology, Aarhus University Hospital, Denmark. All patients who had a TT or completion thyroidectomy (CT) performed were included. Patients with renal disease, concomitant parathyroid pathologies or no 24-iPTH were excluded.

From the medical records we retrieved information on the patients' age, gender and body mass index (BMI). Furthermore, the following clinical parameters were included: pathological diagnosis, procedure (total versus completion thyroidectomy), extirpation of cervical lymph nodes in level VI, pre- and post-operative ionised calcium, 24-iPTH, unintended parathyroid gland exci-

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sion, number of parathyroid glands identified, auto transplanted glands during surgery, post-operative symptoms and treatment of hypocalcaemia, duration of hospital stay and later manifestation of permanent hypocalcaemia.

Biochemistry

Serum levels of ionised calcium were measured by standard laboratory methods. I-Ca^{2+} levels were adjusted to a pH value of 7.4 (reference of i-Ca^{2+}: 1.18-1.32 mmol/l). Post-operative ionised calcium levels were monitored every six hours the first two days and then every 12 hours until discharge. Plasma-intact PTH was obtained 18-24 hours post-operatively and was measured using a second-generation electrochemiluminescent immunoassay (ECLIA) on an automated instrument (Cobas 6000, Roche Diagnostics, GmbH, Mannheim, Germany). The reference of iPTH was 1.6-6.9 pmol/l.

TABLE 1

Demographic and clinical characteristics of 69 patients who underwent total thyroidectomy and had a post-operative intact plasma parathyroid hormone measurement in the January 2013 to March 2014 period.

Patient characterization	
Patients, total, n	69
Gender, n(%)	
Male	14 (20)
Female	55 (80)
Age, yrs, median (range)	47 (21-81)
BMI, kg/m^2, median (range)	25 (15-43)
Diagnosis, n (%)	
Benign:	
Atoxic multinodular goiter	9 (13)
Toxic multinodular goiter	1 (1)
Graves disease	2 (3)
Total	12 (17)
Malignant:	
Papillary carcinoma	45 (65)
Follicular carcinoma	11 (16)
Medullary carcinoma	1 (1)
Total	57 (83)
Lymph node extirpation, n (%)	23 (33)
Lymph node metastasis, n (%)	10 (14)
Surgery, n (%)	
TT	23 (33)
Completion thyroidectomy	46 (67)
Glands identified at surgery, n (%)	
0	5 (7.3)
1	18 (26)
2	26 (38)
3-4	20 (29)
Autotransplantation, n (%)	14 (20)
Inadvertent gland exicision, n (%)	25 (36)
Hospitalization, days, median (range)	4 (2-7)

BMI = body mass index; TT = total thyroidectomy

Definitions

CSH was defined as the need for hypocalcaemic treatment with either calcium or an activated vitamin D analogue. Normocalcaemic patients were defined as those who had an i-Ca^{2+} ≥ 1.18 mmol/l or an i-Ca^{2+} < 1.18 mmol/l but with no need of treatment (clinically insignificant hypocalcaemia). Generally, most doctors followed the local guidelines prescribing treatment if i-Ca^{2+} < 1.10 mmol/l, or if patients developed symptoms. In cases with i-Ca^{2+} < 1.00 mmol/l and especially with concomitant symptoms, activated vitamin D analogues were given. If i-Ca^{2+} < 0.90 mmol/l, patients were treated with calcium intravenously. Permanent hypocalcaemia was defined as the need for treatment with an activated vitamin D analogue (alfacalcidol or calcitriol) six months after surgery.

Statistics

Data were analysed using GraphPad Prism (version 6.05 for Windows, La Jolla, USA). Continuous variables were described as medians with ranges, categorical variables as actual numbers with percentages. In the comparison between groups, the Mann-Whitney U test and Fisher's exact test were used to assess differences. We calculated sensitivity, specificity and predictive values. The discriminative power of the different variables was assessed by constructing receiver-operating characteristic (ROC) curves. Statistical significance was set at 2p < 0.05.

Trial registration: not relevant.

RESULTS

Cohort characteristics

A total of 96 patients underwent either total or completion thyroidectomy. In all, 27 (28%) had no 24-iPTH measurements and were excluded. Demographic and clinical characteristics of the remaining 69 patients are shown in **Table 1**.

Hypocalcaemia

A total of 57 (83%) (95% confidence interval (CI): 72-89%) out of the 69 patients had biochemical hypocalcaemia with an i-Ca^{2+} below 1.18 mmol/l. Twenty-four patients (35%) (95% CI: 25-47%) had CSH, out of whom 15 were treated with oral calcium supplementation, seven with activated vitamin D analogues and two with intravenous calcium. In total, ten of the patients with CSH (14%) (95% CI: 7.8-25%) later developed permanent hypocalcaemia, including the two who had received intravenous treatment and five of the patients who were treated with activated vitamin D. Thus, the remaining 14 patients only had transient hypocalcaemia. Among patients with CSH, symptoms were present in 16 (67%) (95% CI: 47-82%). Almost all (90%) (95% CI: 57-100%) of

those who later developed permanent hypocalcaemia presented with symptoms, whereas only half of the patients with transient hypocalcaemia had symptoms. However, the difference was non-significant (p = 0.079).

Intact plasma parathyroid hormone concentration 24 hours post-operatively

The 24-iPTH levels ranged from 0.50 to 7.2 pmol/l with a median of 2.90 pmol/l. A total of 15 (22%) had a 24-iPTH level below the lower level of the reference interval among whom, 14 (93%) received treatment for CSH including the two patients who needed calcium intravenously. There was a statistically significant difference in the median 24-iPTH levels between normocalcaemic and CSH patients (1.20 pmol/l versus 3.60 pmol/l, respectively, p < 0.0001).

Receiver-operating characteristics (ROC) curve analysis performed to predict patients without CSH showed that the best cut-off value for 24-iPTH was 2.1 pmol/l (**Figure 1**). The area under the curve (AUC) was calculated to 0.920 (p < 0.0001). The sensitivity and specificity of 24-iPTH levels to predict normocalcaemic patients are summarised in **Table 2**.

For instance, 52% of the patients had an iPTH equal to or exceeding 2.8 pmol/l, including two (3%) CSH patients. However, neither of the two patients developed symptoms, permanent hypocalcaemia, or needed active vitamin D analogues or intravenous treatment. The first patient was given calcium because i-Ca^{2+} was decreasing and reached 1.08 mmol/l at its minimum, whereas it was unclear why the other patient was treated.

Serum calcium levels

The i-Ca^{2+} levels 12-72 hours post-operatively were all significantly lower in patients with CSH. There was no significant difference in the preoperative calcium levels (p = 0.275). The nadir of i-Ca^{2+} concentration occurred 36 hours post-operatively with a median of 1.03 mmol/l (range: 0.9-1.16 mmol/l) in patients with CSH and 1.14 mmol/l (range: 1.09-1.27 mmol/l) in normocalcaemic patients (p < 0.0001).

The AUC of the ROC curve was 0.920 (p < 0.0001) with the best cut-off value at 1.16 mmol/l (sensitivity 83%, specificity 86%). However, a cut-off value of 1.18 mmol/l yielded a higher specificity (91%) and a higher positive predictive value (93%). It was noteworthy that only 42% of all the patients had a concentration of calcium equal to or over 1.18 mmol/l.

FIGURE 1

Receiver-operating characteristic curve for 24-h post-operative intact plasma parathyroid hormone concentration as a predictor of normocalcaemia; area under the curve = 0.920, p < 0.0001.

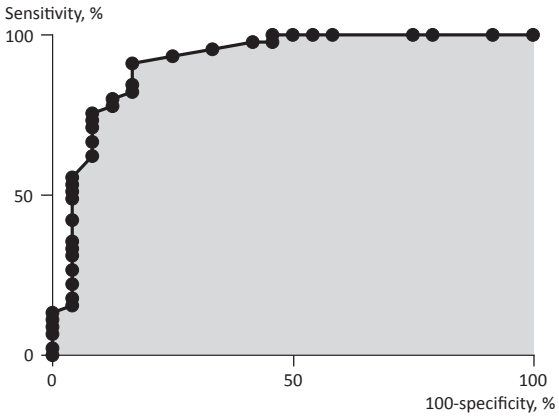

TABLE 2

Sensitivity, specificity with 95% confidence intervals and positive predictive values of several 24- intact plasma parathyroid hormone cut-off values. A value of intact plasma parathyroid hormone 24 hours post-operatively ≥ 2.8 is diagnostic of normocalcaemic patients with a sensitivity of 76%, specificity of 92% and positive predictive value of 94%.

24-iPTH, pmol/l	Sensitivity (95% CI), %	Sensitivity (95% CI), %	PPV, %
≥ 3.3	56 (40-70)	96 (79-100)	96
≥ 2.8	76 (60-87)	92 (73-99)	94
≥ 2.6	80 (65-90)	88 (68-97)	92
≥ 2.1	91 (79-98)	83 (63-95)	91
≥ 1.5	98 (88-100)	54 (33-74)	80

24-iPTH = iPTH 24 h post-operatively; CI = confidence interval; iPTH = intact plasma parathyroid hormone concentration; PPV = positive predictive value.

Other risk factors of developing clinically significant hypocalcaemia

When evaluating other risk factors, patients with CSH had a higher BMI (p = 0.005). Furthermore, it appeared that a TT compared with a CT and being male versus being female increased the risk of developing CSH; however, the differences were not statistically significant (p = 0.059 and p = 0.064, respectively). There were no differences in age, pathology or lymph node metastasis at level VI, etc. See **Table 3**.

DISCUSSION

When the risk of post-operative bleeding, neck haematoma and airway obstruction has receded a couple of hours after surgery, repeated calcium measurements are the main reason for keeping the patient at the hospital after TT [9].

The aim of this study was to evaluate iPTH as a predictor of normocalcaemic patients qualified for discharge 24 hours after TT. In our study, a 24-iPTH cut-off value of 2.1 pmol/l showed the highest sensitivity (91%)

and specificity (82%) in predicting normocalcaemic patients. In the clinical settings, it would be more relevant to reduce the number of false positives, for which reason a cut-off value of 2.8 pmol/l would make 24-iPTH a more reasonable predictor with a PPV of 94%. This would allow 52% of the patients to be discharged compared with the present strategies. The 6% of patients who developed CSH despite 24-iPTH ≥ 2.8 pmol/l had a mild, asymptomatic CSH that was treated with oral calcium supplementation only. Possibly, these patients did not need treatment, but were given calcium prophylactically. Our findings are in accordance with the results from a study published by Australian endocrine surgeons [6]. They concluded that 7% of patients with a normal iPTH developed mild and self-limiting hypocalcaemia.

Furthermore, our findings are in line with other studies in which post-operative iPTH was evaluated. In their study of 160 patients, Toniato et al [11] found a sensitivity, specificity and PPV of 80%, 82% and 82%, respectively, when using iPTH < 9.6 pg/ml (≈ 1.0 pmol/l) on the first post-operative day as a predictor of hypocalcaemia. Similarly, Asari et al [4] conducted a prospective study with 170 TT patients. They found a sensitivity, specificity and PPV of 98%, 83% and 65%, respectively, when using 24-iPTH < 15 pg/ml (≈ 1.6 pmol/l). These findings are in accordance with ours although our cut-off values are higher. It should be noted that our calculations are made with a view to prediction of normocalcaemic patients, not hypocalcaemic patients.

On the other hand, in their follow-up study including 523 consecutive patients, Lombardi et al [17] concluded that iPTH lacked the accuracy needed for prediction of CSH, because they found 70 out of 199 hypocalcaemic patients with normal iPTH levels four hours post-operatively (≥ 10 pg/ml). Similarly, Del Rio et al [18] observed that 52 out of 101 patients with late onset of hypocalcaemia had a normal 24-iPTH and therefore concluded that iPTH at 24 hours after TT could not accurately predict patients who would develop delayed hypocalcaemia.

The discrepancies between our study and previous studies may, in part, be explained by use of different definitions of hypocalcaemia. We chose a clinical approach, focusing on the patients who actually needed treatment. Almost all other studies defined hypocalcaemia as either a low total serum calcium level or the development of symptoms [2-12]. Like the multicentre study of 2,631 patients carried out by Puzziello et al [19], we found that a large proportion of the patients (83%) developed biochemical hypocalcaemia, yet less than half of the cases were clinically significant.

We also reported that the use of 24-hour post-operative i-Ca^{2+} as a predictor of normocalcaemia seems reliable with an AUC of a ROC analysis at 0.920. However, there may be a risk of type one error in our observations due to the definition of CSH, which includes i-Ca^{2+} as a parameter. In the present study, we did not record the precise time point at which CSH was diagnosed; and 24 hours post-operative i-Ca^{2+} may theoretically say more about the prevalence than about the prediction of CSH. In any case, i-Ca^{2+} may, potentially in combination with PTH, make the prediction of normocalcaemic patients more accurate [4, 9].

Another remarkable finding was the significant correlation between a high BMI (> 25 kg/m^2) and the development of CSH. This risk factor has not been considered by other authors and is not mentioned in the comprehensive systematic review of 115 observational studies by Edafe et al [2]. However, BMI seems to be a relevant factor in the risk stratification of patients, and further studies should explore this aspect.

The incidence of permanent hypocalcaemia in our investigation was high compared with that reported in other studies [3, 6, 19]. Selection bias must be con-

TABLE 3

Comparison of demographic characteristics, pathological and surgical factors between patients with and without clinically significant hypocalcaemia.

	CSH	Normocalcaemia	p-value
Patients, total, n	24	45	–
Gender, n (%)			0.064
Male	8 (33)	6 (13)	
Female	16 (67)	39 (87)	
Age, yrs, median	48	45	0.597
BMI, kg/m^2, median	27	23	0.005
Histology, n (%)			1
Benign	4 (17)	8 (18)	
Malignant	20 (83)	37 (82)	
Lymph node metastasis, n (%)	6 (25)	4 (9)	0.141
Lymph node extirpation, n (%)	10 (42)	13 (29)	0.298
PTG identified, n (%)			0.298
0-1	10 (42)	13 (29)	
2-4	14 (58)	32 (71)	
PTG on pathology[a], n (%)	10 (42)	15 (33)	0.601
Thyroidectomy, n (%)			0.059
Total	12 (50)	11 (24)	
Completion	12 (50)	34 (76)	
Symptoms, n (%)	16 (67)	1 (2)	< 0.0001
BMI, n (%)			0.005
≤ 25 kg/m^2	7 (29)	30 (67)	
> 25 kg/m^2	17 (71)	15 (33)	
Hospitalization, days, median	5	3	< 0.0001

BMI = body mass index; CSH = clinically significant hypocalcaemia; PTG = parathyroid glands.
a) Inadvertent excision of PTG identified microscopically in resected specimen.

Hypocalcaemic woman demonstrating Trousseau's sign.

sidered since this study was carried out at a university hospital which is as a tertiary health unit with a strongly selected group of patients. Thus, many patients who have a malignant diagnosis end up having lymph node metastasis and eventually a lymph node extirpation – factors that potentially add to the risk of developing permanent hypoparathyroidism [2].

A limitation to this study was the relatively small sample size. We did not measure iPTH on a routine basis before the beginning of 2013. Additionally, we had no information on the patients' preoperative vitamin D status. As low vitamin D levels may predispose to hypocalcaemia, further studies should aim at examining whether the prediction of CSH may improve if vitamin D is considered as well as whether a replete vitamin D status should be a target prior to surgery.

CONCLUSIONS

Measurement of iPTH 24 hours post-operatively may be used to predict patients who will not develop clinically significant hypocalcaemia after TT. Using a cut-off value of 24-iPTH ≥ 2.8 pmol/l facilitates early discharge of more than 50% of the patients 24 hours after surgery with a sensitivity and a specificity of 76% and 92%, respectively. Our data suggest that an implementation of PTH measurements 24 hours after surgery can reduce the length of hospitalisation after TT.

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