EFFECT OF PARATHYROIDECTOMY ON PATIENTS WITH TERTIARY HYPERPARATHYROIDISM (RETROSPECTIVE STUDY)

By

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ABSTRACT

Objective : The aim of this work was to study the effect of parathyroidectomy on patients with tertiary hyperparathyroidism.

Patients and methods : A total number of 10 patients with tertiary hyperparathyroidism manifestations under went parathyroidctomy, where the patients with adenoma of parathyroid gland under went excision of adenoma or multiple adenomas, and patients with hyperplasia of parathyroid gland underwent total parathyroidectomy and implantation of a part of one parathyroid gland into the sternomastoid muscle .

Results : There were significant changes in clinical and laboratory values between pre- and post operative measures in both types of patients (adenoma and hyperplasia) where there were significant decrease in serum calcium, serum alkaline phosphatase and parathyroid hormone (P.T.H.) and great changes in preoperative manifestations.

Conclusion : From this study we can conclude that the optimal treatment of tertiary hyperparathyroidism is surgical excision of adenoma or adenomas , or total parathyroidectomy and transplantation of a part of one gland into the sternomastoid

muscle in case of hyperplasia of parathyroid gland.

INTRODUCTION

Tertiary hyperparathyroidism (3° HPTH). is essentially a special case of secondary hyperparathyroidism (2° HPTH.) When 2° HPTH persists to the point where parathyroid hormon (PTH) physiology can no longer revent to normal upon correction of the underlying disease, it is called tertiary hyperparathyroidism (3° HPTH). Persistence of elevated PTH after successful renal transplantation is the usual scenario for declaring autonomous irreversible hyperfunction. In most other situations of refractory elevation of PTH in ongoing renal failure, distinguishing failure of compliance from refractory PTH stimulation from true physiologic autonomy is impossible and unnecessary-if indications for surgical management develop, as described as follows, the rationale for surgical intervention is the same. The development of refractoriness to feedback inhibition is probably a gradual process rather than a discrete event. Furthermore, the anatomic hyperplasia accompanying longstanding 2° HPTH probably contributes to persistent hyperfunctioning despite good efforts at medical management to reduce the stimulation of PTH secretion[1].

Although total parathyroidectomy (PTH-x) with autotransplantation is a somewhat more complicated procedure but an elegant and logical solution to the problem of persistent stimulation or autonomous hypersecretion. In this procedure all four (or more) PTH glands are removed, and fragments of one gland totaling 75 to 100 mg, are autotransplanted, usually into the belly of the sternomastoid muscle in the neck, where , if they develop recurrent hyperplasia, they can be conveniently excised under local anesthesia without requiring either general anesthesia or repeat neck exploration. The disadvantages of the autotransplantation procedure are the (1) the patient with behave functionally aparathyroid for 6 weeks to 3 months , and significant medical attention is required to prevent symptomatic hypocalcemia; (2) the immediate postoperative care requires closer monitoring of calcium levels, often requires inpatient parenteral calcium

supplementation, and thus carries a higher cost; and (3) there is always some risk of primary failure of the transplanted tissue.where in case of presence of adenoma we shoud excise the adenoma or the adenomas. then in this study more details about surgical treatment will be conducted[2] .

PATIENTS AND METHODS

This retrospective study had been conducted on chronic renal failure patients (10 patients), with manifestations of tertiary hyperparathyroidism (THPT), all patients had been referred from renal dialysis units .

During the period between September, 2000, and April 2004, all patient underwent parathyroidectomy at endocrine surgery unit - Mansoura University Hospital.

Our patients were collected on data base including serum calcium, inorganic phosphate , alkaline phosphatase, and (parathyroid hormone) PTH.

Preoperative localiz ing studies was used as neck US, neck CT and sestamibi (parathyroid scane).

In case of adenoma patients: we excised the glands which have the adenoma and which are preoperatively localised whether one or multiple adenoma.

In case of hyperplasia patients: we excised the four parathyroid glands and division of one gland into two halves one half is discarded and the other half is divided into (6-8) fragments and transplanted into a pocket in the sternomastoid muscle.

The following is the 10 patients in details.

RESULTS

The ages ranged between 40 - 50 years in patients with adenoma and 30 - 60 years in patients with hyperplasia. They were five males and two females in adenoma patients and two females and one male in hyperplasia patients.

The average duration of dialysis was 30 months in adenoma patients and 20 months in hyperplasia patients (Table 1and figure1,2).

The average preoperative calcium level was 11.0 3,0 mg/dL. The mean preoperative PTH level was 545.21 pg/mL (reference range 15-65 pg/mL). Preoperative serum phosphate and serum alkaline phosphatase levels were 2.14 ± 0.66 mg/dL and 195 ± 171.87 U/L, respectively (Table 2 and figure 3,4)

Two patients presented with bone pain. Nine had musculoskeletal complaints, including myalgias and weakness. Two patients experienced mental status changes. Two patients presented with chronic pancreatitis and ten with renal calculi. Other symptoms on presentation included diarrhea, insomnia, and met-astatic caleifications (Table 3).

The average time between start of renal dialysis and parathyroidectomy was 4.2 ± 0.7 years. The average length of stay in hospital was 3.5 ± 0.3 days. Seven of the patients were found to have either one(n = 3) or two(n = 4) enlarged parathyroid glands, underwent resection of a single or double adenoma (adenoma group). The remainder of the patients (hyper group) underwent subtotal (n = 1) or total parathyroidectomy(n = 2) with autotransplantation into the sternomastoid muscle. One was intrathyroidal. Two of our patients in the hyper group had enlargement of only three glands.

The adenoma patients consisted of 7 patients who underwent limited resection of one or two adenomas. The hyper -plsia patients included all patients who underwent subtotal or total parathyroidectomy with autotransplantation. No differences were noted between these two groups with regard to age, gender, symptoms, duration of dialysis, or time between start of dialysis and parathyroidectomy. We also compared the preoperative laboratory values (serum calcium, PTH, creatinine, and phosphate levels) of the two groups; no significant differences in these values were observed (Table 2).

In comparing the postoperative outcomes of the two groups, there was no significant difference in the mean serum calcium, phosphate, or alkaline phosphatase level, duration of operation, or follow-up (Table 4 and figure 5,6).

There was a significantly higher rate of transient postoperative hypocalcemia in the hyperplasia patients (30%) and than in the adenoma patients (5%) (Table 6). Importantly, one of the patients in the hyperplasia group with enlargement of a single gland underwent a subtotal parathyroidectomy and developed hypocalcemia. Two patients of hyper group underwent total parathyroidectomy with autotransplant. Patients who had transient postoperative hypocalcemia required oral calcium and/or vitamin D supplementation lasting 2 to 18 months. In all patients, hypocalcemia resolved. In contrast, only one of the patients in the adenoma patients required oral calcium and vitamin D supplementation for several weeks. Low serum calcium level coincided with an episode of acute pancreatitis; thus, it is unclear whether the etiology of hypocalcemia was truly secondary to the surgery performed or to the pancreatitis.

Other surgical complications in either group were rare. There were no postoperative hematomas or infections, and only one patient experienced transient, recurrent laryngeal nerve neuropraxia that resolved within 2 weeks.

Follow-Up :

The average follow-up was 36 months. Although there were more instances of recurrence or persistent disease in the hyperpasia patients (n = 1) versus the adenoma patients (n = 0), this did not approach statistical significance (Table 7).

Table (1): Demographics and Presentation

	Adenoma (n= 7)	Hyper (n= 3)	P value
Mean age (years)	45 ± 3.65	34.67 ± 2.52	0.002*
M:F	5 : 2	1 : 2	0.260
Symptomatic	Symptomatic	Symptomatic	–
Duration of dialysis (months)	30.43 ± 3.6	20.67 ± 2.08	0.003*

Table (2): Preoperative laboratory values

	Adenoma (n= 7)	Hyper (n= 3)	P value
Calcium (mg/dL)	11.23 ± 0.67	10.83 ± 0.47	0.384
Phosphate (mg/dL)	2.87 ± 0.44	2.64 ± 0.54	0.502
Creatinine (mg/dL)	2.49 ± 0.43	2.5 ± 0.56	0.966
Alkaline phosphatase (U/L)	189.29 ± 21.3	200.67 ± 10.07	0.413
Intact PTH (pg/mL)	489 ± 77.91	543.3 ± 115.9	0.402

Table (3): Preoprative symptoms

Symptoms	No. of patients
Bone pain	2
Muscular pain	9
Metal status changes	3
Pancreatitis	2
Renal calculi	9
Metastatcic calcifications	3
Diarrhea	3
Insomia	3
Total	**10**

Table (4): Postoperative laboratory values and follow-up data

	Adenoma (n= 7)	Hyper (n= 3)	P value
Calcium	9.12 ± 0.37	9.08 ± 0.16	0.874
Phosphate	3.36 ± 0.29	3.46 ± 0.04	0.583
Alkaline phosphatase	89.93 ± 8.73	98.73 ± 2.04	0.039*
Intact PTH (pg/mL)	54.01 ± 6.14	48.43 ± 2.54	0.177

Table (5): Comparison between pre and post laboratory values.

	Preoperative	Postoperative	P value
P.T.H	505.3 ± 87.87	52.34 ± 5.82	0.000*
Calcium	11.11 ± 0.62	9.11 ± 0.31	0.000*
Phosphate	2.80 ± 0.45	3.39 ± 0.24	0.006*
Alkaline phosphatase	192.7 ± 18.84	92.57 ± 8.36	0.000*

Table (6): Postoperative complications

	Adenoma (n=)	Hyper (n=)	P value
Transient hypocalcemia	1/19(5%)	14/52 (27%)	0.036
Permanent hypocalcemia	0	0	NS
Transient RLN injury	0	1/52 (2%)	NS
Permanent RLN injury	0	0	NS
Recurrence/persistence disease	0	3.52 (6%)	NS
Mean duration of follow-up (months)	69.3 ± 11.5	60.1 ± 7.3	NS

Table (7): Postoprative symptoms

Symptoms	No. of patients
Bone pain	1
Muscular pain	2
Metal status changes	0
Pancreatitis	0
Renal calculi	0
Metastatcic calcifications	0
Diarrhea	1
Insomia	0
Total	10

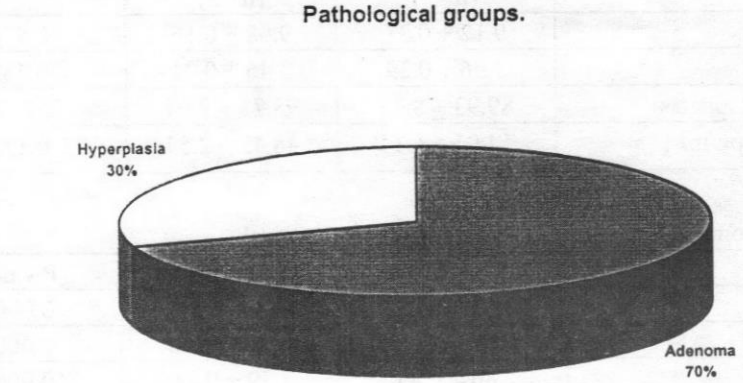


Figure1: show relations between hyperplasia and adenoma patients

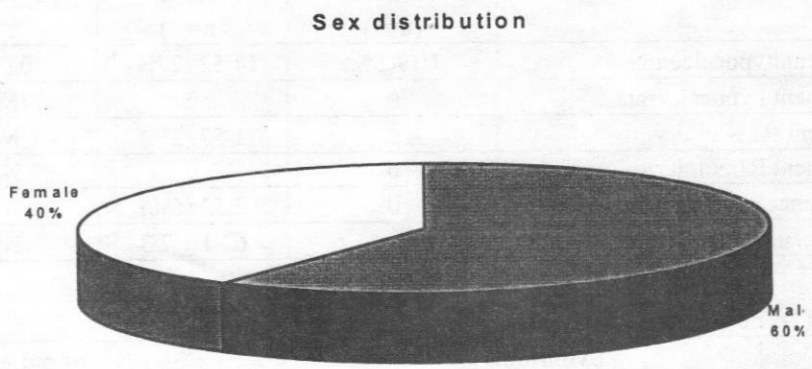


Figure2: show relations between males and females

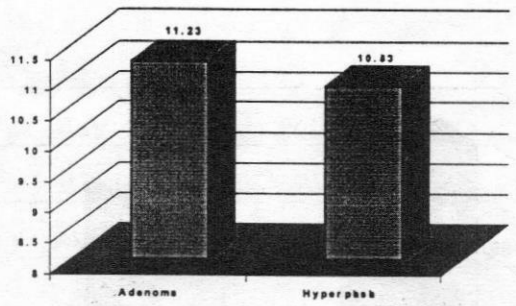


Figure 3: Calcium level preoperative (mg/dL)

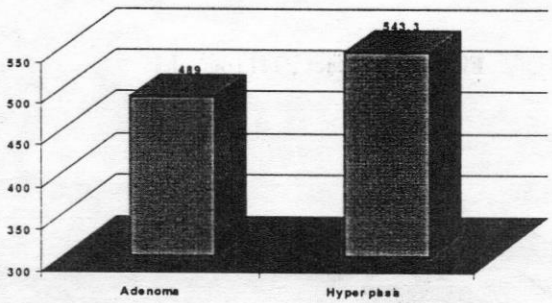


Figure 4 : Intact PTH preoperative (pg/mL

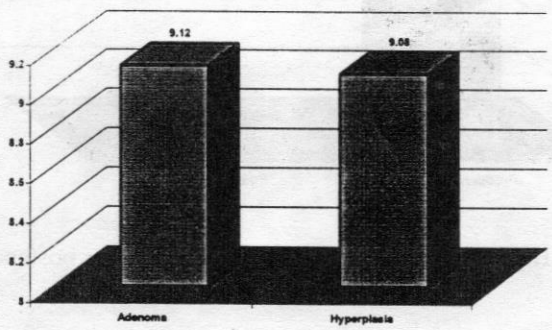


Figure 5 : Calcium level postoperative (mg/dL)

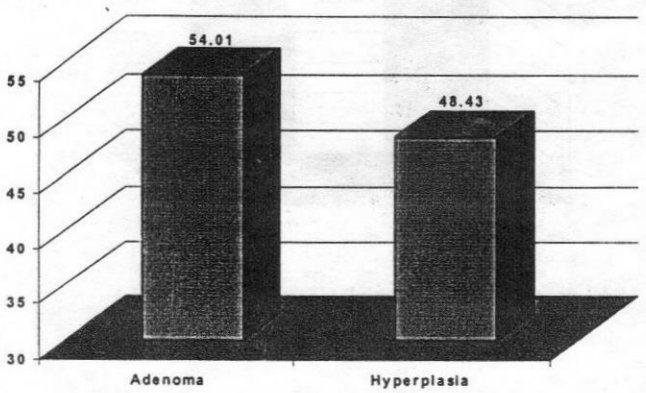


Figure 6 : Intact PTH (pg/mL)

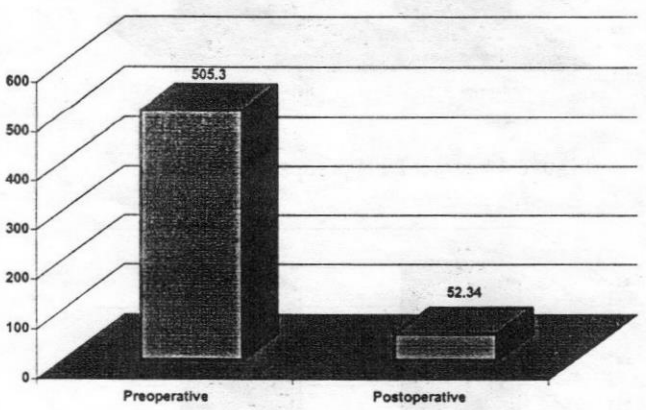


Figure 7 : P.T.H parathyroid hormone preoperative versus postoperative.

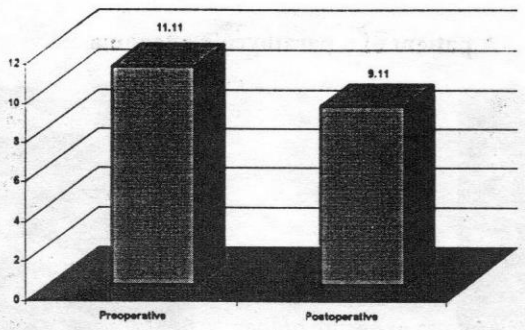


Figure 8 : Calcium level preoperative versus postoperative.

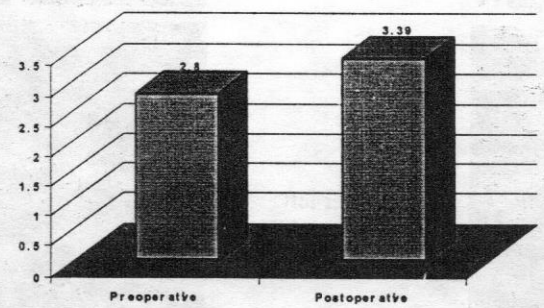


Figure 9 : Phosphate preoperative versus postoperative.

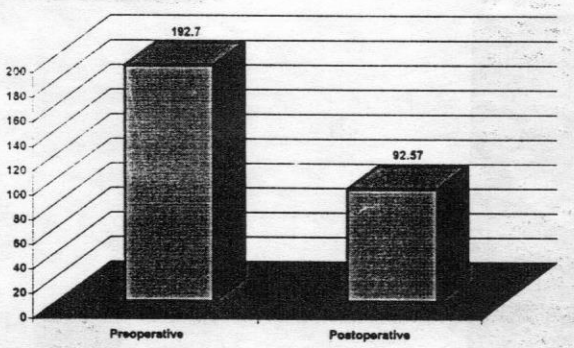
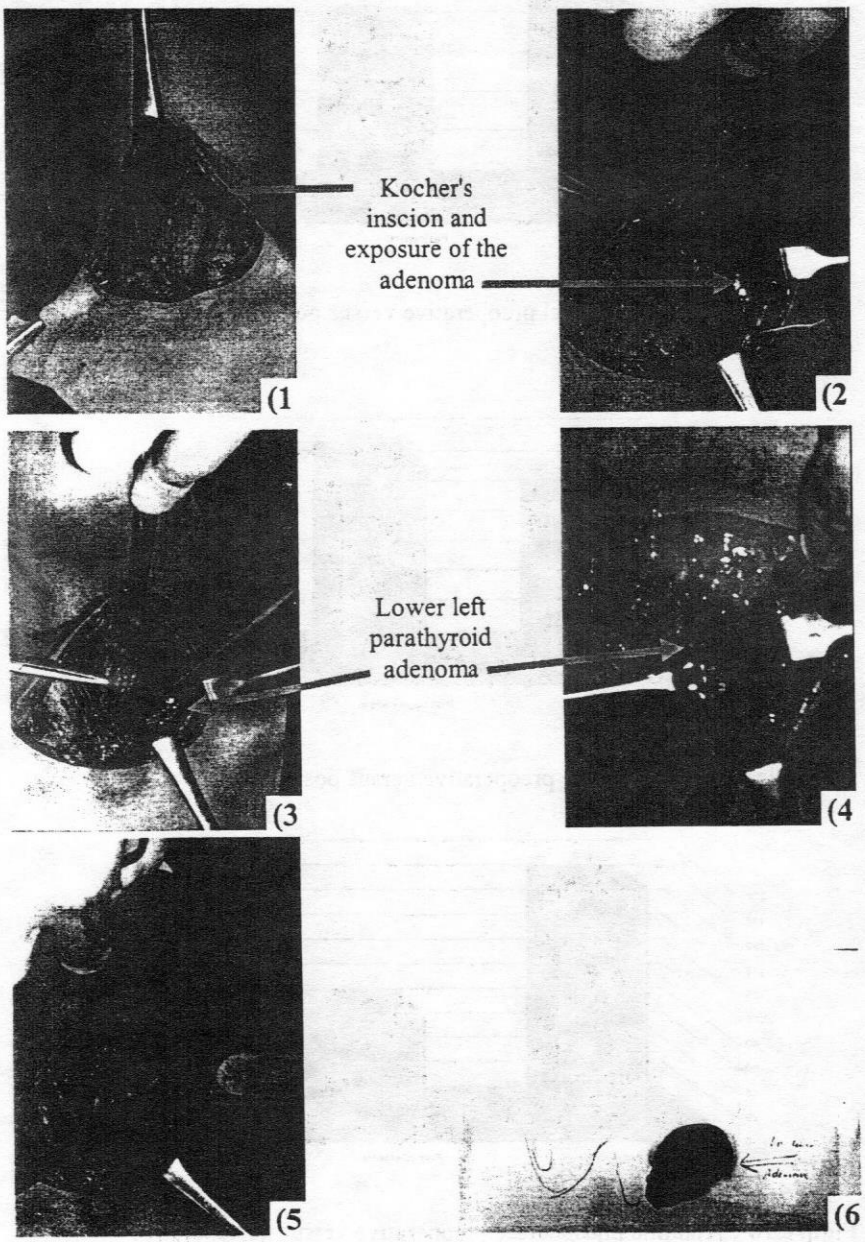


Figure 10 : Alkaline phosphatase preoperative versus postoperative.

A patient of a parathyroid adenoma



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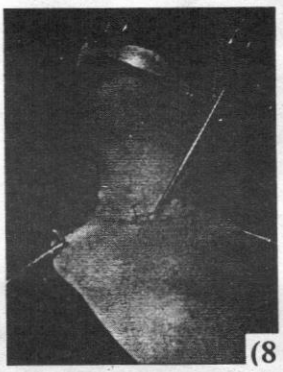

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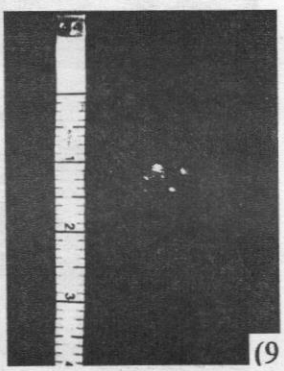
Closure of the incision wound



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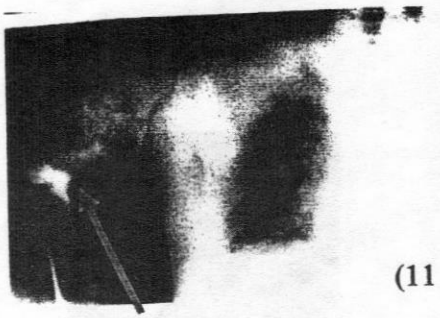
Excision specimen

(1

after 3 months

A patient of parathyroid hyperplasia



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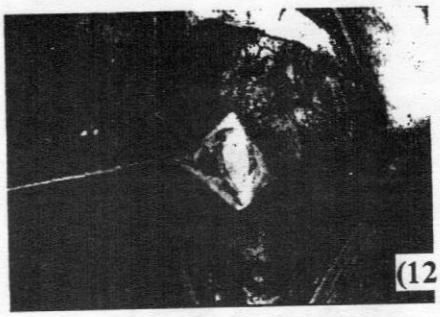

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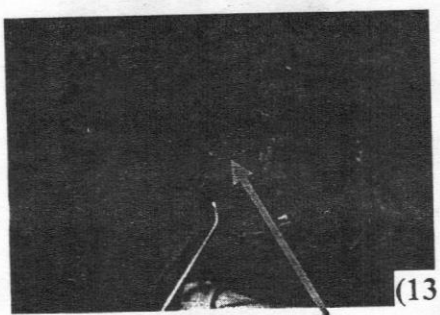
Pathological fracture



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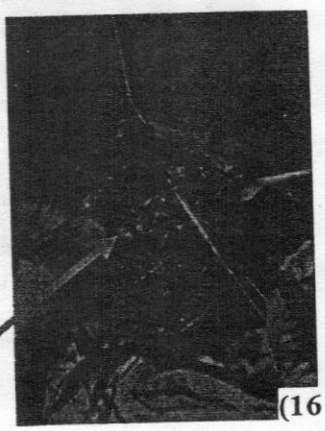
(14

Right and lift lower parathyroid gland hyperplasia

(15



(16

Right and lift upper parathyroid gland hyperplasia

DISCUSSION

We reported our experience and outcomes with surgical management of tertiary hyperparathyroidism. The incidence of this disease is less than 2% in this index population. Nevertheless, it is a disease that produces debilitating symptoms in the majority of patients [7]. Parathyroidectomy in patients with tertiary hyperparathyroidism is associated with a long-term cure rate of 99%. Numerous studies have reported on the incidence of adenoma as the cause of tertiary hyperparathyroidism. The incidence ranges from 0% to 32%. The incidence of single or double adenoma in our series was 30%[5]. As with previous series, several of our patients were found to have asymmetric hyperplasia limited to one or two glands, whereas others had true adenomas on pathologic section[10]. We did not distinguish between these two disease entities at the time of surgery because it would not have altered our surgical approach. Further, patients with either process had similar outcomes. Nevertheless, this issue raises question.

Do patients with asymmetric hyperplasia represent a group in which only one or two glands develop a persistent secondary hyperplastic response after the resolution of uremia?[9]

However, for the purposes of managing patients with enlargement of only one or two glands, distinguishing between these two potential disease entities appears to be unnecessary[8].

The incidence of postoperative complications was 2% and consisted of 1 case of postoperative transient hy-pocalcemia and 1 case of temporary recurrent laryngeal nerve neuropraxia. This is consistent with previous series. The incidence of postoperative transient hypocalcemia was significantly higher in the hyperplasia group. Two of these patients underwent total parathyroidectomy with autotransplantation, for which hypocalcemia is a frequent and well-recognized complication. However, in reviewing a third subset of patients (those with 3-gland disease who underwent 3.5-gland resection), there was a higher rate of hypocalcemia compared with patients with 4-

gland hyperplasia who underwent an identical operation. Further, of the two patients with adenomas who underwent subtotal parathyroidectomy, significant postoperative hypocalcemia developed in one. These findings are consistent with previous studies and suggest that aggressive resection of parathyroid tissue, particularly in patients who do not have four-gland disease, may not leave adequate parathyroid tissue in situ to prevent postoperative hypocalcemia[13].

We hypothesize that patients with enlargement of only one or two glands have a more limited disease process than those with four-gland hyperplasia and do not require a subtotal or total parathyroidectomy with autotransplantation to achieve similar rates of long-term eucalcemia. The lack of recurrent disease in the adenoma group after limited resection suggests that this hypothesis is correct [5]. Alternatively, a more aggressive resection in this group of patients is not only unnecessary but may also subject them to a greater risk of postoperative hypocalcemia. The data presented here support a surgical strategy of resection limited to enlarged glands so that postoperative complications can be minimized[9].

There have been numerous other series, including two from our endocrinesurgery unit, regarding the surgical strategy for tertiary hyperparathyroidism. Several of these operations describe the results of limited resection for single and double adenoma. Results from the latter studies have been mixed. (Gasparri et al) recommended a more aggressive surgical resection because limiting resection to less than a subtotal parathyroidectomy resulted in a very high rate of recurrence of disease. In contrast, (Kilgo et al) described a limited strategy for single and double adenoma with very favorable outcomes and no recurrent disease at follow-up.

Our data support this more limited strategy for the following reasons. First, there is a high incidence of postoperative hypocalcemia after subtotal parathyroidectomy that is even greater with disease limited to less than four glands. Second, our longterm data indicate that limiting resection to the affected glands only in patients with single or double adeno-

ma results in a cure rate of 100% at 3 years of follow-up. Importantly, there was no significant difference in the rate of recurrence between the adenoma and the hyper groups[6].

This surgical strategy is to perform a formal neck exploration with clinically significant tertiary hyperparathyroidism. Because most of these patients will have resolution of their hypercalcemia within this period. Thereafter, all pa-tients with hypercalcemia are explored and the size of all four glands is evaluated to determine whether the disease is due to single or double adenoma or hyperplasia. If disease involves only one or two glands, then the enlarged glands are resected. In patients with hyperplasia, we recommend 3.5-gland resection with tagging of the remaining half-gland with a nonabsorbable, colored suture. We prefer to avoid total parathyroidectomy with autotransplantation for hyper-plasia because of the high postoperative incidence of hypocalcemia and the low rate of recurrence after 3.5-gland parathyroidectomy[11]. If all four glands cannot be identified? then a cervical thymectomy should be per-formed after complete exploration of the neck. With this strategy, we were able to locate seven ectopic glands, without having to perform a median sternotomy(12).

CONCLUSION

The medical management of tertiary hyperparathyroidism has yet to decrease the need for parathyroidectomy, suggesting that although medical such advances as calcitriol administration may improve serum levels of minerals, they have not altered disease progression. Advances in pharmacotherapy and dialysis continue, but medical management remains suboptimal. Parathyroid surgery remains an important, often necessary therapeutic option for patients with hyperparathyroidism associated with renal failure.so from this study we can conclude that the optimal treatment of tertiary hyperparathyroidism is the surgerical exsion of the individual adenoma or adenomas or exsion of (3.5) of parathyroid glands and transplantation of the remaining half in the sternomastoid muscle in case of hyperplasia type.

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تأثير استئصال الغدة الجار درقية على مرضى الفشل الكلوى المزمن والمصحوبة بأعراض زيادة لإفراز الغدة الجار درقية (دراسة إسترجاعية)

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كلية الطب - جامعة المنصورة

مقدمة البحث :

يعتبر زيادة نشاط الغدة الجار درقية الثالثى حالة خاصة من زيادة نشاط الغدة الجار درقية الثانوى وذلك عندما يستمر إفراز الغدة الزائدة الثانوى على الرغم من تصحيح سبب زيادة الإفراز وفى هذه الحالة يطلق عليه إسم زيادة نشاط الغدة الجار درقية الثالثى.

وكذلك بقاء زيادة هرمون الغدة الجار درقية بعد عملية نقل للكلى (زرع كلوى) يعد هو السيناريو المعتاد لتوضيح أن الغدة قد تحولت الى غدة ذات إفراز ذاتى دون تأثير خارجى من قبل الكالسيوم والفوسفات وهى من العناصر الموجودة فى الدم حيث تصبح زيادة الافراز ذاتية وغير مرتجعة.

ومن ثم فإن الحاجة للتدخل الجراحى فى مثل هذه الحالات تزداد بزيادة عدم قابلية هذه الزيادة فى الهرمون للعلاج الطبى - أو تصحيح السبب المباشر للزيادة ومثل هذه الحالات تحدث بالتدريج وعلى فترات طويلة حيث أنه فى خلال تلك الفترة يكون المريض بالفعل قائم بالغسيل الكلوى _ والملاحظة الطبية والتصحيح المستمر للكالسيوم والفوسفات بالدم ومراقبة نسبة هرمون الغدة الجار درقية وعلى الرغم من أنه الاستئصال الكامل للغدة الجار درقية يعد أمر معقد ولكنه من الحلول المنطقية لمثل هذه المشكلة.

خطة البحث :

تم دراسة عدد ١٠ حالات مصابة بأعراض وعلامات زيادة افراز الغدة الجاردرقية وتبين من الدراسة وجود عدد ٧ حالات مصابة بورم أو أورام بسيطة متعددة فى الغدة الجاردرقية. ووجود إصابة (عدد ٣ حالات) زيادة افراز ونشاط الغدة الجاردرقية دون الإصابة بتورم ملحوظ بها

وتم إجراء التحاليل والفحوصات اللازمة قبل إجراء التدخل الجراحى واشتملت على الآتى.

١- تعيين نسبة الكالسيوم والفوسفات فى الدم.

٢- تعيين نسبة هرومون الباراثرمون.

٣- عمل الأشعات المختلفة ومنها الأشعة العادية ، الأشعة التليفزيونية ، الأشعة المقطعية ، الأشعة باستخدام الرنين المغناطيسى إذا اقتضى الأمر.

تم التدخل الجراحى فى الحالات ، تم اجراء استئصال الغدد المصابة بالأورام الحميدة وعددهم ٧ وفى الحالات التى بها زيادة نشاط دون وجود تورمات (عددهم ٣ حالات) تم استئصال الغدد الجاردرقية الأربعة مع أخذ غدة واحدة منهم حيث تم تقسيمها إلى قسمين وأخذ قسم واحد منها حيث تم تقسيمه إلى جزيئات صغيرة من ٦ - ٨ جزيئات تم وضعها فى جيب فى عضلة الرقبة (Sternomastoid)

بعد إجراء العملية تم متابعة المريض أسبوعيا لمدة ثلاثة أشهر حيث تم اجراء التحاليل التالية:

- الكالسيوم بالدم.

- الفوسفات بالدم.

وبعد ثلاثة أشهر من إجراء العملية تم تعيين نسبة هرمون الباراثرمون فى الدم.

الخلاصة:

من هذا البحث تبين أن التدخل الجراحى هوالعلاج الأمثل فى حالات زيادة إفراز الغدة الجاردرقية الثالثى حيث يتم استئصال الورم فى حالات وجود الأورام أو عدد (٣ر٥)غدة جاردرقية فى حالة عدم وجود ورم مع زرع النصف المتبقى فى عضلة الرقبة (sternomastoid muscle).