

Post-thyroidectomy hypocalcemia: The role of calcitonin, parathormone and serum albumin

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Serum calcium, inorganic phosphate, calcitonin, parathormone, albumin, triiodothronine and thyroxine levels were measured during the surgical intervention and in the postoperative period to investigate the pathogenesis of post-thyroidectomy hypocalcemia in 25 female patients undergoing bilateral subtotal thyroidectomy for non-toxic nodular goiter. A highly significant fall in uncorrected serum calcium and albumin levels starting with the completion of lobectomies and a significant correlation between their gradient were observed. Early peak of calcitonin corresponded well with the falls in corrected calcium and inorganic phosphate levels. An overt parathyroid response to hypocalcemia was not encountered. On the basis of postoperative hypoalbuminemia, calcitonin leak triggered the early onset of hypocalcemia while insufficient parathyroid response contributed to post-thyroidectomy hypocalcemia. [Turk J Med Res 1994; 12(3): 127-130]

Key Words: Thyroid, Surgery, Post-thyroidectomy hypocalcemia

Though much work have been accomplished on the subject, the mechanism of post-thyroidectomy hypocalcemia still remains uncertain. Permanent hypocalcemia generally appears after 24-48 hours since the operation and related to ablation, devascularisation and infarction of the parathyroid glands (1-3). This is generally associated with radical thyroid surgery (2,4,5). The transient hypocalcemia occurring within 24 hours is seen more frequently. Many theories have been suggested to explain this complication. According to Michie's (6) hypothesis, acute reversal of thyrotoxic osteodystrophy after thyroidectomy in thyrotoxic patients cause hypocalcemia (5,7,8). Many authors (9,10-13) object to, this hypothesis which falls short in explaining the hypocalcemia seen in patients with non-toxic goiter or why the thyrotoxic patients become euthyroid by medication before the operation. It was first Suzuki (14) who suggested that the leak of calcitonin during the surgical manipulation of the thyroid gland may be the cause of hypocalcemia. Rasmusson (15) and Watson (16) showed strong evidences about the release of calcitonin during the manipulation

causing hypocalcemia. Busetto (17) and Franz (12) found a postoperative rise in calcitonin levels but could not demonstrate a correlation between calcitonin and calcium. Although many others (3,5,10,12,13) opposed the thyrocalcitonin theory, Sawers (10), Franz (12), Falk (3) and Eforakopoulou (13) suggested that the fall in parathormone levels might be a contributing factor in the pathogenesis of transient post-thyroidectomy hypocalcemia. According to another hypothesis from Franz (12) and Falk (13), post-thyroidectomy hypoalbuminemia is the factor responsible from hypocalcemia. They found a significant correlation between the decline in serum calcium and albumin levels. However in all these previously done trials heterogeneous groups were used (eg: thyrotoxicosis versus euthyroid, total thyroidectomies versus nodulectomies, benign diseases versus malignancies). Thus, the results might have been influenced from the presence of many hypocalcémie factors.

The aim of this study is to investigate the possible role of calcitonin, parathormone and serum albumin on post-thyroidectomy hypocalcemia by using a homogeneous group.

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MATERIALS AND METHODS

This prospective study was carried out to elucidate the pathogenesis of post-thyroidectomy hypocalcemia, in 25 consecutive female patients undergoing bilateral

subtotal thyroidectomy for non-toxic nodular goiter at the Department of General Surgery, Medical School of Ankara University between March 1992 and November 1992. The patients treated with nodule excision, unilateral thyroidectomy, total thyroidectomy and neck dissection were not included in the study to obtain a homogeneous group as well as the cases in whom unilateral or bilateral truncal ligation of inferior thyroid arteries were performed. Patients with thyrotoxicosis or thyrotoxic osteodystrophy with elevated serum alkaline phosphatase were also exempted. 25 female patients with an age range of 18 to 58 years and a mean of 34.3 years were included in the study.

Superior thyroid vessels were ligated and bisected during bilateral subtotal thyroidectomy. Truncal ligation of its inferior thyroid arteries were avoided, only intracapsular ligation of its distal branches were performed during the resection of the lobes. The posterior capsule of the lobes and the parathyroid glands which were preserved in situ.

The standard anesthetic procedure (atropine, diazepam premedication; sodium thiopentotal induction; nitrous oxide-halothane-oxygen mixture maintenance) were used in all patients.

Serum calcium, inorganic phosphate, alkaline phosphatase, calcitonin, parathormone, total protein, albumin, triiodothyronine (T3) and thyroxine (T4) levels were measured in all patients just prior to the operation (t0). Patients with high alkaline phosphatase were eliminated. These measurements were repeated as soon as the resection of the lobes were completed (t1), one hour after the resection (t2), during the second (t3) and sixth (t4) postoperative hours and during the first (t5), second (t6) and third (t7) days postoperatively. Considering the alterations in total serum calcium levels by changes in protein concentrations, corrected calcium figures were used in the statistical analysis. For every 0.1 gr/dl where serum albumin exceeded 4.6 gr/dl, 0.09 mg/dl calcium was subtracted from the measured total serum calcium level. The procedure was reversed for albumin values below 4.6 gr/dl. The corrected serum calcium levels less than 8.5 gr/dl were defined as hypocalcemia. Serum calcium, inorganic phosphate, alkaline phosphatase, total protein and albumin were assayed by standard chemical methods and serum calcitonin, parathormone, T3 and T4 were assayed by radioimmunoassay. Paired t test was used for evaluating the changes during to -t7 of each variable. Correlations between variables were obtained by using Pearson moment product correlation test.

RESULTS

The perioperative serum calcium (uncorrected and corrected), inorganic phosphate, calcitonin, parathormone, albumin, triiodothyronine and thyroxine figures are shown in Table 1.

The mean preoperative corrected serum calcium levels (9.3 mg/dl) revealed a sharp decline during the operation and early postoperative period (Figure 1). The figures measured at t4 (8.8 mg/dl) and t5 (8.9 mg/dl) were found significantly lower when compared with preoperative value ($p < 0.01$ and $p < 0.05$ respectively). Corrected serum calcium figures started to rise on the first postoperative day and reached to its preoperative value on the third postoperative day.

After a sharp peak during operation reaching to 3-4 times of preoperative values, serum calcitonin figures started to fall continuously till t7 (Figure 1). The rises during t1 and t2 in respect to t0 were found statistically significant ($p < 0.01$, $p < 0.05$ respectively). The relation between the levels of corrected serum calcium and calcitonin during t1-t7 were not statistically significant.

Serum parathormone levels showed nonspecific changes with declines and rises during t1-t7 (Figure 1). Serum parathormone and corrected calcium levels showed no significant correlation.

All T3 figures measured during the operation and postoperative period were found significantly lower with respect to preoperative value ($p < 0.05$ for t1, t2, t3 and $p < 0.001$ for t4, t5, t6, t7) (Figure 1). After a marginal rise during t1 and t2 serum T4 levels showed a progressive fall which the figures during t5 and t7 were found significantly lower with respect to preoperative figure ($p < 0.05$ for each).

Serum inorganic phosphate levels during and after the operation were found to be lower than the preoperative level with the significant falls at t1 and t3 ($p < 0.05$ and $p < 0.01$ respectively) as seen in Table 1. A significant rise in serum calcitonin and a significant fall in serum inorganic phosphate were observed in t1 but no correlation between calcitonin and inorganic phosphate levels were seen during t2-t7.

Serum albumin and uncorrected calcium levels identically showed significant falls during t1-t7 with respect to t0 (for albumin figures $p < 0.01$ for t1, t5, t6, t7; $p < 0.001$ for t2, t3; $p < 0.001$ for t4 and for uncorrected serum calcium figures $p < 0.01$ for t3, t5, t6, t7; $p < 0.001$ for t1, t2, t4) (Figure 1). Serum albumin and uncorrected calcium levels correlated significantly during t1-t5 ($p < 0.01$ for t1, $p < 0.001$ for t3, t4, t5).

Clinical hypocalcemia developed in only one patient (4%) with positive Chvostek's sign that appeared on the 10th postoperative hour. Laboratory hypocalcemia, all within the first 24 hours, developed in 8 of 25 patients (32%).

Permanent hypocalcemia or recurrent nerve paralysis not encountered.

DISCUSSION

Our patients undergoing bilateral subtotal thyroidectomy showed a transient fall in corrected serum cal-

Table 1. Perioperative mean (SE) serum calcium, inorganic phosphate, calcitonin, parathormone, albumin, T3 and T4 levels.

	t0	t1	t2	t3	t4	t5	t6	t7
Uncorrected Ca (mg/dl)	9.3 (0.1)	8.4* (0.2)	8.4* (0.2)	8.8° (0.1)	8.5* (0.1)	8.6° (0.2)	8.6° (0.2)	8.6° (0.1)
Corrected Ca (mg/dl)	9.3 (0.1)	9.0 (0.2)	8.9 (0.2)	9.1 (0.1)	8.8° (0.1)	8.9" (0.1)	9.1 (0.1)	9.2 (0.1)
I.Phosphate (mg/dl)	3.7 (0.3)	3.2 (0.2)	3.3 (0.2)	3.0° (0.1)	3.5 (0.2)	3.6 (0.2)	3.4 (0.2)	3.4 (0.1)
Calcitonin (pg/ml)	3.4 (0.7)	12.2° (3.1)	14.8° (4.9)	6.5 (1.5)	6.3 (2.5)	6.1 (1.4)	4.2 (0.9)	4.0 (1.0)
Parathormone (ng/dl)	27.4 (5.3)	24.7 (4.6)	39.8 (7.5)	25.0 (6.6)	23.2 (6.9)	18.5 (3.6)	41.6 (14.6)	26.0 (6.5)
Albumin (gr/dl)	4.5 (0.07)	4.0° (0.17)	4.2" (0.14)	4.3" (0.09)	4.2* (0.06)	4.2° (0.08)	4.2° (0.07)	4.1° (0.08)
T3 (ng/ml)	1.35	1.07" (0.17)	1.05" (0.14)	1.10" (0.09)	0.94* (0.06)	0.74* (0.08)	0.83* (0.07)	0.80* (0.08)
T4 (µg/dl)	10.4 (0.5)	10.6 (0.4)	11.1 (0.5)	10.0 (0.4)	9.3 (0.4)	9.3" (0.4)	9.7 (0.5)	9.2" (0.4)

t0: before the operation, t1: immediately after the resection, t2: one hour after the resection, t3: second postoperative hour, t4: sixth postoperative hour, t5: first postoperative day, t6: second postoperative.

- * : significant difference, p<0.001
- ° : significant difference, p<0.01
- " : significant difference, p<0.05

cium values; maximal at the sixth postoperative hour and regaining its normal level after 3 days. All the cases with clinical (4%) and laboratory (32%) hypocalcemia were detected within the first 24 hours.

Calcitonin is known as a serum calcium lowering hormone with a potentiated effect in hyperthyroidism. It's effect on post-thyroidectomy hypocalcemia is expected to be early and short, since it's half life is only 2-15 minutes (18). In our study, the sharp peak in calcitonin and the marginal rise in T4 during operation suggests that the thyroid hormones may leak from the damaged thyroid remnant during surgical manipulation.

Although no statistically significant correlation between corrected calcium and calcitonin levels during t1-t7 were found, the significant rise at t1, t2 and the fall at t3 in calcitonin levels corresponded with the sharp decrease at t1, t2 and the fall at t3 in calcium.

While-Watson (16) demonstrated a significant correlation between calcium and calcitonin during the first 12 postoperative hours, Falk (13), Franz (12) and Eforakopoulou (13) disagree. This controversy was possibly because of the lack of early estimations of calcium and calcitonin in the latter group. Our results suggest that calcitonin may be a contributing factor on the early onset of postthyroidectomy hypocalcemia.

Serum inorganic phosphate levels during t1-t7 were all lower than the preoperative value, with elevations and falls. An overt parathyroid response to

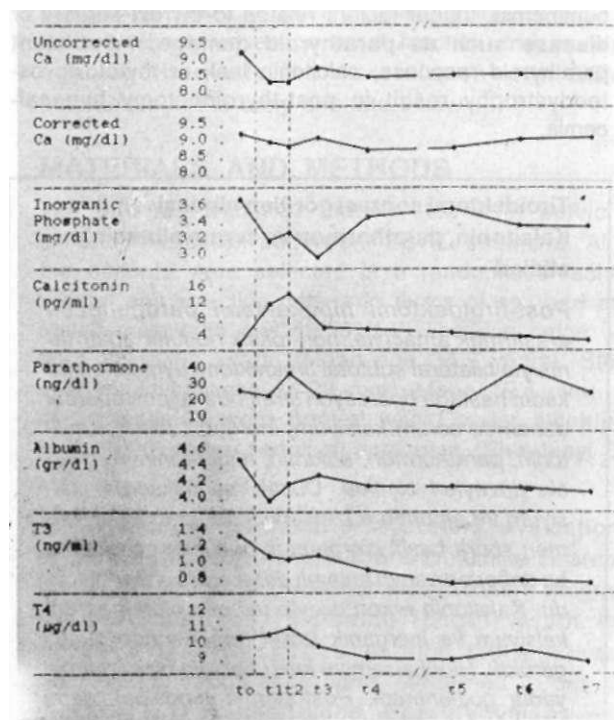


Figure 1. Serial changes in serum uncorrected Ca, corrected Ca, inorganic phosphate, calcitonin, parathormone, albumin, T3 and T4 perioperatively. Vertical lines indicate the duration of operation.

hypocalcemia was not observed. In contrast to Franz (12), Falk (13) and Eforakopoulou (13) we could not find a correlation between calcium and parathormone in the early post-thyroidectomy hypocalcemia.

All the values for uncorrected serum calcium and albumin measured during the operation and postoperative period were significantly lower with respect to preoperative values. The highly significant correlation between their pattern within the first 24 hours (t1, t3, t4, t5) indicates the importance of postoperative hypoalbuminemia on post-thyroidectomy hypocalcemia. Similarly in two different studies Franz (12) and Falk (3) demonstrated a strong correlation between post-thyroidectomy hypoalbuminemia and hypocalcemia. Hypoalbuminemia is also seen after nonthyroid surgery. Percival (11) has shown a marginal fall in serum calcium level in 11 patients who underwent minor abdominal surgery where the fall was less marked than in partial thyroidectomy. Falk (3) has reported a decline in serum calcium and albumin levels after nonthyroid surgery in 6 patients although the falls were not significant.

Postoperative hypoalbuminemia is possibly related to the hemodilutional effect of antidiuretic hormone and to the transcapillary leak accuring during the stress of surgery. Calcitonin leak played a trigger mechanism on the very early onset of hypocalcemia.

We conclude that postoperative hypoalbuminemia is the major factor in the pathogenesis of post-thyroidectomy hypocalcemia. On the basis of hypoalbuminemia, trigger factors related to thyroid surgery or disease such as parathyroid damage, insufficient parathyroid response, calcitonin leak or thyrotoxic osteodystrophy result in post-thyroidectomy hypocalcemia.

Tiroidektomi sonrası görülen hipokalsemi: Kalsitonin, parathormon ve serum albumin'in etkileri

Post-tiroidektomi hipokalsemi patogenezi araştırmak amacıyla, non-toksik nodüler guatr tanısıyla bilateral subtotal tiroidektomi uygulanan 25 kadın hastada operasyon sırasında ve postoperatif dönemde serum kalsiyum, inorganik fosfat, kalsitonin, parathormon, albumin, triiodotironin ve tiroksin düzeyleri ölçüldü. Düzeltilmemiş serum kalsiyum ve albumin düzeylerinde lobektomiden hemen sonra başlayan anlamlı düşüşler görüldü ve bu değerlerin seyri anlamlı derecede benzer bulundu. Kalsitonin erken pikiyle uyumlu olarak serum kalsiyum ve inorganik fosfat değerlerinde düşüş görüldü. Hipokalsemiye karşı belirgin bir paratiroid yanıtı gözlenmedi. Postoperatif hypoalbuminemi zemininde kalsitonin saliminin erken hipokalsemi başlangıcını tetiklediği, yetersiz paratiroid yanıtının posttiroidektomi hipokalsemiyi ortaya çıkardığı sonucuna varıldı. [Turk J Med Res 1994; 12(3): 127-130]

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