Original Research

METABOLIC DISEASES

Evolution of metabolic disorders after resection of pheochromocytomas and paragangliomas: a single-center study

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Abstract

Background and aims. Pheochromocytomas and paragangliomas are rare neuroendocrine tumors, responsible for inappropriate secretion of catecholamines, inducing metabolic disorders, increasing basal metabolic rate. Our study aimed to analyze the metabolic profile pre- and post-operatively in patients undergoing surgery for pheochromocytomas and paragangliomas and additionally to determine the predictive factors of metabolic remission.

Methods. This was a retrospective, unicentric, descriptive, and analytical study with a duration of 9 years. It includes data from 35 patients followed up for pheochromocytoma or paraganglioma in the Endocrinology-Diabetology and Nutrition Department of a University Hospital Center. All patients underwent surgery for pheochromocytoma or paraganglioma.

Results. Among the 35 patients, 51.4% of the patients with pheochromocytomas had diabetes mellitus, and 42.8% had dyslipidemia. We found that high levels of catecholamines were associated with the onset of diabetes. We also noted that patients with a long history of the disease were statistically at greater risk of developing dyslipidemia. After surgery, the body mass index of our patients had statistically increased, and 50% of patients experienced resolution or improvement of their diabetes. Improvement of dyslipidemia was observed in 53% of patients. We also found that the percentage of dyslipidemia was higher in patients who did not resolve their diabetes.

Conclusion. Diabetes mellitus and dyslipidemia are metabolic complications that must be investigated in patients with pheochromocytoma. Post-operative monitoring of body mass index and changes in glycemic and lipid levels is essential to adapt therapeutic management.

Keywords: pheochromocytoma, metabolic diseases, diabetes mellitus, catecholamines, basal metabolism

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Background and aims

Pheochromocytomas and paragangliomas are rare neuroendocrine tumors, derived from the chromaffin cells of the adrenal medulla for pheochromocytomas, and sympathetic and parasympathetic ganglia for paragangliomas [1,2]. In addition to cardiovascular complications, such as hypertension, arrhythmias, acute coronary syndrome, dilated cardiomyopathy, and thromboembolism; these neuroendocrine tumors can induce carbohydrate tolerance disorders by reducing insulin secretion, and inducing insulin resistance [3-5]. Dyslipidemia is also often associated with elevated catecholamine levels, affecting weight gain [6,7]. Therefore, several studies focused on the impact of pheochromocytomas and paragangliomas, especially on carbohydrate metabolism, lipid metabolism, and weight gain [7]. Many studies have also been interested in the evolution of these parameters after surgical treatment [8]. However, few studies have focused on the factors predisposing to metabolic disorders and the remission factors postoperatively. Therefore, the primary objective of our study was to evaluate the metabolic profile (diabetes, lipid profile, BMI) pre- and post-operatively in patients undergoing surgery for pheochromocytoma and paraganglioma. The secondary objective is to assess the risk factors influencing the occurrence of metabolic disorders.

Methods

Study design and patients

This was a retrospective, descriptive, and analytical study. It was conducted for a duration of 9 years. It involved data from 35 patients followed up for pheochromocytoma or paraganglioma in the Endocrinology-Diabetology and Nutrition Department of Mohammed VI University Hospital Center of Oujda, Morocco. We included all patients who underwent surgery for pheochromocytoma or paraganglioma. Patients who received steroids postoperatively and those with incomplete records were excluded.

Study protocol

The clinical data that were collected, included age, sex, weight, body mass index (BMI), blood pressure, and the presence or absence of preoperative clinical symptoms. The term symptomatic was defined by the presence of the classic Menard triad: headache, sweating, and palpitations. Hypertension was defined as systolic blood pressure greater than 140 mmHg and diastolic blood pressure greater than 90 mmHg, confirmed on several measurements. Pre- and postoperative catecholamine levels were assessed, as were tumor characteristics such as size and localization. The diagnosis of pheochromocytoma was based on measuring metanephrines or normetanephrines in plasma (metanephrine < 65 ng/l, normetanephrine < 196 ng/l, using Liquid chromatography-tandem mass spectrometry (LC-MSMS)) or 24-hour urine (Normetanephrine: 0.40-2.50 µmol/l, Metanephrine: 0.2-1.5 µmol/l, using LC-MSMS), and positive imaging. Computed tomography (CT) scan or magnetic resonance imaging (MRI) were used for imaging. The diagnosis was confirmed histologically after an anatomopathological study [1,2]. Postoperative catecholamine levels were within the normal range. Not all patients had both blood and urine tests performed. Therefore, preoperative urine and blood tests were converted into fold changes over the upper limit of normal. The fold change will be referred to as ‘catecholamines’. Postoperative catecholamine levels were within the normal range.

Pre- and postoperative glycemic data were collected, as well as medication adjustments. BMI was calculated according to the formula: weight in kg/height in m². A BMI greater than 25 kg/sqm was defined as overweight, and a BMI greater than 30 was defined as obesity. Diabetes mellitus was defined as glycated hemoglobin (HBA1c) ≥ 6.5%, fasting plasma glucose ≥ 1.26 g/l, and prediabetes as HBA1c ≥ 5.7% (using high-performance liquid chromatography (HPLC)). The resolution of diabetes after surgery was defined by either a reduction of medication used, an improvement in HBA1c, or its normalization. Dyslipidemia was defined by a value above or under the normal range depending on each parameter: Total cholesterol (TC) > 2 g/l, Triglycerides (TG) ≥ 1.50 g/l, High-density lipoproteins (HDL) < 0.5 g/l in women, and < 0.4 in men. The (Low-density lipoprotein-cholesterol) LDL value interpretation was done according to the cardiovascular risk [9]. Spectrophotometry was used for the lipid profile workup.

Statistical Analysis

Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS), version 21. Quantitative results were presented as mean ± standard deviations and qualitative results as frequencies. Variables were analyzed using the Student’s test and Chi-square tests. To study the predictive factors of metabolic remission we used univariate logistic regression. A p-value <0.05 indicated statistical significance.

Ethics

The ethical review committee approved the study design and protocol. The informed consent was waived due to the fact that the study was retrospective.

Results

During the study period, 28 patients underwent surgery for pheochromocytoma and 7 for paragangliomas. The preoperative characteristics of all patients were collected in table I. Out of the 35 patients, 18 (51.1%) met the criteria of preoperative evidence of diabetes. All the patients complicated with diabetes mellitus were treated using oral medication, insulin, or a combination of both. The prevalence of dyslipidemia was 42.8%.

Table I. Preoperative characteristics of patients undergoing adrenalectomy for pheochromocytoma.

	Patients with pheochromocytoma n=35
Age at surgery, years	48.17 ± 17.4
Female [n (%)]	22 (62.8)
Male [n (%)]	13 (37.1)
BMI	23.2 ± 5.04
Symptomatic [n (%)]	21 (60)
Incidentaloma [n (%)]	14 (40)
Duration of symptoms before diagnosis	24.3 ± 34
Hypertension [n (%)]	20 (57)
Tumor location [n (%)]	
Unilateral	25 (71.4)
Bilateral	3 (8.6)
Extra-adrenal (paraganglioma)	7 (20)
Size on preoperative imaging, cm	5.1 ± 2.9
Fold change catecholamines (range)	14.8 (1.11 - 102)
Diabetes [n (%)]	18 (51.1)
Dyslipidemia [n (%)]	15 (42.85)

In table II, we compared the preoperative characteristics of patients with (n=18) and without diabetes (n=17). As illustrated in the table, patients with diabetes were statistically older than patients without diabetes. Furthermore, the fold change of catecholamine levels was statistically higher in patients with diabetes. The percentage of dyslipidemia was also higher in patients with preoperative diabetes. The rest of the studied parameters were non-significant (Table II).

Table III compares the preoperative data of patients with and without dyslipidemia. The presence of diabetes was statistically correlated with the presence of dyslipidemia. There was also a statistically significant difference in the duration of symptoms before the diagnosis between patients who developed dyslipidemia and those who did not. There was no statistical difference for the other studied parameters (Table III).

After a median follow-up of 60 months (range: 12-108 months), there was a statistically significant increase in post-operative BMI, a decrease in the percentage of dyslipidemia (20% vs. 42.8%), with a significant decrease in the rate of arterial hypertension after adrenalectomy (Table IV).

Table II. Comparison of pheochromocytoma patients with and without preoperative diabetes.

	Diabetes [n=18]	No diabetes [n=17]	p-Value
Age at diagnosis, years	58 ± 14.3	38.28 ± 14.7	0.019
Female [n (%)]	10 (55.6)	12 (70.6)	0,321
Male [n (%)]	8 (44.4)	5 (29.4)	
BMI	25.37 ± 5.7	20.9 ± 2.9	0.098
Hypertension [n (%)]	14 (77.7)	6 (35.2)	0.091
Symptomatic [n (%)]	12 (66.6)	9 (52.9)	0.922
Incidentaloma [n (%)]	6 (33.4)	8 (47.1)	
Duration of symptoms before diagnosis	35.73 ± 49.78	10.1 ± 13	0.148
Tumor location [n (%)]			
Unilateral	13 (72.2)	12 (70.6)	0.082
Bilateral	1 (5.6)	2 (11.8)	
Extra-adrenal (paraganglioma)	4 (22.2)	3 (17.6)	
Size on preoperative imaging, cm	6.2 ± 2.8	4.1 ± 2.8	0.632
Fold change catecholamines (range)	22.8 (1.11-102)	7.3 (1.26-31)	0.032
Dyslipidemia [n (%)]	12 (66.6)	4 (23.5)	0035

Table III. Comparison of pheochromocytoma patients with and without preoperative dyslipidemia.

	Dyslipidemia [n=15]	No dyslipidemia [n=20]	p-Value
Age at diagnosis, years	54.67 ± 15.21	43.52 ± 17.87	0.053
Female [n (%)]	10 (66.7)	12 (60)	0.440
Male [n (%)]	5 (33.3)	8 (40)	
BMI	23.3 ± 5.8	23.2 ± 4.41	0.524
Hypertension [n (%)]	10 (66.6)	10 (50)	0.592
Symptomatic [n (%)]	9 (60)	12 (60)	0.793
Incidentaloma [n (%)]	6 (40)	8 (40)	
Duration of symptoms before diagnosis	38.08 ± 54.99	13.4 ± 16	0.047
Tumor location [n (%)]			
Unilateral	12 (80)	13 (65)	0.806
Bilateral	1 (6.7)	2 (10)	
Extra-adrenal (paraganglioma)	2 (13.3)	5 (25)	
Size on preoperative imaging, cm	1.3± 4.1	4.8 ± 2.9	0.150
Fold change catecholamines (range)	20.06 (1.11-102)	11.37 (1.26-37)	0.202
Diabetes [n (%)]	11 (73.3)	7 (35)	0.029

Table IV. Changes in metabolic parameters of pheochromocytomas patients before and after adrenalectomy.

	Pheochromocytomas and paragangliomas [n=35]		
	Pre-operatively	Post-operatively	p-Value
BMI	23.2 ± 5.04	24.8 ± 5.1	0.000
Dyslipidemia [n (%)]	15 (42.8)	7 (20)	0.000
Arterial hypertension [n (%)]	20 (57.14)	7 (20)	0.009

Table V. Univariable logistic regression analysis of remission factors in diabetes.

	Resolution n=9	No resolution n=9	p-Value
Age at diagnosis, years	58.89 ± 16.29	57.22 ± 13	0.626
Female [n (%)]	5 (55.6)	5 (55.6)	0.644
Male [n (%)]	4 (44.4)	4 (44.4)	
BMI	24.2 ± 4.42	26.5 ± 6.81	0.323
Hypertension [n (%)]	7 (77.8)	7 (77.8)	0.342
Symptomatic [n (%)]	6 (66.7)	6 (66.7)	0.690
Incidentaloma [n (%)]	3 (33.3)	3 (33.3)	0.312
Duration of symptoms before diagnosis	18.14 ± 18.40	51.12 ± 63.91	0.226
Fold change catecholamines (range)	22.85 (2-40)	22.79 (1.11-102)	0.766
Tumor location [n (%)]			0.277
Adrenal	6 (66.7)	8 (88.9)	
Extra-adrenal (paraganglioma)	3 (33.3)	1 (11.1)	
Size on preoperative imaging. cm	7.05 ± 2.14	5.64 ±3.24	0.775
Dyslipidemia [n (%)]	3 (33.3)	8 (88.9)	0.030

Table VI. Univariable logistic regression analysis of remission factors in dyslipidemia.

	Resolution N=8	No resolution n=7	p-Value
Age at surgery, years	57.13 ± 14.43	51.86 ± 16.71	0.440
Female [n (%)]	4 (50)	5 (71.4)	0.757
Male [n (%)]	4 (50)	2 (28.6)	
BMI	21. ±5.04	25.04 ± 6.54	0.226
Hypertension [n (%)]	5 (62.5)	5 (71.4)	0.715
Symptomatic [n (%)]	6 (75)	3 (42.9)	0.215
Incidentaloma [n (%)]	2 (25)	4 (57.1)	
Duration of symptoms before diagnosis	15.16 ± 14.67	61 ± 71	0.563
Fold change catecholamines (range)	16.16 (1.26-44)	24.5 (1.11-102)	0.270
Tumor location [n (%)]			0.999
Adrenal	6 (75)	7 (100)	
Extra-adrenal (paraganglioma)	2 (25)	0	
Size on preoperative imaging, cm	5.8 ± 2.8	5.4 ± 3.4	0.800
Diabetes [n (%)]	6 (75)	5 (71.4)	0.658

Regarding diabetes, nine patients (50%) had a post-operative improvement or resolution of their diabetes (Table V). In detail, six patients were put postoperatively on dietary hygiene measures alone without any oral or insulin treatment, one switched from insulin treatment to a single oral antidiabetic treatment, and two improved their HBA1c on oral medication.

Patients who had improved or resolved their diabetes were compared with those who had maintained the same treatment with no improvement. The results are shown in Table V. The percentage of dyslipidemia in patients with improved diabetes was lower. The patients who had resolved their diabetes had a lower BMI with a larger tumor size, but the relationships were both non-significant (Table V).

In terms of dyslipidemia, seven patients (46.6%) resolved their dyslipidemia. When comparing the two groups of patients, patients without post-operative dyslipidemia had lower BMI with a shorter duration of progression, but these relationships were not statistically significant (Table VI).

Discussion

In this study, we examined patients who underwent surgery for pheochromocytoma and paraganglioma. Among the 35 patients, 51.4% of the patients with pheochromocytoma had diabetes mellitus, and 42.8% had dyslipidemia. We found that high levels of catecholamines were associated with the onset of diabetes. We also noted that patients with a long history of the disease were statistically at greater risk of developing dyslipidemia. After surgery, the BMI of our patients had statistically increased, and 50% of patients experienced resolution or improvement of their diabetes. Improvement of dyslipidemia was observed in 53% of patients. We also found that the percentage of dyslipidemia was higher in patients who did not resolve their diabetes.

Among the 35 patients in our series, 51.4% had diabetes mellitus. This percentage was higher than the range of 12.41%-40% reported in similar studies [5]. Our patients with diabetes were also found to be older than those without diabetes. Considering that in the general population, the incidence of diabetes is associated with older age and higher BMI, we could suggest that older patients are more likely to develop diabetes if they are exposed to supplementary factors such as pheochromocytoma [10]. However, our study has not shown a relationship between BMI and the development of diabetes, which has been reported in a similar study [5]. The development of diabetes mellitus is very complex and may be due to genetic predisposition, obesity, overweight, reduced physical activity, and inflammatory processes, in addition, weight loss is associated with increased metabolism and lipolysis induced by high catecholamines levels, which could mask the relationship between BMI and diabetes [10]. There was no statistical difference in tumor size between patients with and without diabetes, although the difference was found in a few studies. Beninato et al. [11] reported that patients with diabetes had larger tumors. The same study also showed that large tumor size was associated with high levels of catecholamines, therefore, tumor size may influence the onset of diabetes through increased levels of catecholamines. In our study, we found that high levels of catecholamines were associated with the onset of diabetes regardless of the tumor size. The rate of dyslipidemia was higher in patients who had developed diabetes, but few data are available regarding the effect of catecholamines on lipid metabolism [12]. However, it is well known that dyslipidemia increases the risk of developing diabetes mellitus [9].

Among our 35 patients, 42.8% of patients with pheochromocytoma had dyslipidemia. This percentage was within the range of 31% to 65% regarding the prevalence of dyslipidemia reported in previous studies [12]. There was no significant difference between age in patients with dyslipidemia and those without dyslipidemia, although age is considered an independent risk factor for dyslipidemia [13]. We also noted that patients with a long history of the disease were at greater risk of developing dyslipidemia. Studies have shown that the long history of pheochromocytoma is correlated with a long period of exposure to high levels of catecholamines, which are responsible for the lipolysis phenomenon in adipose tissue [4]. A decrease in the activity of lecithin-cholesterol acyltransferase, the enzyme that breaks down free cholesterol, was also observed in patients with pheochromocytoma compared with patients without pheochromocytomas [12]. This may suggest that elevated catecholamine levels play a role in hyperlipidemia by increasing the synthesis or decreasing the catabolism of lipoproteins [5]. In our study, no significant difference in catecholamine levels was observed between dyslipidemic and non-dyslipidemic patients. Studies have highlighted that glucose intolerance in pheochromocytoma leads to elevated LDL and triglyceride levels, and reduced HDL levels [14]. Also, the reduction in inhibition of lipolysis by insulin has a lipolytic effect on adipose tissue [4].

The BMI of our patients had statistically increased postoperatively, a result similar to previous studies [7,15]. The weight gain can be explained by a return to the baseline metabolic rate after postoperative normalization of catecholamine levels [17].

After surgery, half of our patients experienced resolution or improvement of their diabetes. Other studies have shown different percentages ranging between 78% and 100% [3,5,11,18,19].

Concerning diabetes remission factors, studies have shown that BMI is an independent factor for the remission of preoperative diabetes [19]. Patients with a high BMI are more likely to develop diabetes independently of pheochromocytoma [20]. It can be concluded that patients with a high BMI have less chance of resolving their diabetes despite resection of the pheochromocytoma and may require medication to control their diabetes. In our study, we did not find a significant difference in BMI between patients who resolved or improved their diabetes and patients who remained with unresolved diabetes. However, the BMI in our remitted patients was lower. We also found that the percentage of dyslipidemia was higher in patients who did not resolve their diabetes, even though dyslipidemia is considered to be an independent factor in the onset and progression of diabetes mellitus, regardless of the influence of catecholamine levels [9]. Tumor size and catecholamine levels were higher in patients who had had their diabetes resolved. However, there was no statistically significant difference, which suggests that the main culprit behind the metabolic abnormalities is the tumor itself without any other risk factors, which points to the role of tumor resection in improving metabolic parameters.

Improvement of dyslipidemia was observed in 53% of patients in our study, which was similar to other studies [12]. Dyslipidemia is known to be a cardiovascular risk factor, and it has been reported that resection of these tumors is associated with an improvement of heart function through the improved cardiomyopathy induced by elevated levels of catecholamines [21]. Post-operative improvement of dyslipidemia may therefore reduce cardiovascular risk [22]. Our study did not identify any remission factor of preoperative dyslipidemia, even though several studies have identified a relationship between elevated catecholamine levels and dyslipidemia [4].

There are several limitations to this study. First, the study is a retrospective review of a single institution experience, and therefore there is a lack of information on further interesting endpoints. Secondly, our small sample size underpowered the comparison of metabolic parameters before and after surgery. Additionally, factors such as diet and exercise may influence the parameters assessed in patients with long interval follow-up, same as obesity, lipid-lowering medications, and genetic predisposition. Finally, familial hyperlipidemia was not evaluated.

Conclusion

Our study revealed an important rate of diabetes mellitus and dyslipidemia in patients with pheochromocytomas and paragangliomas. These metabolic complications require investigation in patients with pheochromocytomas. Due to the association between elevated catecholamine levels and the onset of diabetes, and the long history of the disease, the patients are at greater risk of developing dyslipidemia. Postoperative monitoring of changes in body mass index and glycemic and lipid profile was necessary to adapt therapeutic management.

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