ORIGINAL ARTICLE



Hypoparathyroidism after total thyroidectomy in patients with previous gastric bypass

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Abstract

Purpose Case reports suggest that patients with previous gastric bypass have an increased risk of severe hypocalcemia after total thyroidectomy, but there are no population-based studies. The prevalence of gastric bypass before thyroidectomy and the risk of hypocalcemia after thyroidectomy in patients with previous gastric bypass were investigated.

Methods By cross-linking The Scandinavian Quality Registry for Thyroid, Parathyroid and Adrenal Surgery with the Scandinavian Obesity Surgery Registry patients operated with total thyroidectomy without concurrent or previous surgery for hyperparathyroidism were identified and grouped according to previous gastric bypass. The risk of treatment with intravenous calcium during hospital stay, and with oral calcium and vitamin D at 6 weeks and 6 months postoperatively

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was calculated by using multiple logistic regression in the overall cohort and in a 1:1 nested case-control analysis.

Results We identified 6115 patients treated with total thyroidectomy. Out of these, 25 (0.4 %) had undergone previous gastric bypass surgery. In logistic regression, previous gastric bypass was not associated with treatment with i.v. calcium (OR 2.05, 95 % CI 0.48–8.74), or calcium and/or vitamin D at 6 weeks (1.14 (0.39–3.35), 1.31 (0.39–4.42)) or 6 months after total thyroidectomy (1.71 (0.40–7.32), 2.28 (0.53–9.75)). In the nested case-control analysis, rates of treatment for hypocalcemia were similar in patients with and without previous gastric bypass.

Conclusion Previous gastric bypass surgery was infrequent in patients undergoing total thyroidectomy and was not associated with an increased risk of postoperative hypocalcemia.

Keywords Total thyroidectomy · Gastric bypass · Postoperative hypoparathyroidism · Cohort study

Introduction

Several case reports indicate that previous bariatric surgery for morbid obesity constitutes a risk factor for severe hypocalcemia after total thyroidectomy (TT) [1–3]. Gastric bypass surgery (GBP) is the most commonly performed procedure for morbid obesity, and due to the worldwide obesity epidemic, the prevalence of previous GBP is increasing [4]. Hypocalcemia is the most common complication of TT [5] [6] and is caused by intraoperative injury to the parathyroid glands or their blood supply [7]. Low level vitamin D can also aggravate postoperative hypocalcemia [8]. Patients with GBP are at risk of developing nutritional deficiencies [9] [10]. In GBP, the absorption of calcium and vitamin D is diminished, possibly due to the exclusion of the duodenum and proximal jejunum, where active vitamin D-associated calcium uptake occurs [11]. Accordingly, patients with GBP have lower levels of vitamin D (25OHD) than the general population [12]. However, it has been shown that 25OHD levels in GBP patients are equally low before and after GBP [13]. Low levels of 25OHD also persist at long-term follow up after GBP, together with the increased levels of parathyroid hormone (PTH), decreased bone mineral density, and increased risk of fractures [12–14]. This has led to the recommendation of calcium and vitamin D supplementation after GBP [15]. Thus, patients with previous GBP could be at increased risk of hypocalcemia after TT.

Hypocalcemia after TT can cause unpleasant symptoms, leading to increased costs for sick leave, follow-up visits, and readmission [16] [17]. Therefore, identifying risk factors for hypocalcemia is important. Patients with increased risk for this complication could benefit from a longer hospital stay, increased surveillance, and/or preoperative treatment with calcium and/or vitamin D.

Apart from case reports [1-3], there has been no population-based study investigating hypocalcemia after TT in relation to GBP. Thus, we aimed to investigate the frequency and severity of postoperative hypocalcemia in patients with previous GBP undergoing TT, and whether GBP increases the risk for hypocalcemia after TT, using data from nationwide, clinical registers.

Material and methods

Data sources

SQRTPA

The Scandinavian Quality Registry for Thyroid, Parathyroid and Adrenal Surgery (SQRTPA, www.thyroidparathyroidsurgery.com) started in 2004 and is recognized by the Swedish National Board for Health and Social Welfare as the national quality registry for endocrine surgical procedures in Sweden. Currently, 35 Swedish units report to the registry, covering 88 % of all procedures during the study period. Coverage is assessed by calculating the proportion of patients registered in the SQRTPA in relation to those registered in the Inpatient Register of the Swedish National Board of Health and Welfare. The quality of data for the registered patients is checked by external audit, comparing registered data to hospital medical records. The audit has demonstrated good data quality, with an error rate of <5 % [18, 19].

SOReg

national coverage is 97 % and regular data quality evaluations have shown that >98 % of data are correct [20].

Study cohort

Patients operated with TT between 1 January 2004 and 31 December 2015 were identified in the SQRTPA. Patients with concurrent or previous surgery for hyperparathyroidism were excluded, as were patients with missing information on post-operative hypocalcemia. By cross-linking with the SOReg, information on GBP was obtained.

Ethical considerations

This study was approved by the research ethics committee at Lund University, DNR 2015/543 and 2016/83.

Data

Endpoint data concerning postoperative oral and intravenous (i.v.) calcium and vitamin D treatment during hospital stay, at discharge, and at 6 weeks and 6 months postoperatively were extracted from the SQRTPA. Further, data on age, sex, indication for thyroidectomy, and lymph node dissection were retrieved.

Statistical analysis

The risk of hypocalcemia after TT in patients with and without previous GBP was investigated both in the whole cohort and in a 1:1 nested case-control subset. In the nested case-control group, patients with TT with previous GBP were randomly matched to patients without previous GBP, on the factors age, gender, lymph node dissection or not, and indication for surgery.

Means and standard deviations (SD) were calculated for continuous variables except for age. Age is reported as median and range. Numbers and column percentages were calculated for categorical variables.

In the whole cohort, risk for treatment with calcium and vitamin D at different times of follow-up, in patients with and without GBP, was investigated with uni- and multivariate logistic regression, adjusting for possible confounding variables: age, gender, indication for surgery, and lymph node dissection. In the nested case-control subset, ANOVA, chi-square, or Fisher's exact tests were used to determine the association of primary endpoints with previous GBP. All analyses were performed with STATA 13 (StataCorp LP, College Station, TX, USA). A p value of less than 0.05 was considered statistically significant.

This study was performed and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology statement [21].

Results

Baseline patient and procedure characteristics in the overall cohort

There were 7600 patients who underwent TT. Of these, we excluded 217 patients due to prior or concurrent parathyroidectomy. Another seven patients lacked information on treatment for postoperative hypocalcemia. Patients that were operated before 1 May 2007 (start date of the SOReg) were also excluded (N = 1261). This left 6115 patients for analysis. By cross-linking with SOReg, 25 patients with GBP before TT were identified, corresponding to a rate of 25/6115 (0.4 %).

The median age in the cohort was 46 (33–59), male to female ratio was 1:4, and the indication for surgery was thyrotoxicosis in half of the patients. Mean (SD) postoperative total calcium was 2.13 (\pm 0.20; Table 1) at day one. Total calcium at 6-week and 6-month follow-up were 2.30 (\pm 0.17) and 2.25 (\pm 0.17), respectively. At 6-week follow-up, 841 (13.8 %) had oral calcium and 554 patients (9.1 %) vitamin D substitution for hypocalcemia. These numbers were 290 (4.7 %) and 214 (3.5 %) at 6-month follow-up. Baseline characteristics are summarized in Table 1.

The number of patients without follow-up information for oral calcium treatment at 6 weeks and 6 months were 481 (7.9 %) and 641 (10.5 %), respectively.

Patient and procedure characteristics in patients with and without previous GBP

In the whole cohort, there were no statistically significant differences between patients with and without previous GBP regarding age (median, (IQR)) 48 (41–52) vs 46 (33–59); p = 0.977), male to female ratio (4/21 vs 1230/4860; p = 0.602) and postoperative total calcium (mean, (SD) 2.13 (±0.16) mmol/l vs 2.12 (±0.20) mmol/l; p = 0.997). However, there was a significant difference for the indication for thyroidectomy (p = 0.015). The most common indication for TT overall was thyreotoxicosis; in patients with previous GBP, it was compression symptoms.

Total serum calcium and rates of calcium and/or vitamin D substitution at 6-week and 6-month follow-up after thyroidectomy did not differ significantly between patients with and without previous GBP in the whole cohort (Table 2).

Logistic regression analysis of hypocalcemia, vitamin D and calcium treatment at discharge and follow-up in the whole cohort

In the multivariate logistic regression analysis including age, gender, lymph node dissection, and indication for surgery, previous gastric bypass was not associated with in hospital treatment with i.v. or oral calcium (2.07 (0.48–9.07); 0.89

Table 1Characteristics of patients operated with total thyroidectomyregistered in the SQRTPA from 1 May 2007–2015 (N = 6115)

	N = 6115 (100 %)
Age median (IQR)	46 (33–59)
Sex	
Male	1234 (20.2)
Female	4881 (79.8)
Indication for thyroidectomy	
Recurrent cyst	12 (0.2)
Completion operation	17 (0.3)
Excluding malignancy	457 (7.5)
Malignancy	956 (15.6)
Compression	1586 (25.9)
Thyrotoxicosis	3063 (50.1)
Other	24 (0.4)
Lymphnode dissection	
Yes	1068 (17.5)
No	5047 (82.5)
Gland weight (grams)	74.2 (±94.0)
Oral perioperative calcium treatment	
Yes	2055 (33.6)
No	4060 (66.4)
Intravenous calcium treatment	
Yes	250 (4.1)
No	5865 (95.9)
Peroral calcium treatment	
At discharge (yes/no)	1776 (29.0)/4339 (71.0)
At 6 weeks follow-up (yes/no)	841 (13.8)/4793 (78.4)
At 6 months follow-up (yes/no)	290 (4.7)/5184 (84.8)
Total serum calcium	
Postoperative day 1	2.13 (±0.20)
At 6 weeks follow-up	2.30 (±0.17)
At 6 months follow-up	2.25 (±0.17)
Peroral vitamin D treatment	
At discharge (yes/no)	909 (14.9)/5206 (85.1)
At 6 weeks follow-up (yes/no)	554 (9.1)/5087 (83.2)
At 6 months follow-up (yes/no)	214 (3.5)/5333 (87.2)

IQR interquartile range, GBP gastric bypass

(0.37–2.11)), oral calcium, and/or vitamin D at discharge (0.75 (0.29–1.91); 1.37 (0.50–3.76)), at 6 weeks (1.11 (0.37–3.31); 1.25 (0.36–4.27)), or 6 months postoperatively (1.45 (0.33–6.36); 2.01 (0.46–8.77); Tables 3 and 4).

Endpoints in patients with and without previous GBP in the nested case-control group

For the matched nested case-control analysis, the 25 patients with GBP before TT were successfully matched to an equal

	No previous GBP $N = 6090 (100 \%)$	Previous GBP $N = 25 (100 \%)$	p value
Age median (IQR)	46 (33–59)	48 (41–52)	0.977
Sex			
Male Female	1230 (20.2) 4860 (79.8)	4 (16.0) 21 (84.0)	0.602
Indication for thyroidectomy			
Recurrent cyst Completion operation	12 (0.2) 17 (0.3)	0 (0.0) 0 (0.0)	0.015
Excluding malignancy	454 (7.5)	3 (12.0)	
Malignancy	949 (15.6)	7 (28.0)	
Compression	1575 (25.9)	11 (44.0)	
Thyreotoxicosis	3059 (50.2)	4 (16.0)	
Other	24 (0.4)	0 (0.0)	
Lymphnode dissection			
Yes No	1061 (17.4) 5029 (82.6)	7 (28.0) 18 (72.0)	0.164
Gland weight (grams)	74.1 (±94.0)	80.7 (±72.2)	0.748
Oral perioperative calcium treatment			
Yes No	2047 (33.6) 4043 (66.4)	8 (32.0) 17 (68.0)	0.865
Intravenous calcium treatment			
Yes No	248 (4.1) 5842 (95.9)	2 (8.0) 23 (92.0)	0.322
Peroral calcium treatment			
At discharge (yes/no)	1770 (29.1)/4320 (70.9)	6 (24.0)/19 (76.0)	0.578
At 6 weeks follow-up (yes/no)	837 (13.7)/4773 (78.4)	4 (16.0)/20 (80.0)	0.651
At 6 months follow-up (yes/no)	288 (4.7)/5163 (84.8)	2 (8.0)/21 (84.0)	0.373
Total serum calcium			
Postoperative day 1	2.12 (±0.20)	2.13 (±0.16)	0.997
At 6 weeks follow-up	2.30 (±0.17)	2.27 (±0.13)	0.305
At 6 months follow-up	2.25 (±0.17)	2.26 (±0.10)	0.901
Peroral vitamin D treatment			
At discharge (yes/no)	904 (14.8)/5186 (85.2)	5 (20.0)/20 (80.0)	0.470
At 6 weeks follow-up (yes/no)	551 (9.0)/5066 (83.2)	3 (12.0)/21 (84.0)	0.616
At 6 months follow-up (yes/no)	212 (3.5)/5311 (87.2)	2 (8.0)/22 (88.0)	0.278

 Table 2
 Endpoint characteristics of group without and with previous GBP in the overall cohort (N = 6115)

IQR interquartile range, GBP gastric bypass

number of controls. Mean postoperative total calcium on day one was 2.13 (± 0.16) mmol/l in patients with previous GBP, vs 2.16 (± 0.15 ; p = 0.450) mmol/l in patients without. Mean total serum calcium and rates of calcium and/or vitamin D substitution at 6-week and 6-month follow-up after thyroidectomy did not differ between patients with and without previous GBP (Table 5).

Discussion

Case reports and our own experience have suggested that patients with previous GBP suffer an increased risk of severe hypocalcemia after TT [1–3], compared to patients without GBP. GBP, the most common bariatric procedure, is associated with nutritional deficiencies [22], such as low levels of 250HD and diminished uptake of dietary calcium. Low levels of 250HD have been shown to be a risk factor for postoperative hypocalcemia after TT and central neck dissection [8]. An increased risk of hypocalcemia after TT with previous GBP compared to TT without previous GBP is therefore plausible.

However, the hypothesis that patients with previous GBP have an increased risk of hypocalcemia after TT could not be confirmed in this large, population-based, nationwide cohort study. GBP was not a risk factor for hypocalcemia in uni- or

Factor	In hospital i.v. calci	mi	Per oral calcium at e	discharge	Per oral calcium at	6 weeks	Per oral calcium at	6 months
	OR (95 % CI)	OR ^a (95 % CI)	OR (95 % CI)	OR ^a (95 % CI)	OR (95 % CI)	OR ^a (95 % CI)	OR (95 % CI)	OR ^a (95 % CI)
Age	0.98 (0.97–0.98)	0.98 (0.97–0.99)	1.00 (1.01–1.42)	(66.0–66.0) 66.0	1.00 (0.99–1.00)	1.00 (0.99–1.00)	1.00 (0.99–1.00)	0.99 (0.99–1.00)
Lympn node dissection Indication for surgery	1.07 (1.24–2.23) 1.09 (1.03–1.16)	2.04 (1.48–2.82) 1.06 (0.99–1.14)	1.05 (1.02–1.07) 1.05 (1.02–1.07)	2.49 (2.10–2.89) 1.07 (1.04–1.10)	2.03 (1.72–2.40) 1.03 (1.00–1.07)	2.20 (1.88–2.70) 1.07 (1.02–1.11)	2.85 (2.22–3.60) 0.97 (0.92–1.02)	2.97 (2.27–3.88) 1.01 (0.94–1.08)
Gender	0.84 (0.60–1.17)	0.85 (0.60–1.19)	1.02 (0.89–1.17)	0.94 (0.81–1.08)	1.06 (0.89–1.27)	0.97 (0.81–1.16)	1.10 (0.83–1.47)	0.94 (0.70–1.26)
Previous GBP	2.05 (0.48–8.74)	2.07 (0.48–9.07)	0.77 (0.31 - 1.93)	0.75 (0.29–1.91)	1.14 (0.39–3.35)	1.11 (0.37–3.31)	1.71 (0.40–7.32)	1.45 (0.33–6.36)
Factor	Per oral vita	umin D at discharge		Per oral vitamin D a	at 6 weeks	Per (oral vitamin D at 6 mo	nths
Factor	Per oral vita	umin D at discharge		Per oral vitamin D	at 6 weeks	Per	oral vitamin D at 6 mo	nths
	OR (95 % C	CI) OR ^a	" (95 % CI)	OR (95 % CI)	OR ^a (95 %	CI) OR	(95 % CI)	OR ^a (95 % CI)
Age)-86.0) 66.0	0.99 (0.99	(0.98-0.99)	0.99(0.99-1.00)	0.99 (0.99–1	1.00) 1.00	(0.99–1.00)	0.99 (0.99–1.00)
Lymph node dissection	2.17 (1.84-2	2.55) 2.52	(2.12-3.01)	2.00 (1.64–2.44)	2.29 (1.85-2	2.84) 2.72	(2.04-3.62)	2.85 (2.09–3.88)
Indication for surgery	1.04(1.01-)	1.08) 1.05	(1.01-1.10)	1.04(1.00-1.08)	1.05 (1.00–)	0.98	(0.92-1.04)	1.02 (0.94-1.10)
Gender	0.91 (0.76–1	1.09) 0.84	1 (0.70–1.01)	0.92 (0.73–1.15)	0.85 (0.67–)	1.12 1.12	: (0.80–1.55)	$0.95\ (0.68{-}1.34)$
Previous GBP	1.43 (0.54-2	3.83) 1.37	' (0.50–3.76)	1.31 (0.39-4.42)	1.25 (0.36→	1.27) 2.28	(0.53-9.74)	2.01 (0.46-8.77)

^a Adjusted for age, lymph node dissection, indication for surgery, gender, and previous GBP

GBP gastric bypass

 Table 5
 Results of 1:1 nested

 case-control analysis

	No previous GBP <i>N</i> = 25 (100 %)	Previous GBP <i>N</i> = 25 (100 %)	p value
Age median (IQR)	48 (41–52)	48 (41–52)	1.000
Sex			
Male Female	4 (16.0) 21 (84.0)	4 (16.0) 21 (84.0)	1.000
Indication for thyroidectomy			
Recurrent cyst Completion operation	0 (0.0) 0 (0.0)	$\begin{array}{c} 0 \ (0.0) \\ 0 \ (0.0) \end{array}$	1.000
Excluding malignancy	3 (12.0)	3 (12.0)	
Malignancy	7 (28.0)	7 (28.0)	
Compression	11 (44.0)	11 (44.0)	
Thyreotoxicosis	4 (16.0)	4 (16.0)	
Other	0 (0.0)	0 (0.0)	
Lymphnode dissection			
Yes No	7 (28.0) 18 (72.0)	7 (28.0) 18 (72.0)	1.000
Gland weight (grams)	74.0 (±61.7)	80.7 (±72.2)	0.737
Oral perioperative calcium treatment	nt		
Yes	10 (40.0)	8 (32.0)	0.556
No	15 (60.0)	17 (68.0)	
Intravenous calcium treatment			
Yes No	0 (0.0) 25 (100.0)	2 (8.0) 23 (92.0)	0.149
Peroral calcium treatment			
At discharge (yes/no)	8 (32.0)/17 (68.0)	6 (24.0)/19 (76.0)	0.935
At 6 weeks follow-up (yes/	6 (24.0)/17 (68.0)	4 (16.0)/20 (80.0)	0.727
At 6 months follow-up (yes/	2 (8.0)/20 (80.0)	2 (8.0)/21 (84.0)	0.599
Total serum calcium			
Postoperative day 1	2.16 (±0.15)	2.13 (±0.16)	0.450
At 6 weeks follow-up	2.31 (±0.14)	2.27 (±0.13)	0.276
At 6 months follow-up	2.14 (±0.18)	2.26 (±0.10)	0.160
Peroral vitamin D treatment			
At discharge (yes/no)	6 (24.0)/19 (76.0)	5 (20.0)/20 (80.0)	0.733
At 6 weeks follow-up (yes/	4 (16.0)/19 (76.0)	3 (12.0)/21 (84.0)	0.329
At 6 months follow-up (yes/ no)	1 (4.0)/21 (84.0)	2 (8.0)/22 (88.0)	0.188

IQR interquartile range, GBP gastric bypass

multivariate logistic regression, and the rate of hypocalcemia was similar between previous GBP and no previous GBP in a nested case-control subset. Further, the frequency of previous GBP in patients undergoing TT was low, only 0.4 %.

The number of patients who underwent both first gastric bypass surgery and then total thyroidectomy was low in this study. However, taking into account that two nationwide registers, based on the whole Swedish population of about nine million people, were used; we consider this finding a strength rather than a weakness.

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Another potential explanation for the lack of an association could be missing observations. The Swedish Obesity Register, SOReg, started in May 2007, and no bariatric procedures performed before this date could be included in our study. Hence, it is possible that our study underestimates the rate of previous GBP in patients with TT. However, this seems to be rather unlikely since only 6–18 operations/100,000 were performed 2002–2006 and 24–89 operations/100,000 were performed 2007–2014 (Fig. 1S). Furthermore, the SOReg has a coverage of almost 100 % and it is unlikely that GBPs performed after May 2007 were missed in the patients in the present study [20].

The possibility of inaccurate data must also be taken into account. If treatment for hypocalcemia is inaccurately reported to the registry, the true frequency of this complication could be underestimated. However, the SQRTPA is audited regularly and data quality has been shown to be good. Further, data on treatment for hypocalcemia would likely be missing or inaccurate at random, and it is unlikely that this would systematically bias the results.

With only 25 patients with previous GBP, the study might be underpowered to detect a true difference in the rate of hypocalcemia after TT with and without previous GBP. While we did not observe any difference, it must be emphasized that our study does not prove the absence of such a difference.

The rate of calcium and/or vitamin D treatment in the whole cohort and in the nested control group was rather high, 4.7 %. This high rate could make it difficult to detect a true increase in the risk of hypocalcemia after TT in patients with previous GBP. An explanation for the high rate of hypocalcemia in the whole cohort could be the inclusion of low-volume hospitals in the registry. Another reason for the high rate of hypocalcemia overall in this study could be the high proportion of TT for thyrotoxicosis, more than 50 %, since previous studies indicate that TT for thyrotoxicosis carries a higher risk of long-term hypocalcemia. However, when adjusting for thyrotoxicosis in the multivariate logistic regression analysis, there was no significant increased risk of hypocalcemia after TT with previous GBP.

Another explanation for the disagreement with the present study and previous case reports [1-3] could be that patients with previous GBP in the present study had sufficient levels of 25OHD, and that patients in case reports had insufficient levels of 25OHD. Unfortunately, we did not have information about levels of 25OHD.

Furthermore, the time between GBP and TT could be important. Calcium and vitamin D depletion could aggravate over time after GBP. Perhaps GBP does not increase the risk of hypocalcemia after TT during the first years postoperatively, and this might be another explanation to the lack of association between GBP and hypocalcemia after TT in our study, since the time interval was in no patient longer than 7 years.

Similar to previous studies [23–25], age, gender, indication for surgery, and lymph node dissection were risk factors for postoperative hypocalcemia in our study.

The major strengths of this study include the large number of patients with TT; the truly population-based design with registers having wide national coverage; the high external validity including 35 Swedish units, ranging from small rural county hospitals to large university hospitals; and the high data quality in terms of coverage and accuracy, with nearly 100 % coverage for obesity surgery. Further, there were low numbers of patients with missing information for oral calcium treatment at 6 weeks and 6 months [18–20].

Conclusion

In conclusion, the results of this large observational study did not provide evidence for an increased risk for hypocalcemia after TT compared to patients without previous GBP. This study does neither support giving any extra supplementation to nor taking any extra blood tests in patients with previous GBP before TT, since their risk of hypocalcemia does not seem to markedly differ from the overall TT cohort.

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Authors' contributions Study conception and design: MA, AB. Acquisition of data: JO, AM, HH, KL, AB, MA. Analysis and interpretation of data: RD, MA, AB. Drafting of manuscript: RD, MA. Critical revision of manuscript: JO, AM, AB.

Compliance with ethical standards This study was approved by the research ethics committee at Lund University, DNR 2015/543 and 2016/83.

Conflict of interest statement None declared. The present study was submitted and accepted for oral presentation at the 7th Biennial Congress of the European Society of Endocrine Surgeons (ESES). Apart from this, the results presented in this paper have not been published previously in whole or part.

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