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RESEARCH ARTICLE

Does surgical treatment improve diabetes in pheochromocytoma patients? A comparative study before and after tumor resection in a series of 23 patients

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Objective: The present study aimed to assess the prevalence of diabetes in a cohort of pheochromocytoma patients registered at the Pathology Departments of two County Hospitals. Additionally, diabetes status was re-evaluated following tumor resection to determine whether surgery had an impact on improving or alleviating the condition.

Methods: We performed a retrospective study including all patients who underwent adrenalectomy and were diagnosed with pheochromocytoma based on histopathological findings in Mureș County (2017-2022) Hospital and Mureș County Emergency (2000-2022), Romania, respectively. All patients that were alive and whose contact details were available, participated in a phone survey and provided clinical data. Information on the presence of diabetes at the time of pheochromocytoma diagnosis and their diabetes status after tumor resection was recorded. The follow-up period ranged from 24 to 216 months.

Results: We identified 35 patients with a histopathological diagnosis of pheochromocytoma. Complete histopathological and clinical data were obtained for 23 patients; 13/23 (56.5%) were women and 10/23 (43.59%) were men; the mean age at surgery was 52.73 ±14.22 years-old (range 24-78). Of these, eight patients (n=8/23; 34.7%) were diagnosed with diabetes prior to surgery. All diabetic patients showed improvements in their carbohydrate metabolism and 5 (62.5%) of them revealed a restored normal glucose tolerance after surgery.

Conclusions: Our study highlights that overt diabetes mellitus is present in more than one-third of patients with pheochromocytoma. Tumor removal improves dysglycemia in all diabetic pheochromocytoma patients and cures diabetes in a significant proportion of them.

Keywords: pheochromocytoma, diabetes, adrenal surgery

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Introduction

Pheochromocytoma continues to be a fascinating and intriguing tumor, often described as a true pharmacological "time bomb" due to its potential to cause devastating complications or even death.

Considered extremely rare before the development of imaging techniques, these tumors arising from the adrenomedullary chromaffin tissue, have become more prevalent due to enhanced patient access to high-performance diagnostic imaging tools [1]. An extensive review of 12 studies (1949-2019) found a significant increase in pheochromocytoma and paraganglioma incidence, rising from 0.19/100,000/year before 2000 to 0.58/100,000/year after 2010 [2]. The increased detection rate can be also attributed to improvements in biochemical testing, as metanephrine/normetanephrine measurements are now widely available. Additionally, the recognition of high germline mutation rates in pheochromocytoma patients, along with genetic testing and monitoring of at-risk family members, might explain the recent rise in pheochromocytoma cases.

Pheochromocytomas produce and secrete catecholamines that cause numerous and diverse clinical manifestations including headache, sweating, paroxysmal or sustained hypertension, and heart palpitations. Carbohydrate disturbance such as glucose intolerance or diabetes mellitus are also observed in 15-35% of pheochromocytoma patients [3–5]. The key pathogenetic mechanism of secondary diabetes mellitus in patients with pheochromocytoma especially of adrenergic phenotype is impaired insulin secretion. Both adrenergic and noradrenergic phenotypes also exhibit insulin resistance displayed by impaired glucose utilization, excessive lipolysis, perturbed adipokine expression, inflammation, enhanced gluconeogenesis and glycogenolysis, as well as by stimulation of glucagon secretion [6]. Previous studies have shown that surgery for pheochromocytoma has a significant impact on the recovery of insulin resistance and insulin secretion. As a result, more than 50% of cases experience a complete resolution of the glycemic disorder [3,5,6]. It is still unknown which

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factors contribute to the development of diabetes in these patients or which patients will recover from this condition after pheochromocytoma surgery.

The aim of the present study was first to assess the prevalence of diabetes in a series of pheochromocytoma patients registered in our departments. Diabetes status was further re-evaluated following tumor resection in order to determine whether surgery improved or was a contributing factor in releasing of the disease.

Methods

Database and Study Design

We performed a retrospective study including all patients who underwent adrenalectomy at County Emergency Hospital (between 2000 and 2022) and County Hospital (between 2017 and 2022) in Târgu-Mureș, Romania and received a histopathological diagnosis of pheochromocytoma. The study was approved by the Ethics Committee of the Târgu-Mureș Emergency County Hospital (Letter of approval no.4467/16.02.2023), and County Hospital (Letter of approval no.12527/09.08.2023).

Case selection and clinical data

The demographic information (age, gender of the patients), year of diagnosis, clinical diagnosis, histopathological diagnosis (tumor type, size and site of mass of resected specimen) and patients contact information were collected from original pathological reports and institutional database registries of the Department of Pathology from both Hospitals.

The National Health Insurance Platform was consulted to verify if the patient was alive, and if deceased, the date of death was documented. All patients who were alive, and whose contact details were available, participated in a phone questionnaire. This questionnaire provided data related to the symptoms they experienced at the time of diagnosis: headache, sweating, heart palpitations (classic triad). Details concerning the presence of diabetes and arterial hypertension at the time of pheochromocytoma diagnosis (before surgery), as well as the treatment administered for these conditions, were documented. Patients with diabetes were defined as those who had a documented confirmed diagnosis and were using antidiabetic medications. Further on, the patients were questioned regarding the diabetes status after the tumor resection and all changes were recorded; these changes included: the reduction in the number or doses of antidiabetic drugs or even the cessation of antidiabetic treatment, based on the recommendation of the diabetologist. Resolution of diabetes was defined by the complete withdrawal of antidiabetic medication following clinical evaluation and confirmation by a specialist in diabetology.

Patients were asked to provide anthropometric data, such as height and weight, at the time of their pheochromocytoma surgery, as they were evaluated during their hospitalization. The body mass index (BMI) was calculated for each patient using the following formula: BMI=weight (kg)/ height (m^2). Overweight was defined as BMI ≥ 25 kg/m^2 and obesity as BMI ≥ 30 kg/m^2 according to World Health Organization (WHO) criteria. The follow-up period ranged from 24 to 216 months.

Pathological data

The histopathological diagnosis of pheochromocytoma was established according to WHO Classification of Tumors of Endocrine Organs, 2nd (2000), 3rd (2004) and 4th (2017) edition, respectively [7–9]. According to the WHO 2017 Classification of Endocrine Tumors, all pheochromocytomas are now considered to have metastatic potential, replacing the previous designations of benign or malignant pheochromocytomas. Currently, there are no validated and reliable pathological criteria to predict whether the tumor will develop metastasis in the future. Therefore, it is recommended to maintain long post-surgical follow-up for all operated patients.

The Pheochromocytoma of the Adrenal Gland Scaled Score (PASS), proposed by Thompson in 2002, [10] was used to assess the malignant potential, in accordance guide. A score ≥ 4 indicates a higher concern for malignancy in these tumors, but the presence of metastasis is the definitive and absolute criterion for diagnosing malignancy.

Exclusion criteria

We excluded from the study the patients who could not be contacted for the interview, or whose medical records with the necessary information were not available. Patients with relapse of their pheochromocytoma were included only for the first episode.

Statistical Analysis

Statistical analyses were performed using the Excel 2021, and Minitab Statistics Software 20.3 (2025) programs. Descriptive statistical analyses were done. The data were expressed as binominal, ordinal or quantitative variables. Numbers and percentages were used to express qualitative variables. The frequencies of the categorial variables were compared using the Chi-squared test. Differences between two independent groups were analyzed using Student's T-test. To assess the differences between pre- and post-surgery means of the study groups' parameters, Two-Sample T-Test was applied.

The normality of continuous variables was assessed using the Kolmogorov–Smirnov test or by visual inspection of histograms. Normally distributed continuous variables were expressed as mean ± standard deviation (SD). The analysis of variance (ANOVA) test was used to compare multiple mean values. Statistical significance was defined as $p < 0.05$, with a 95% confidence interval.

Results

From the institutional database registers, we identified 35 patients who had a histopathological diagnosis of pheo-

chromocytoma. Complete histopathological and clinical data were obtained for only 23 patients: 13 (56.5%) women and 10 (43.59%) men. The mean age at surgery was 52.73 ± 14.22 years (range 24-78). Among the 23 patients, 8 (34.7%) had a diagnosis of diabetes at the time of surgery, Figure 1.

Table 1 illustrates clinical and demographic characteristics of all pheochromocytoma patients, in comparison diabetic *versus* non-diabetic patients.

No significant differences in age or sex were observed between patients with diabetes prior to surgery and those without (55.87 *versus* 51.06 years, M/W: 3/5 *versus* 7/8). Although the mean BMI was similar for both groups (~27 kg/m^2) overweight proportion (46.6% *versus* 37.5%) and obesity (33.3% *versus* 25.0%) was slightly higher in the group of patients without diabetes.

Three (20%) non-diabetic and two (25%) patients with diabetes were smokers (p=0.782).

High blood pressure was diagnosed in all diabetic patients (n=8/8, 100%) and in the majority of non-diabetic patients (n=13/15, 86.6%). The classic symptoms triad: headache, sweating, and palpitations, were reported by half of the patients with diabetes and only by a quarter of those without (p=0.263).

In both study groups, tumors were more frequently observed on the right side (60% *versus* 62.5%, p=0.907). Interestingly, diabetic patients had smaller tumors compared to non-diabetic patients (64.8 mm *versus* 54.8 mm, p=0.343). The average PASS score for these tumors was below the threshold suggestive of malignancy, at 3.5 points. By contrast, the average PASS score for the tumors of non-diabetic patients was 4.6 points.

The distribution of diabetic cases by age, sex, and pheochromocytoma size is illustrated in Figure 2. The bubble plot shows that tumor size in diabetic patients with pheochromocytoma varies by age and gender, with larger tumors being more frequently observed in older women.

After a median follow-up of 66 months (range 24-216), the proportion of diabetic patients among all participants decreased to 13.04%, Figure1. All diabetic patients (n=8)

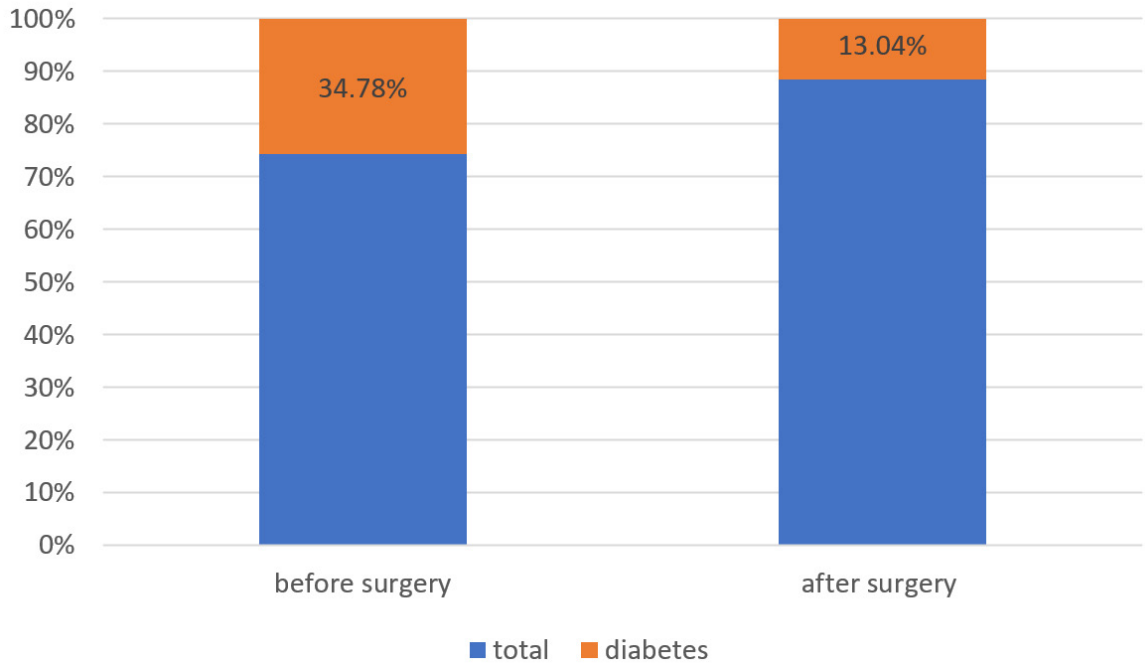

Fig. 1. The proportion of pheochromocytoma patients with diabetes before and after surgery

Table1 Clinical and demographic characteristics of all pheochromocytoma patients, with a comparative analysis of those with and without diabetes at the time of surgery.

	All patients [n=23]	No Diabetes [n=15]	Diabetes [n=8]	p -Value
Men [n/total (%)]	10/23 (43.5)	7/15 (46.7)	3/8 (37.5)	0.673
Women [n/total (%)]	13/23 (56.5)	8/15 (53.3)	5/8 (62.5)	
Age at surgery (years) [mean ± SD]	52.73±14.54	51.06 ±14.65	55.87 ±14.76	0.468
Body mass index (kg/m2) [mean ± SD]	27.35 ±5.73	27.43 ±4.16	27.21±8.16	0.945
Overweight [n/total (%)] (BMI 25-29.9 kg/m2)	10/23 (43.5)	7/15 (46.6)	3/8 (37.5)	
Obesity [n/total (%)] (BMI ≥ 30kg/m2)	7/23 (30.4)	5/15 (33.3)	2/8 (25.0)	
Smokers [n/total (%)]	5/23 (21.7)	3/15 (20.0)	2/8 (25.0)	0.782
Laterality [n/total (%)]				
Right	14/23 (60.8)	9/15 (60.0)	5/8 (62.5)	0.907
Left	9/23 (39.2)	6/15 (40.0)	3/8 (37.5)	
Arterial Hypertension [n/total (%)]	21/23 (91.3)	13/15 (86.6)	8/8 (100)	-
Classic Triad [n/total (%)]	8/23 (34.8)	4/15 (26.6)	4/8 (50.0)	0.263
Max Diameter Tumor (mm), [mean ± SD]	61.3 ±24.38	64.8 ±25.39	54.8 ±22.44	0.343

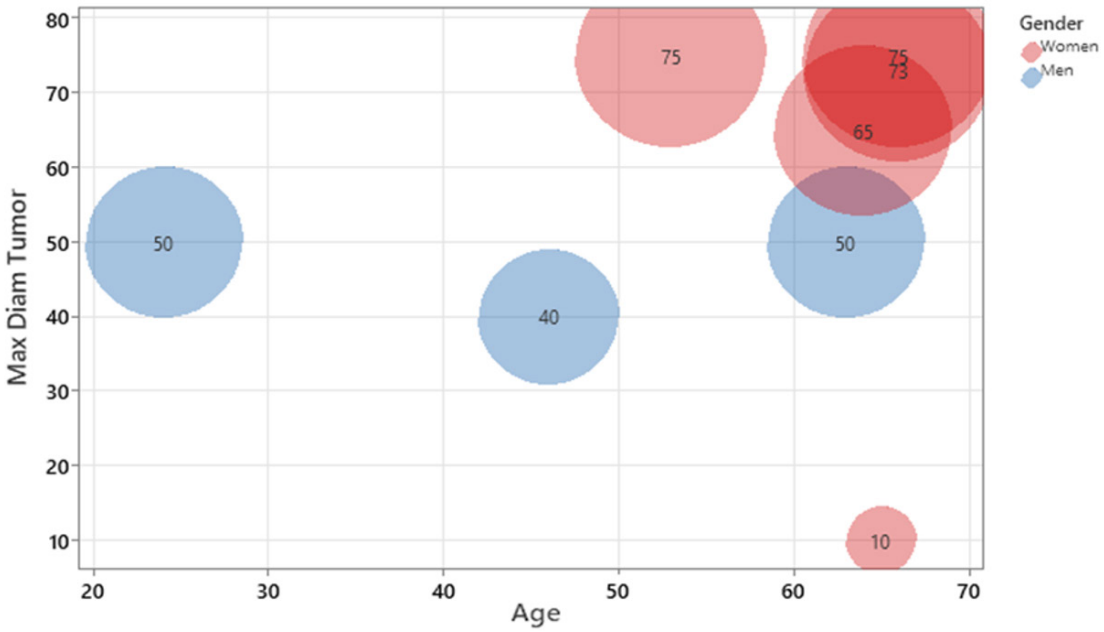

Fig. 2. Distribution of demographic data (age and sex) for diabetic patients (n=8) according to pheochromocytoma tumors diameter (mm).

showed improvements in their carbohydrate metabolism, as follows: (1) 62.5% (n=5) of these patients revealed a restored normal glucose tolerance after surgery, without diabetic treatment and (2) the remaining 37.5% (n=3) were recommended to reduce the dose or the number of antidiabetic drugs.

Finally, we examined the differences between patients whose diabetes status was restored following surgery *versus* patients who were still under treatment, but with a reduced drug dose, Table 2. Although not statistically significant and somewhat unexpected, it was observed that patients who restored their diabetes status were older (58.80 *versus* 51.00 years, p=0.636) and had a slightly higher BMI (28.20 *versus* 25.57 kg/m^2, p=0.620).

The tumor size was similar between the two study groups (57.7 *versus* 53.0 mm, p=0.763). However, patients who no longer needed antidiabetic medication had tumors with a higher average PASS score (4.4 *versus* 2 points, p=0.272) and were more likely to show symptoms compared to the other group (60.0% *versus* 33.3%, p=0.465).

Discussions

Our study investigated the prevalence of diabetes in patients with pheochromocytoma, as well as the likelihood of achieving normoglycemia following tumor removal. Additionally, the study aimed to identify demographic and tumor characteristics associated with the presence of diabetes and its improvement or resolution following pheochromocytoma resection.

Of the 35 patients diagnosed with pheochromocytoma, our study included only 23 who provided the complete and necessary data. Among them, 34.78% (n=8) were confirmed diabetic patients and were receiving antidiabetic treatment.

Previous studies have shown that glucose intolerance may affect approximately 50% of patients with pheochromocytoma [4,14,15] and 15-35.6% of these patients being diagnosed with diabetes mellitus [3,4,14,15].

Previous studies have highlighted an association between glucose intolerance and pheochromocytoma. However, the exact mechanisms by which catecholamines interact with

Table 2. A comparative analysis of diabetic patients after surgery: individuals with reduced use of antidiabetic medication versus those with restored diabetes control (no antidiabetic medication).

	Reduced antidiabetic medication [n=3]	No antidiabetic medication [n=5]	p -Value
Men [n/total (%)]	2/3 (66.7)	1/5 (20.0)	0.187
Women [n/total (%)]	1/3 (33.3)	4/5 (80.0)	
Age at surgery (years), [mean ± SD]	51.0 ±23.4	58.80 ±8.87	0.636
Body mass index (kg/m^2) [mean ± SD]	25.57 ±3.06	28.2 ±10.4	0.620
Overweight [n/total (%)](BMI 25-29.9 kg/m^2)	1/3 (33.3)	1/5 (20.0)	
Obesity [n/total (%)] (BMI ≥ 30kg/m^2)	0/3 (0.0)	2/5 (40.0)	
Smokers [n/total (%)]	1/3 (33.3)	1/5 (20.0)	-
Laterality			
Right	2/3 (66.7)	3/5 (60.0)	0.850
Left	1/3 (33.3)	2/5 (40.0)	
Arterial Hypertension [n/total (%)]	3/3 (100)	5/5 (100)	-
Classic Triad [n/total (%)]	1/3 (33.3)	3/5 (60.0)	0.465
Max Diameter Tumor (mm), [mean ± SD]	57.7 ±13.3	53.0 ±28.0	0.763
PASS score [mean, range]	2 (2)	4.4 (0-8)	0.272

glucose metabolism in these conditions remain complex and yet not fully elucidated [6]. It's still unclear whether impaired insulin secretion or increased insulin resistance plays the more significant role in the glucose homeostasis alterations seen in patients with pheochromocytomas [11].

High levels of catecholamines play a significant role in suppressing insulin secretion from pancreatic β-cells, primarily mediated through adrenergic α2 receptors [11]. Insulin resistance is related to multiple mechanisms: activation of α2 and β2 receptors on pancreatic α cells, increases glucagon secretion [11,12]; activation of hepatic α and β-adrenergic receptors, increases glucose production and glucagon breakdown, while reducing glucose uptake by the liver, leading to hyperglycemia; promote lipolysis in adipose tissue to generate energy substrates, while simultaneously inhibiting glucose uptake, thereby sparing glucose for skeletal muscles and vital organs [6,11]. The tumor's secretory phenotype can influence glucose metabolism differently: epinephrine, with higher affinity for adrenergic α2 receptors, suppresses insulin secretion, whereas norepinephrine, with higher affinity for adrenergic α1 receptor, is linked to insulin resistance [11,13].

Several factors potentially influencing the association between pheochromocytoma and diabetes were evaluated in our study. No statistically significant correlations were identified between age, sex, or smoking habits and the presence of diabetes. Additionally, BMI was assessed, revealing that many patients with diabetes did not have elevated BMI, with fewer being overweight or obese.

Similar results have been reported by other studies, which did not find a positive relationship between BMI and the risk of diabetes [3,4,15]. It is important to note that the reduced BMI in these patients is often a consequence of catecholamine-induced lipolysis and an elevated metabolic rate.

Diabetic patients in our study more commonly reported to experience headaches, sweating, and heart palpitations. Furthermore, all of them had also high blood pressure. In the study by L. Zhao., it was observed that higher age, hypertension, and 24-hour urine excretion concentration were independently associated with preoperative glucose imbalance [15]. Additionally, Beninato in his study notes that pheochromocytoma symptomatic patients were more frequently diabetic [3]. According to the 2020 Consensus of the European Society of Hypertension [16], the presence of hypertension and diabetes in patients under 50 years of age with a normal BMI strongly suggests pheochromocytoma, and biochemical testing is therefore recommended.

Regarding the tumor size, in our study there was no statistically significant difference in tumor size between patients with and without diabetes, although patients with diabetes had slightly smaller tumors and a lower PASS score. Similar results, showing no statistical difference in tumor size, have also been reported in other studies [4,5,15]. However, Beninato et al. found that patients with diabetes were more likely to have larger tumors [3], consistent with the theory that larger tumors produce more catecholamines. Nonetheless, in Z.-H. Liu's study, no difference in catecholamine levels was found between patients with diabetes and those without diabetes [5].

After surgery and a median follow-up of 66 months (range 24-216), we observed a favorable outcome in all subjects with diabetes. The proportion of patients with diabetes decreased from 34.78% to 13.04%, and even these patients achieved improved glycemic control, with the diabetologist's recommendation to either reduce the dosage of antidiabetic medications or decrease the number of medications. In total, 62.5% of diabetic patients achieved normal glucose tolerance following surgical resection.

Studies have shown that tumor removal is more effective than phentolamine, an alpha-blocker, in restoring normal glucose and insulin homeostasis [14,17]. It has been suggested that the effects on insulin secretion may not be entirely mediated through α-adrenergic receptor stimulation. Resection usually leads to the resolution of diabetes, unless other predisposing factors are present [3].

Several studies have demonstrated that diabetes resolution is highly achievable for patients undergoing pheochromocytoma tumor removal. A study from 1984 has reported that all pheochromocytoma patients with a diagnosis of diabetes prior to surgery (24% of the total cases) had restored their diabetic status following tumor removal [18]. Another study from 2003 has reported that only 10% of patients with incomplete tumor resection did not achieve diabetes resolution [19]. In Pogorzelski's series of 67 pheochromocytoma patients, 90% of those with diabetes achieved complete resolution after tumor removal [20]. Similarly, Beninato et al. reported that nearly 79% of diabetic had their condition resolved after surgery [3], and Liu et al. found that almost 61% of cases resolved postoperatively [5].

Although no statistically significant differences were found, we observed that patients who achieved diabetes resolution tended to be older and more symptomatic than those who still required antidiabetic medication. Tumor size was similar for both groups, although those who were considered cured of diabetes had a higher PASS score suggesting a more aggressive tumor progression. Similar data regarding tumor size was observed by Elenkova [4], while Liu noted that patients with a larger preoperative tumor diameter were more likely to experience reversal of dysglycemia after tumor resection [5].

Contrary to findings from other studies [3–5], our analysis revealed that patients who successfully normalized their blood glucose levels post-surgery had a slightly higher BMI compared to those who required continued antidiabetic medication.

Since no positive relationship was found between tumor characteristics and the risk of diabetes, other factors must contribute to the likelihood of developing diabetes in patients with pheochromocytomas. These factors may include genetic predisposition, lifestyle, underlying meta-

bolic conditions or the duration of exposure to elevated catecholamine levels that could influence the course of glucose homeostasis.

This study has several limitations that should be acknowledged. The sample size is a limitation, but the relatively small size reflects the rarity of pheochromocytoma and strict histological inclusion criteria, ensuring data reliability while limiting generalization. The retrospective design of the study presents inherent limitations, such as potential selection and information biases, along with the inability to fully control confounding variables. Efforts were made to minimize these limitations through structured questionnaires and corroboration of clinical records where possible. These limitations do not diminish the relevance of the findings, they underscore the need for larger, prospective studies with standardized data collection protocols to validate and expand upon them.

Conclusion

Our data revealed that diabetes mellitus was present in more than one-third of patients with pheochromocytoma in our series. Tumor removal has improved glucose balance in all diabetic pheochromocytoma patients and cured diabetes in a significant proportion of them. The occurrence and post-surgery resolution of dysglycemia can be multifactorial and variable from patient to patient, making blood glucose monitoring essential for pheochromocytoma patients.

Authors' contributions

RC (Conceptualization; Methodology; Validation; Investigation; Resources; Data curation; Writing – original draft; Project administration; Funding Acquisition)
ANB (Conceptualization; Methodology; Validation; Data Curation; Writing – Review &Editing; Visualization)
SM (Software; Formal analysis; Data Curation)
AB (Conceptualization; Validation; Writing – Review &Editing; Supervision)

Conflict of interest

The authors declare that they have no conflict of interest**.**

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Informed consent statement

Informed consent was obtained from all subjects involved in the study.

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