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Rom J Diabetes Nutr Metab Dis. **20**(1):063-067
doi: 10.2478/rjdnmd-2013-0008

GLUCOSE HOMEOSTASIS IN PATIENTS WITH PHEOCHROMOCYTOMA

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received: December 13, 2013 *accepted*: January 14, 2013
available online: March 15, 2013

Abstract

Background and Aims. *Previous studies have shown that impaired glucose tolerance is present in patients with pheochromocytoma with a prevalence of 25–75%. The aim of this study was to examine glucose tolerance in 12 patients with pheochromocytoma, before and after medical and surgical treatment.* ***Material and Methods****. We evaluated 12 patients aged between 44 and 60 years with confirmed pheochromocytoma. Plasma insulin, fasting blood glucose and 2h glucose levels during the oral glucose tolerance test (OGTT) were measured before and three months after surgical removal of the tumor.* ***Results.*** *Surgical removal of the tumor generated significant changes in plasma and urinary metanephrines (plasma normetanephrine 191.15±13.22 pg/ml after treatment vs. 792.54±86.74 pg/ml at baseline, p<0.0001, plasma metanephrine 86.69±4.48 pg/ml vs. 363.62.±21.69 pg/ml, p<0.0001, urinary normetanephrine 718.54±37.59 µg/day after treatment vs. 1855.77±116.54 µg/day at baseline and urinary metanephrine of 258.31±34.00 µg/day vs. 745.38±65.14 µg/day, p<0.0001) but not in insulin, fasting and 2h glucose levels during OGTT.* ***Conclusion.*** *In our study, the prevalence of impaired glucose tolerance in patients with confirmed pheochromocytoma was 8.33% (1 patient with a previous family history of diabetes). After surgical removal of the tumor, normalization of mean glucose levels of OGTT was not achieved.*

key kords: *pheochromocytoma, impared glucose tolerance, surgical treatment.*

Introduction

Pheochromocytoma is a neuroendocrine tumor of the medulla of the adrenal glands that secretes high amounts of catecholamines, usually norepinephrine and epinephrine. Catecholamines interfere with carbohydrate metabolism by stimulation of adreno-receptors with subsequent modulation of pancreatic insulin and glucagon release. Stimulation of

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alpha 2 adreno-receptors by catecholamines results in inhibition of insulin secretion by the pancreas while stimulation of beta receptors in the liver leads to an increase in glucose production by enhanced glycogenolysis and gluconeogenesis [1].

Previous studies have shown that impaired glucose tolerance is present in patients with pheochromocytoma, with a prevalence ranging between 25-75% [2,3]. Decrease of plasma catecholamines after removal of adrenal tumors results in an improvement of carbohydrate metabolism [4].

The aim of our study was to examine glucose tolerance in 12 patients with pheochromocytoma, before and after medical and surgical treatment.

Materials and Methods

We evaluated 12 patients aged between 44 and 60 years, with a confirmed diagnosis of pheochromocytoma. The study group included 8 men (66.66%) and 4 women (33.33%) and the median age was 51±6.22 years (49.5±8.4 years in males and 52.2±6.9 years in female). 1 patient (8.33%) had a positive family history for diabetes. The diagnosis of pheochromocytoma was based on the presence of suggestive symptoms and signs and biochemical determinations (by measuring metanephrines in plasma or through a 24-hour urine collection). The term "metanephrines" describes two catecholamine metabolites: normetanephrine, and metanephrine. Plasma metanephrines were measured using commercial ELISA kits (normal range for plasma normetanephrine is <200 pg/ml and for metanephrine <90 pg/ml). Urinary metanephrines were determined by high-performance liquid chromatography (HPLC) analysis (normal range for urinary normetanephrine is <779 µg/day in males and <632 µg/day in females while for urinary metanephrine <276 µg/day in males and <375 µg/day in females). After biochemical confirmation of the diagnosis, preoperative localization of pheochromocytoma was achieved by computerized tomography. Serum insulin, fasting blood glucose and 2h glucose levels during the oral glucose tolerance test (OGTT) were evaluated before and three months after the surgical removal of the tumor. Insulin was evaluated using an ELISA kit and plasma glucose was determined using automatic devices.

Statistical analysis

Data are presented as mean ± standard deviation (SD). Clinical characteristics were compared using the t Student Test. Pearson's moment-product correlation coefficients were calculated to evaluate correlations between variables. Significance was defined at the 0.05 level of confidence. All calculations were performed using the Statistical Package for Social Sciences Software (SPSS) version 15.

Results

Plasma metanephrines and urinary metanephrines before and after surgical removal of the tumor are shown in Table 1 Figure 1 and Figure 2.

As shown, surgical removal of the tumor generated significant changes in plasma metanephrines. Thus, plasma normetanephrine decreased significantly, from 792.54±86.74 pg/ml at baseline to 191.15±13.22 pg/ml after treatment *(*p<0.0001). In the same time, plasma metanephrine significantly decreased from 363.62.±21.69 pg/ml at baseline to 86.69±4.48 pg/ml after surgical removal of the tumor (p<0.0001).

Table 1. Plasma and urinary metanephrines levels before and after surgical removal of the tumor.

	Before treatment	After treatment	p *vs.* baseline
Plasma normetanephrine (pg/ml)	792.54±86.74	191.15±13.22	p<0.0001
Plasma metanephrine (pg/ml)	363.62±21.69	86.69±4.48	p<0.0001
Urinary normetanephrine (µg/day)	1855.77±116.54	718.54±37.59	p<0.0001
Urinary metanephrine (µg/day)	745.38±65.14	258.31±34.00	p<0.0001

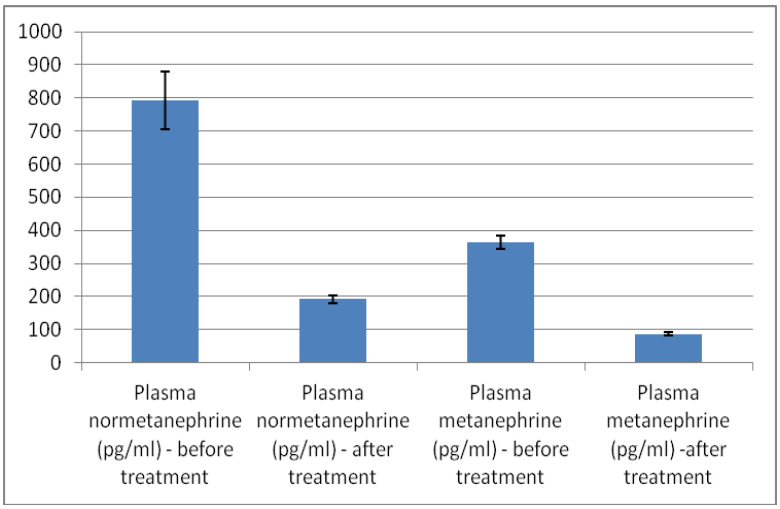

Figure 1. Changes in plasma metanephrines before and after surgical removal of the tumor.

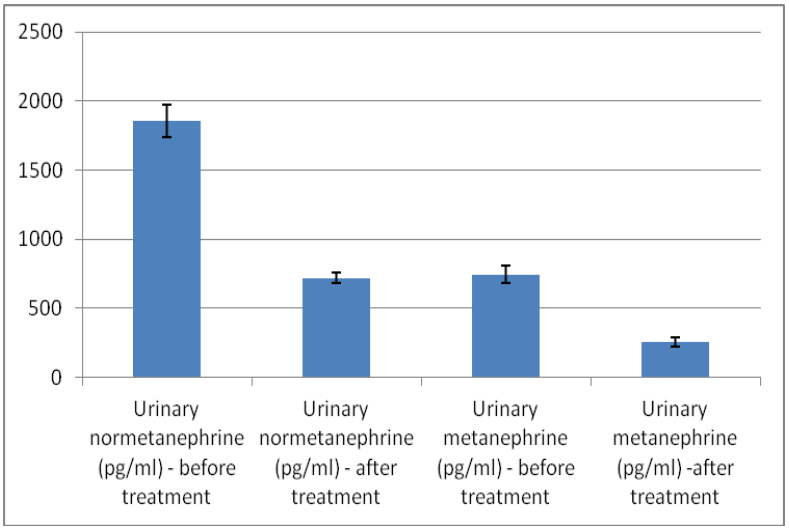

Figure 2. Changes in urinary metanephrines before and after surgical removal of the tumor.

Meanwhile, surgical removal of the tumor generated significant changes also in the levels of urinary metanephrines (Figure 2). Thus, urinary normetanephrine decreased significantly, from 1855.77±116.54 µg/day at baseline to 718.54±37.59 µg/day after treatment while urinary metanephrine decreased from 745.38±65.14 µg/day at baseline to 258.31±34.00 µg/day after treatment (p<0.0001).

Insulin, fasting blood glucose and 2h glucose levels during OGTT, before and after surgical removal of the tumor are given in Table 2 and Figure 3.

Table 2. Insulin, fasting blood glucose and 2h glucose levels during OGTT before and after treatment.

	Before treatment	After treatment	p *vs.* baseline
Insulin (µU/ml)	5.76±0.37	5.57±0.32	p=0.052
Fasting plasma glucose (mg/dl)	85.92±8.44	84.69±9.64	p=0.021
2h glucose (mg/dl) during OGTT	127.54±14.11	124.54±10.76	p=0.064

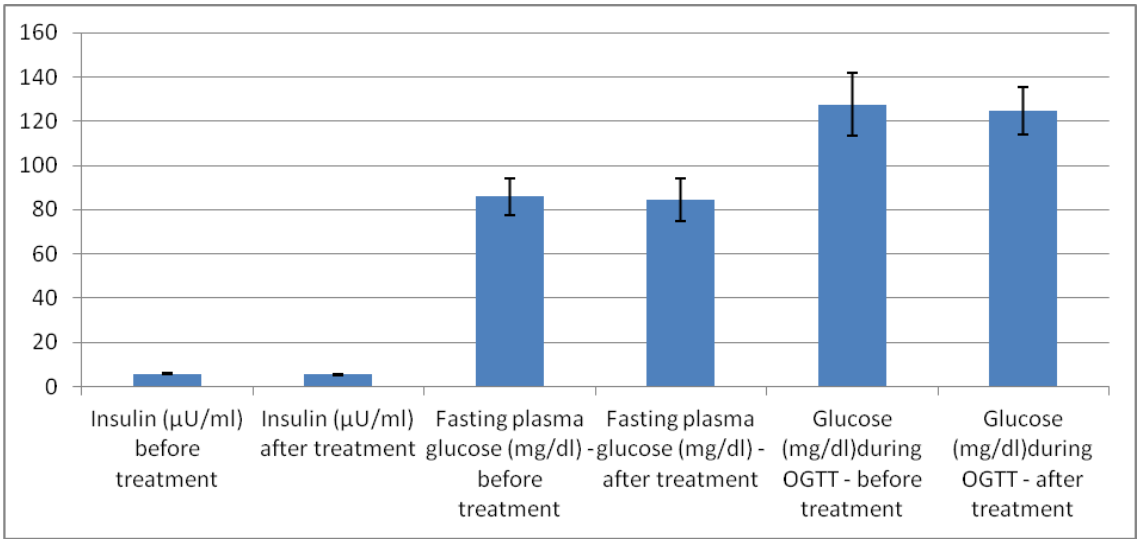

Figure 3. Changes in serum insulin, fasting blood glucose and 2h glucose levels during OGTT before and after treatment.

As shown, a slight decrease of serum insulin levels was recorded after surgery (5.57±0.32 µU/ml vs. 5.76±0.37 µU/ml at baseline), decrease that was not statistically significant. The same was true for 2h blood glucose level during OGTT, with a slight decrease from 127.54±14.11 mg/dl at baseline to 124.54±10.76 following surgery (p = NS).

We also observed a marginally significant (p = 0.021) decrease of the fasting blood glucose levels from 85.92±8.44 mg/dl at baseline to 84.69±9.64 mg/dl following surgery.

Discussion

In all patients, complete removal of the pheochromocytoma was achieved, Previous studies reported that impaired glucose tolerance is present in patients with pheochromocytoma with a prevalence ranging from 25 to 75% [2,3]. In our study we found that mean fasting plasma glucose and 2h plasma glucose levels during OGTT were normal in 11 patients (91.66%) while impaired glucose tolerance was present in 1 patient (8.33%) with pheochromocytoma (a patient with a positive family history of diabetes). After surgical removal of the tumor, normalization of mean glucose levels of OGTT in the patient with impaired glucose tolerance was not achieved.

There are relatively few studies that evaluated glucose tolerance in patients with pheochromocytoma, A study performed by Diamanti-Kandarakis *et al.* analyzed five patients (3 women and 2 men) with pheochromocytoma before and after medical and surgical treatment. They found that mean glucose levels during OGTT were abnormally increased before any medical treatment while

surgical removal of the tumor led to the normalization of mean glucose levels during OGTT [1]. Wiesner *et al*. published in 2003 in the *Journal of Clinical Endocrinology & Metabolism* an article entitled "*Improvement of insulin sensitivity after adrenalectomy in patients with pheochromocytoma*" [4]. The authors evaluated 10 patients (6 women and 4 men) with pheochromocytoma, and reported that: "*Lowering of plasma catecholamines after removal of adrenal tumors resulted in an improvement of insulin sensitivity in all patients. However, a normalization of the glucose infusion rate required to maintain euglycemia during the clamp as determined by euglycemic hyperinsulinemic clamp was only achieved in two patients. In these patients, insulin treatment could be stopped. In two patients, insulin treatment could be converted into oral antidiabetic treatment (metformin) after surgery and in another patient the daily insulin dose could be significantly decreased. The improvement of insulin action is further supported by decreased hyperinsulinemia in all patients after adrenalectomy*".

In our study normalization of 2h glucose level during OGTT in the patient with impaired glucose tolerance was not achieved following surgical treatment.

Conclusion

In our study, the prevalence of impaired glucose tolerance in patients with confirmed pheochromocytoma was 8.33% (1 patient with a positive family history of diabetes). After surgical removal of the tumor, normalization of mean 2h glucose levels following OGTT was not achieved.

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