

Long-Term Persistence of Glycemic Dysregulation in Patients With a History of Pheochromocytoma/Paraganglioma

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Abstract

Context: Pheochromocytomas and paragangliomas (PPGLs) are rare endocrine tumors that frequently produce catecholamines. Catecholamine-induced cardiometabolic complications substantially contribute to increased morbidity and mortality in PPGL patients prior to surgical resection.

Objective: To determine whether markers of elevated cardiometabolic risk persist in patients following PPGL resection.

Methods: In this retrospective analysis of a multicenter cohort of patients with PPGLs participating in the prospective ProsPheo study and the ENS@T registry, cardiometabolic risk factors, including glycemic status, dyslipidemia, and body mass index (BMI), were assessed in patients with PPGL at diagnosis and during follow-up. Patients with a history of resected PPGL were compared to a control group with nonfunctioning adrenal adenomas from the ENS@T registry.

Results: Patients with a present PPGL or a history of PPGL ($n = 188$), a metastatic PPGL ($n = 27$), or a known susceptibility gene pathogenic variant (PV) for the development of PPGL without a history of PPGL ($n = 44$) were included. We compared the asymptomatic PV carriers to patients with a history of PPGL: those with a history of PPGL showed a significantly higher prevalence of hyperglycemic disorders ($P = .013$) compared with asymptomatic PV carriers. In patients with a history of PPGL and at least 12 months of follow-up post surgery ($n = 113$), the prevalence of hyperglycemic disorders ($P < .001$), as well as the mean HbA1c (5.63%, SD 0.43%), were significantly higher, compared to a control group with nonfunctioning adrenal adenomas ($n = 76$) of similar age and BMI (HbA1c 5.45%, SD 0.40%; $P = .004$).

Conclusion: Glycemic disturbances persist long-term after the resection of PPGL.

Key Words: pheochromocytoma, paraganglioma, diabetes, glucose intolerance, HbA1c, cardiometabolic risk

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Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; ENS@T, European Network for the Study of Adrenal Tumors; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MASLD, metabolic dysfunction-associated steatotic liver disease; PPGL, pheochromocytoma/paraganglioma; PV, pathogenic variant.

Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine neoplasms characterized by their origin from neural crest–derived cells (1, 2). Paragangliomas develop from the paraganglia of the sympathetic or parasympathetic nervous system. Pheochromocytomas arise from the chromaffin cells of the adrenal medulla and are, according to the new World Health Organization classification, intra-adrenal paragangliomas representing the classical sympathetic form of a paraganglioma (2). These tumors are notable for their high heritability, with approximately 30% to 35% of patients harboring germline pathogenic variants (PVs) and an additional 35% to 40% presenting with somatic mutations (3–6). Approximately 10% to 15% of pheochromocytomas and 35% to 40% of paragangliomas are metastatic, as defined by the presence of distant metastases in sites where chromaffin cells are normally absent, such as bones or lymph nodes (2, 7, 8).

The clinical manifestations of PPGLs can vary widely; while some tumors are biochemically active and produce catecholamines such as epinephrine, norepinephrine, and dopamine, others may be silent (9–15). Many clinical signs and symptoms of PPGLs, such as headache, hypertension, and hyperhidrosis, are nonspecific and may initially be attributed to various other conditions. However, certain symptoms are more indicative of PPGLs, including pallor, tremor, nausea, and palpitations, especially when they occur episodically. Additional signs and symptoms that can arise from catecholamine secretion include postural hypotension, anxiety, panic, abdominal pain, constipation, weight loss, and hyperglycemia (12, 16, 17). These symptoms are reflective of adrenoceptor overstimulation due to elevated catecholamine levels (9).

Cardiovascular complications of the catecholamine secretion such as catecholamine-induced cardiomyopathy (Takotsubo cardiomyopathy), myocardial infarction, hypertensive emergency or urgency, shock, syncope, arrhythmia, dissecting aortic aneurysm, acute kidney injury, and hemorrhagic or ischemic stroke, significantly increase mortality and morbidity in PPGL patients (18). Cardiac function, particularly left ventricular dysfunction, appears to improve after the removal of a pheochromocytoma (19), but there may be persistent structural and functional abnormalities (20).

Catecholamine-induced hyperglycemia may lead to new-onset or worsening diabetes mellitus (21–23). Notably, plasma norepinephrine levels have been associated with higher HbA1c and lower body weight in PPGL patients (24). After surgical resection, a decrease in catecholamine levels correlated in the short-term with improved HbA1c despite an increase in body weight, while persistent catecholamine elevation and weight loss were observed in patients with malignant or recurrent PPGL (24–26).

However, long-term cardiometabolic outcomes in patients with resected PPGLs remain poorly investigated. In one of the few published studies on long-term outcomes, Weismann et al reported in 2015 that the majority of patients with a history of PPGL remained hypertensive after tumor removal when compared to healthy controls (27). It remains crucial to determine whether the elevated cardiometabolic risk observed prior to PPGL resection persists post surgery, and whether

patients with resected PPGLs require specialized cardiometabolic follow-up. This study, therefore, aimed to explore the burden of cardiometabolic disease and biomarkers indicative of a higher cardiometabolic risk in patients enrolled in the ongoing ProsPheo study.

Methods

Study Population

The current study included 272 patients enrolled in the prospective “Multicenter Evaluation of Pheochromocytoma and Paraganglioma Diagnostic Testing, Subdifferentiation, Therapy, Outcome and Genetics,” referred to as the *ProsPheo* study (NCT03344016). Participants enrolled in the ProsPheo study are either newly diagnosed with a PPGL, have a history of PPGL, or are carriers of genetic PVs predisposing them to develop a PPGL. Patients were extracted from the study database in February 2024 and last updated in June 2024. From the original cohort of 272 patients, 13 patients were removed due to missing data. Consequently, the data of 259 patients were analyzed as part of this study. Additionally, a control group comprising 76 patients with nonfunctioning adrenal adenomas included in the *European Network for the Study of Adrenal Tumors* (ENS@T) registry was included in this study. The study flow chart is presented in Fig. 1.

Inclusion criteria for the study group were as follows: (i) first diagnosis of PPGL or previous history of PPGL at the time of inclusion in the ProsPheo study; or (ii) presence of a germline PV associated with a predisposition for PPGL. Furthermore, the availability of at least one plasma laboratory assessment and a clinical evaluation was required. Metastatic PPGL was defined by the presence of distant metastases in locations where chromaffin cells are not physiologically present.

Laboratory analysis, along with measurements of blood pressure, height, weight, and current medications, was conducted during initial inclusion and follow-up visits in the ProsPheo study, adhering to current guidelines for monitoring patients with a history of PPGL. The patient’s blood pressure was assessed while seated, and the mean systolic blood pressure was calculated from at least 3 consecutive measurements.

The control group consisted of patients with adrenal adenomas which were tested negative for hormonal activity and therefore considered nonsecretory. Exclusion of aldosterone and cortisol secretion was based on an aldosterone-renin ratio and 1 mg dexamethasone suppression test in the reference range, and catecholamine excess was excluded by nonelevated plasma (nor)metanephrine and nonelevated 3-methoxytyramine levels. Patients with active solid or hematologic cancers, as well as those undergoing glucocorticoid treatment, were excluded. Patient data, including laboratory assessments, were collected between January 2014 and May 2024.

This study was conducted in accordance with the principles of the Declaration of Helsinki and adhered to the laws and regulations of the Ethics Commission of the Canton of Zurich. Written informed consent was obtained from all participants. The ENS@T study was accepted under reference number BASEC 2017-00771 and the ProsPheo study under

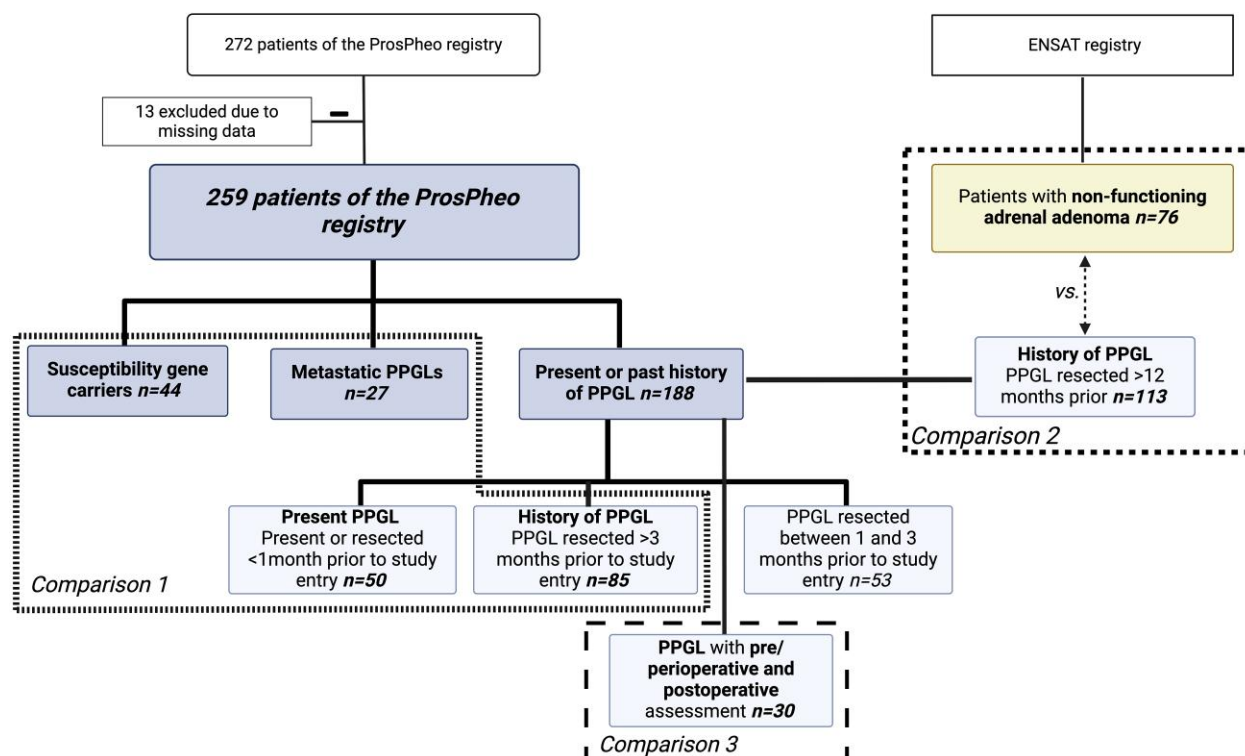


Figure 1. Study flow chart. Created in BioRender.com.

the reference number BASEC 2017-00963 by the local ethics committee.

Definitions

According to the “Standards of Care in Diabetes, version 2024,” prediabetes was defined as a glycated hemoglobin (HbA1c) above 5.6% (37.7 mmol/mol) without treatment with oral or subcutaneous antidiabetic medications (28). Diabetes mellitus was defined by a HbA1c equal to or higher than 6.5% (47.5 mmol/mol) with or without antidiabetic medications (28). Patients on antidiabetic medications were categorized as having diabetes mellitus independent of the HbA1c value. For patients on insulin therapy, a medical history for type 1 diabetes was assessed and, if present, patients were excluded. Fasting glucose levels were not included in this study since fasting, defined as no caloric intake for at least 8 hours, could not be guaranteed.

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m²). Dyslipidemia was defined by the presence of any of the following lipid abnormalities: total cholesterol levels of 5 mmol/L (193 mg/dL) or higher, high-density lipoprotein (HDL) cholesterol levels less than 1 mmol/L (40 mg/dL), or low-density lipoprotein (LDL) cholesterol levels above 3 mmol/L (116 mg/dL). Additionally, the use of statin medication was also considered an indicator of dyslipidemia.

PPGLs can be categorized into 3 main molecular clusters based on gene expression: (1) the pseudohypoxia cluster (subdivided into [1A] involving Krebs cycle gene mutations: *SDHA/B/C/D*, *FH*, *MDH2*, *IDH*, *GOT2*, *SLC25A11*, *DLST*, *SUCLG2*; and [1B], involving hypoxia pathway genes: *PHD1/2*, *VHL*, *HIF2A/EPAS1*, *IRP1*); (2) the kinase-signaling cluster (mutations in *RET*, *NF1*, *TMEM127*,

MAX, *HRAS*, *FGFR1*, *MET*, *BRAF*, *MERTK*, and *NGFR*); and (3) the Wnt-signaling cluster (*MAML3* fusions and *CSDE1*) (29, 30).

Statistical Analysis

Categorical variables were compared using the Pearson chi-square test, Fisher exact test, or multivariable analysis of variance, as appropriate (nominal or ordinal). Continuous variables were tested for normal distribution using the Shapiro-Wilk test and visual inspection; Levene’s test was used to assess homogeneity of variances. For normally distributed variables, one-way ANOVA with Tukey post hoc testing was performed. Independent *t* tests were used to compare continuous variables between the study and control groups. For non-normally distributed variables, the Mann-Whitney U or Kruskal-Wallis test with post hoc analysis and *P* values adjusted with the Bonferroni method was applied. Logistic regression analysis (linear and binary) was employed to identify variables that significantly influence the presence of hyperglycemia in follow-up after resection of a PPGL. All reported *P* values are two-sided, with a significance level set at *P* < .05. Statistical analyses were conducted using the open-source statistics software R (version 4.3.2, R Foundation for Statistical Computing, Vienna, Austria) (31).

Results

This study analyzed a total of 259 patients from the ProsPheo study, of which 139 were female (53.7%). Of the cohort, 44 patients (17.0%) were carriers of susceptibility gene PVs without a history of PPGL, while 27 (10.4%) patients had metastatic disease (described in detail in Table 1). Of the patients with a present (including metastatic) PPGL or a history

Table 1. Characteristics of the study cohort

At timepoint of ProsPheo study entry	
Number of patients in total	259
Sex, f/m	139 (53.7%)/120 (46.3%)
Median age in years (min, max)	51 (9, 83)
Susceptibility gene carriers without history of PPGL	44 (17%)
Metastatic PPGL	27 (10.4%)
History or presence of nonmetastatic PPGL	188 (72.6%)
Location	
Intra-adrenal paraganglioma (pheochromocytoma)	139/215 (64.7%)
Extra-adrenal paraganglioma	72/215 (33.5%)
Intra- and extra-adrenal paragangliomas	4/215 (1.9%)
Genetics	
Cluster 1 PV in patients with PPGL	SDHA: 8 SDHB: 19 SDHC: 6 SDHD: 8 FH: 1 MDH2: 1 VHL: 8
Cluster 2 PV in patients with PPGL	MAX: 3 NF1: 5 RET: 7
No germline PV in patients with PPGL	94
No germline sequencing available	55
PVs in the group of susceptibility gene carriers	SDHA: 3 SDHB: 19 SDHC: 5 SDHD: 4 FH: 1 MAX: 1 NF1: 1 RET: 6 TMEM: 1 VHL: 3
Overall PV in SDHB	38/259 (14.7%)

Abbreviations: PPGL, pheochromocytoma/paraganglioma; PV, pathogenic variant.

of PPGL, data on PVs were available for 160/215 (74.4%) patients. Of these, 51/215 (23.7%) patients had PVs in genes belonging to Cluster 1, 15/215 (7%) patients had PVs in Cluster 2 genes, while in 94/215 (43.7%) patients no germline PVs were detected. Pheochromocytoma/adrenal paraganglioma was diagnosed in 143/215 (66.5%) patients (Table 1).

The cohort of patients with a present PPGL or a history of PPGL was divided into 3 groups. The first group included patients whose laboratory assessments were available either prior to resection or within 1 month following resection of a nonmetastatic PPGL (n = 50; 7 head and neck paragangliomas) (group with *present PPGL*). The second group consisted of patients with a *history of PPGL*, where the first laboratory assessments were obtained at least 3 months post resection (n = 85, 11 head and neck paragangliomas). The median time since surgery in this group was 56 months (range, 3–508 months). Patients whose first laboratory assessments were available between 1 and 3 months post resection (n = 53) were excluded

from the analysis, since laboratory parameters, especially HbA1c, might still reflect residual catecholamine exposure or intraoperative blood loss during this period.

Characteristics of the group with present PPGL and the group with a history of PPGL were then compared to the group of susceptibility gene carriers without PPGL history and the group of patients with metastatic PPGL (Table 2; Fig. 1—*Comparison 1*) at study entry. The median age was significantly different between these patient groups, with a median age of 43 years (range, 18–80 years) in the susceptibility gene carrier group compared to older patients with present PPGL (median age 50, range 9–76 years), with a history of PPGL (median age 53, range 19–83 years), and with metastatic PPGL (median age 51.5; range, 25–73 years); $P = .01$. Subsequently, the 4 groups were investigated for differences in the use of cardiometabolic-relevant medication and clinical parameters. A statistically significant difference was observed in the number of antihypertensive drugs: Patients with metastatic PPGL had an average of 1.15 antihypertensive agents, compared to 0.41 in the susceptibility gene carrier group and 0.62 in the group with a history of PPGL ($P = .03$). There were no significant differences in mean systolic blood pressure measured during in-office visits across the groups. The percentage of patients under statin therapy was significantly higher in the group with a history of PPGL (24/85 patients, 39.3%), compared to the group of susceptibility gene carriers (3/44 patients, 6.8%) ($P = .02$) (Table 2). No significant differences between the groups were observed in the majority of cardiometabolic risk factors and related laboratory parameters, including BMI, HbA1c, cholesterol levels, triglycerides, estimated glomerular filtration rate (eGFR), hemoglobin, and NT-proBNP levels (Table 2).

Mean HbA1c levels were lowest in the susceptibility gene carrier group (5.43%, SD 0.5%) and similar in patients with present PPGL (5.57%, SD 0.6%), a history of PPGL (5.63%, SD 0.4%) and metastatic PPGL (5.62%, SD 0.8%). We then categorized patients based on the presence of glycemic disorders (prediabetes or diabetes, as defined under “Methods”); there were significantly fewer patients with glycemic disorders in the susceptibility gene carrier group (20.5%), compared to the groups with present PPGL (36%) or with a history of PPGL (49.4%) ($P = .004$). The comparison between the susceptibility gene carrier group (20.5%) and the group with a history of PPGL (49.4%) showed a particularly strong significant difference ($P = .013$) (Table 3, Fig. 2).

Comparison of Patients With a History of PPGL to a Control Group

To further investigate the persistence of cardiometabolic risk factors, particularly hyperglycemic disorders, in patients with a history of PPGL, we added a control group consisting of 76 subjects with nonfunctioning adrenal adenomas not undergoing glucocorticoid treatment included in the ENS@T registry at the University Hospital Zurich (Fig. 1—*Comparison 2*). This group was compared to 113 patients with a history of PPGL (without present or recurrent PPGL or metastatic disease) with clinical and laboratory data available at least 12 months after surgery (median time since surgery: 47 months; range, 12–533 months). Patients with head and neck paraganglioma who were treated with nonsurgical interventions (embolization, external radiotherapy, or radiofrequency ablation) were excluded from this analysis. The group

Table 2. Characteristics of the investigated subgroups

	Susceptibility gene carrier without history of PPGL	Present PPGL ^a	Metastatic PPGL	History of PPGL ^b	P value
Number of patients	44	50	27	85	
Sex, f/m	22 (50%)/22 (50%)	27 (54%)/23 (46%)	9 (33.3%)/18 (66.7%)	48 (55.6%)/37 (43.5%)	.21
Age median (min, max)	43.0 (18, 80)	50 (9, 76)	51.5 (25, 73)	53 (19, 83)	.01 <i>history of PPGL vs gene carrier</i> <i>P = .005</i>
Current smoker (yes/no/unknown)	4/18/22	12/30/8	2/19/6	12/36/37	.22
Intra-adrenal paraganglioma (pheochromocytoma)	0	35	14	65	
Extra-adrenal paraganglioma	0	17	13	20	
Head and neck paraganglioma	0	7	3	11	
Secreting catecholamines	0	26	14	12	
Median time since surgery in months (range)	—	−1 (−14 to +1)	112 (1 to 407)	56 (3 to 508)	
Mean (SD) number of antihypertensive medications	0.41 (0.90)	0.78 (1.2)	1.15 (1.23)	0.62 (SD 0.95)	.03 <i>metastatic vs gene carrier P = .02</i>
Statin (yes/no)	3/41	9/41	3/24	24/61	.02 <i>history of PPGL vs gene carrier P = .03</i>
Antidiabetics (yes/no)	3/41	6/44	1/26	4/81	.73
BMI (mean, SD) in kg/m ²	26.1, 4.7	26.2, 5.6	25.6, 4.2	27.2, 4.8	.47
In-office systolic blood pressure in mmHg (mean, SD)	128, 17	134, 16	133, 18	131, 18	.41
HbA1c in % (mean, SD)	5.43, 0.5	5.57, 0.6	5.62, 0.8	5.63, 0.4	.24
Hb in g/L (mean, SD)	11.3, 3.1	12.1, 2.7	11.5, 2.5	11.5, 3.1	.59
LDL-cholesterol in mmol/L (mean, SD)	2.65, 0.85	2.77, 0.97	2.93, 1.01	2.72, 1.1	.85
HDL-cholesterol in mmol/L (mean, SD)	1.33, 0.36	1.38, 0.33	1.49, 0.49	1.46, 0.35	.43
Total cholesterol in mmol/L (mean, SD)	4.50, 0.93	4.65, 1.11	5.10, 1.13	4.62, 1.05	.37
Triglyceride in mmol/L (mean, SD)	1.27, 1.23	1.20, 0.66	1.63, 1.11	1.18, 0.8	.32
eGFR in mL/min (mean, SD)	94.5, 15.8	90.4, 20.23	88.0, 20.86	85.4, 18.1	.07
Median (min, max) proBNP in ng/L	37 (5, 570)	61 (6, 3332)	98 (18, 678)	48 (5, 312)	.12

Statistically significant values are shown in bold.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PPGL, pheochromocytoma/paraganglioma.

^aLaboratory and clinical assessment before surgical resection or up to 1 month after surgery (nonmetastatic).

^bSurgical resection of a nonmetastatic PPGL at least 3 months before laboratory and clinical assessment.

Table 3. Presence of dyslipidemia and prediabetes/diabetes in the subgroups

	Susceptibility gene carrier without a history of PPGL	Present PPGL ^a	Metastatic PPGL	History of PPGL ^b	P value
Number of patients	44	50	27	85	
Dyslipidemia (yes/no)	11 (52.4%)/10 (47.6%)	24 (70.6%)/10 (29.4%)	10 (58.8%)/7 (41.2%)	34 (68%)/16 (32%)	.49
No diabetes	35 (79.5%)	32 (65.3%)	21 (77.8%)	43 (50.6%)	
Prediabetes	6 (13.6%)	11 (22.4%)	4 (14.8%)	38 (44.7%)	
Diabetes	3 (6.8%)	7 (12.2%)	2 (7.4%)	4 (4.7%)	.001
Hyperglycemic disorder (yes/no)	9 (20.5%)/35 (79.5%)	18 (36%)/32 (64%)	6 (22.2%)/21 (77.8%)	42 (49.4%)/43 (50.6%)	.004

Statistically significant values are shown in bold.

Abbreviation: PPGL, pheochromocytoma/paraganglioma.

^aLaboratory and clinical assessment before surgical resection or up to 1 month after surgery (nonmetastatic).

^bSurgical resection of a nonmetastatic PPGL at least 3 months before laboratory and clinical assessment. Cholesterol measurements were not consistently available across all patients.

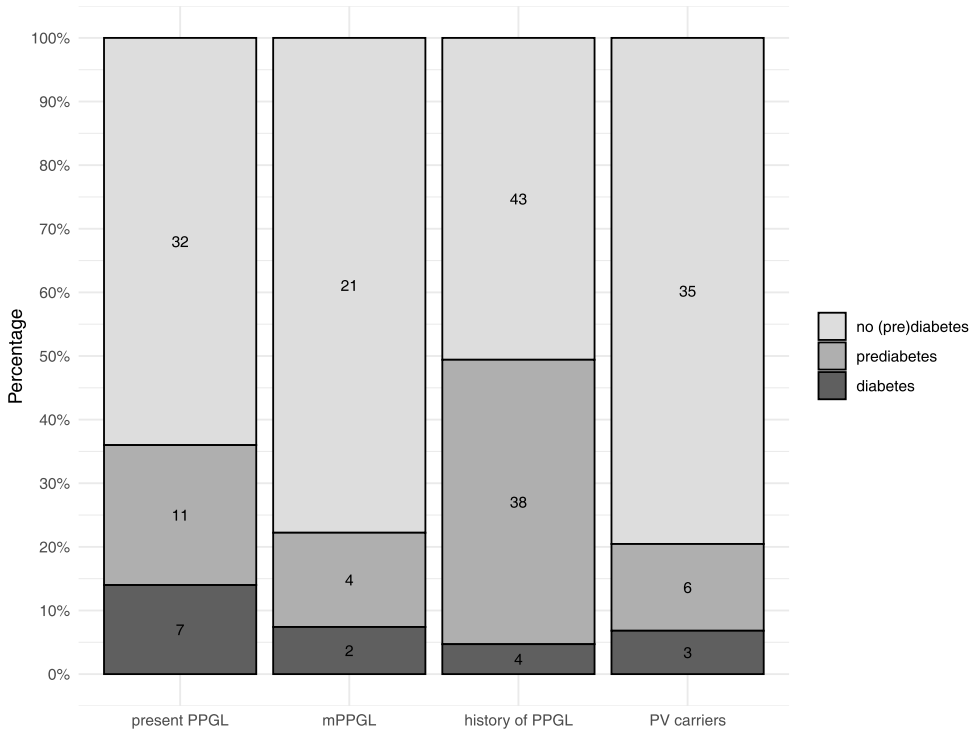


Figure 2. Percentage of patients with no diabetes/no prediabetes, prediabetes, and diabetes within the different subgroups.

Abbreviation: mPPGL, metastatic pheochromocytoma/paraganglioma.

of patients with a history of PPGL (median age 53 years; range, 12-85; 55.8% female) and the group of patients with nonfunctioning adrenal adenomas (median age 56 years; range 25-77; 53.9% female) did not significantly differ regarding age or sex ($P = .09$ and $P = .8$, respectively; Table 4) and was, therefore, considered comparable to the group with PPGL history.

There was no difference in the number of antihypertensive agents or statin use between the groups; however, mean in-office blood pressure was significantly lower in the group with a history of PPGL (129 mmHg, SD 17), compared to the control group (134 mmHg, SD 18) ($P = .045$). BMI was similar between the groups, with both in the overweight range (27.2 kg/m² in the group with history of PPGL vs 27.6 kg/m² in the control group) (Table 4).

However, there was a significant difference in HbA1c levels ($P = .004$) and the number of patients with hyperglycemic disorders ($P < .001$) between the groups: the group with a history

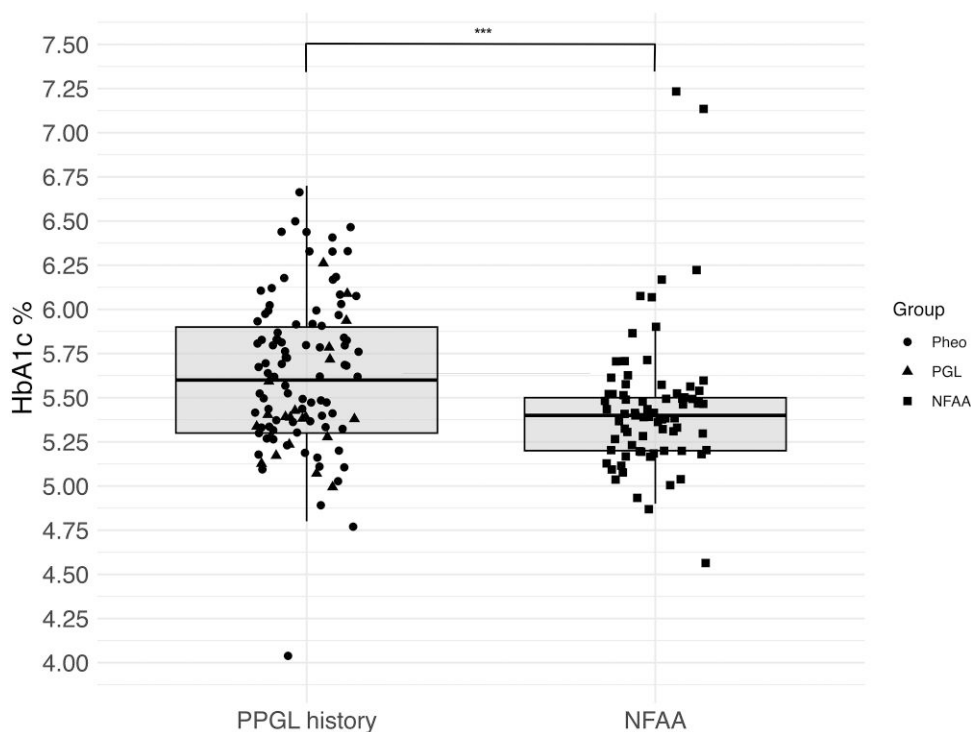
of PPGL showed a significantly higher mean HbA1c (5.63%, SD 0.43) compared to the control group (5.45%, SD 0.40) (Table 4, Fig. 3). Prediabetes was identified in 36.3% (41/113) of patients with a history of PPGL, whereas only 11.8% (9/76) of patients with nonfunctioning adrenal adenoma showed prediabetes. Consistently, diabetes was present in 6.2% (7/113) of patients with a history of PPGL, compared to only 2.6% (2/76) of patients with nonfunctioning adrenal adenomas.

A multiple linear regression was then conducted to identify potential correlations of HbA1c with other cardiometabolic risk factors in the 113 patients with a history of PPGL. The model included pheochromocytoma vs paraganglioma status, age, statin use, BMI, systolic blood pressure at follow-up, and eGFR at follow-up. The analysis revealed a significant negative association between eGFR and HbA1c ($\beta = -.012$, $P = .005$). The other variables (pheochromocytoma vs

Table 4. Comparison of patients with a history of PPGL to patients with nonfunctioning adrenal adenoma

	Nonfunctioning adrenal adenoma	History of PPGL	<i>P</i> value
Number of patients	76	113	
Sex, f/m	41 (53.9%)/35 (46.1%)	63 (55.8%)/50 (44.2%)	.8
Median age (min, max)	56 (25, 77)	53 (12, 85)	.09
Mean (SD) number of antihypertensive medications	0.9, 1.2	0.62, 1.0	.2
Number of patients on statin	12 (15.8%)	23 (20.4%)	.5
BMI (mean, SD) in kg/m ²	27.6, 5.2	27.2, 5.2	.7
In-office systolic blood pressure in mmHg (mean, SD)	134, 18.3	129, 16.6	.045
HbA1c in % (mean, SD)	5.45, 0.40	5.63, 0.43	.004
Median (min, max) proBNP in ng/L	54 (5, 386)	55 (5, 1027)	.4
eGFR in mL/min (mean, SD)	88, 17.0	85, 19.7	.3
Dyslipidemia, yes/no	30 (63.8%)/17 (36.2%)	46 (63.9%)/26 (36.1%)	.9
No diabetes	65 (85.5%)	65 (57.5%)	
Prediabetes	9 (11.8%)	41 (36.3%)	
Diabetes	2 (2.6%)	7 (6.2%)	
Hyperglycemic disorder, yes/no	11 (14.5%)/65 (85.5%)	48 (42.5%)/65 (57.5%)	<.001
Median time since surgery in months (range)	—	46.6 (12 to 533)	

In patients with a history of PPGL, assessment was performed at least 12 months after surgical resection of the pheochromocytoma or paraganglioma. Cholesterol measurements were not consistently available across all patients. Statistically significant values are shown in bold.

**Figure 3.** HbA1c level in patients with a history of PPGL compared to a control group with nonfunctioning adrenal adenomas (NFAA).

paraganglioma, age at last HbA1c measurement, statin use, BMI, systolic blood pressure) were not significant in this model.

Impact of Cardiometabolic Risk Factors on HbA1c Following PPGL Surgery

To assess the potential influence of the BMI and age following PPGL surgery on HbA1c in individual patients with a history

of PPGL, a linear regression analysis for presurgery and post-surgery data was performed. Only patients with HbA1c measurements collected before surgery, or within a maximum of 1 month after surgery and with at least one follow-up HbA1c value, were included for this specific subanalysis (Fig. 1—Comparison 3). A total of 30 patients were analyzed (22 with pheochromocytoma, 8 with paraganglioma, and 18 with documented elevated plasma (nor)metanephrine or 3-methoxytyramine before surgery; mean age at surgery:

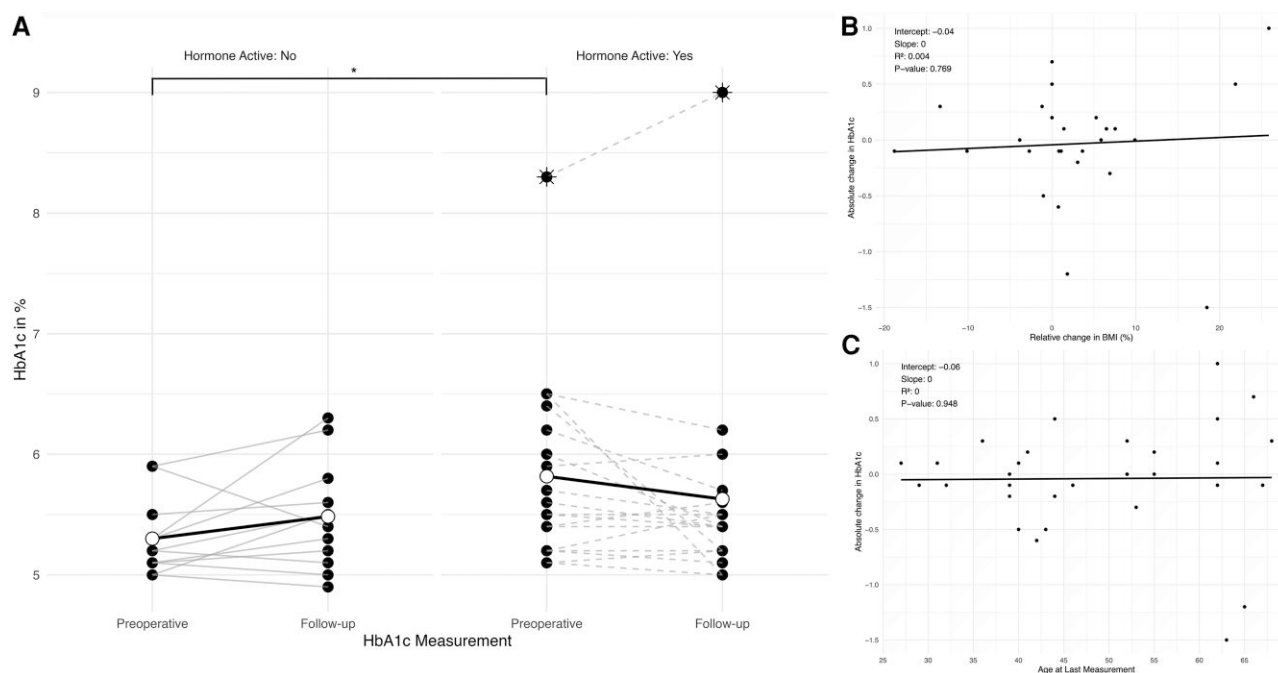


Figure 4. A, HbA1c before and after resection of PPGL in patients with catecholamine-secreting vs nonsecreting PPGLs. Outliers are depicted with star signs. The mean HbA1c in each group is represented with a white dot. B, Changes in HbA1c vs changes in BMI during follow-up after resection of PPGL. C, Changes in HbA1c vs age at last biochemical assessment during follow-up after resection of PPGL.

47 years). The mean follow-up duration was 20.6 months (SD 11.9).

Before surgery/within 1 month after resection, HbA1c was higher in patients with catecholamine-secreting PPGLs compared to nonsecreting PPGLs (mean HbA1c 5.82% vs 5.3%, $P = .02$). However, follow-up HbA1c did not differ between the 2 groups (mean HbA1c 5.6% in secreting PPGLs vs 5.5% in nonsecreting PPGLs, $P = .56$) (Fig. 4A). BMI did not differ between patients with catecholamine-secreting PPGLs and nonsecreting PPGLs but after PPGL resection, a trend toward an increase (mean change of $\Delta 0.6$ kg/m², SD 2.3) was observed. However, regression analysis did not reveal any statistically significant association between changes in HbA1c and BMI, nor between HbA1c and age (Fig. 4B and 4C). Mean systolic blood pressure showed a downward trend post surgery, decreasing by 4 mmHg (SD 15) from an initial value of 135 mmHg.

Discussion

The primary finding of this study is the long-term persistence of chronic hyperglycemia up to 5 years after PPGL resection. This finding highlights the long-term metabolic consequences of these catecholamine-producing tumors, even after successful surgical intervention. Previous research has largely focused on the immediate postoperative changes in metabolism (32). Our study, in contrast, reveals that chronic hyperglycemia may remain a long-term health problem in these patients.

Our initial analysis of the ProsPheo study population at study entry revealed no significant differences in metabolic parameters such as HbA1c, cholesterol levels, triglycerides, BMI, or systolic blood pressure between patients with a history of PPGL and those with present or recently (within 1 month) resected PPGL. Particularly, both groups had similar HbA1c levels, and there were no significant differences in the use

of statins or antidiabetic agents. These findings suggest that the metabolic disturbances caused by PPGL might not be fully reversible with tumor removal or, vice versa, preexisting chronic hyperglycemia might promote PPGL development. Consistently, the percentage of patients with prediabetes was significantly higher in those with a history of PPGL compared to susceptibility gene carriers (without a history of PPGL). However, the latter group was significantly younger, and the potential influence on glucose metabolism of genetic alterations in genes such as *SDHx* or *VHL* cannot be ruled out. Hyperglycemia may increase the risk of PPGL development in individuals predisposed due to specific PVs. Notably, type 2 diabetes and obesity, both conditions associated with insulin resistance, are linked to a higher incidence of neuroendocrine tumors in the pancreas and small intestine (33, 34). This raises the possibility that the higher prevalence of hyperglycemic disorders we observed in patients with a history of PPGL could similarly serve as a predisposing factor for the development of PPGLs in susceptible individuals. However, if this does indeed occur, the possible mechanism for this effect is unclear.

On the other hand, hyperglycemia is a well-known complication of secreting PPGL. Specifically, previous studies suggested that up to 50% of patients with PPGL have disturbances of glucose metabolism before treatment (22, 23, 35–37). In line with this, we found that 36% (18/50) of patients with a present PPGL had disturbances in glucose metabolism. In particular, elevated plasma norepinephrine levels have been associated with higher HbA1c and lower body weight in PPGL patients (24). In our, albeit small, cohort of patients with preoperative assessment of catecholamine secretion, patients with elevated plasma (nor)metanephrines had a higher HbA1c at diagnosis compared to patients without measurable plasma (nor)metanephrines. However, in follow-up, we found no such difference in HbA1c between the 2 groups,

while additionally their BMI did not differ. The initial diagnosis (pheochromocytoma vs paraganglioma) was not significantly associated with hyperglycemia in our study. Interestingly, in our cohort, the percentage of patients with prediabetes or diabetes did not significantly differ between those with present metastatic PPGL, present nonmetastatic PPGL, and those with a history of resected PPGL. In metastatic PPGL, alpha-adrenoceptor blockade may blunt catecholamine-induced hyperglycemia, while anorexia in these patients may additionally lower glucose levels. Additionally, systemic therapies may increase red blood cell turnover, and consequently lower HbA1c.

Importantly, our study found that, among patients during follow-up for at least 12 months after resection of PPGL, disturbances in glucose metabolism persisted, with 42.5% (48/113) of patients showing elevated HbA1c levels—36.3% had prediabetes, and 6.2% had diabetes. This is a significant finding, especially when compared to a control group with nonfunctioning adrenal adenoma, which, despite being slightly older, included only 14.5% of patients (11/76) with glucose metabolism disturbances. In a regression analysis, we did not find a correlation of rising HbA1c with typical risk factors for diabetes, such as older age and weight gain, suggesting an independent pathophysiological mechanism. Statin use as a potential risk factor for hyperglycemia (38) was also not significantly different between patients with history of PPGL and those with nonfunctioning adrenal adenomas. Statins were used by 20.4% of patients with a history of PPGL in comparison to 16% of patients with nonfunctioning adenomas. When compared to epidemiological studies in Western Europe, the prevalence of prediabetes (36.3%) in our study population with a history of resected PPGL is notably higher than expected. For instance, in a French study, the prevalence of prediabetes in the population aged 50 to 70 years was reported to be 13.7%, with diabetes affecting 15.25% of this age group (39). These findings suggest that a history of PPGL may increase the risk of moderate glucose disturbances more than previously recognized, although it does not necessarily lead to diabetes. Nonetheless, as presented in an umbrella review, prediabetes was positively associated with an increased risk of all-cause mortality, as well as the incidence of coronary heart disease, stroke, chronic kidney disease, cancer, and dementia (40). Therefore, the increased presence of prediabetes in patients with a history of PPGL may further elevate their risk for these serious conditions, including PPGL recurrence.

One hypothesis for sustained moderate hyperglycemia, manifest as prediabetes rather than clinical diabetes, is that the excessive and prolonged release of catecholamines before the detection and resection of PPGL may lead to persistent hyperglycemia. This acute effect occurs primarily due to the inhibition of insulin secretion, which reduces glucose uptake by peripheral tissues (41). The prolonged suppression of insulin before resection might impair pancreatic beta-cell function, diminishing their ability to respond effectively even after catecholamine levels normalize. Following PPGL resection, the normalization of catecholamine levels likely alleviates these inhibitory effects, thus allowing for partial recovery of glucose homeostasis. In a small study of 18 patients with pheochromocytomas with an adrenergic phenotype, pancreatic α - and β -cell function and glucagon-like peptide 1 (GLP-1) secretion were evaluated using a liquid-meal test before and after surgical resection (42). The authors reported suppressed pancreatic

function and impaired GLP-1 secretion before surgery, with significant improvements after resection (42). In accordance with our findings, diabetes mellitus persisted in 2 patients (11%) and prediabetes in 7 patients (39%) 1 year after surgery (42). Additionally, catecholamines are known to induce insulin resistance, particularly in the liver and muscle, which may further hinder the normalization of glucose levels, even after the excess catecholamine exposure is resolved (43).

Patients with metabolic risk factors such as prediabetes and obesity are at risk of developing metabolic dysfunction associated steatotic liver disease. Feigelson et al demonstrated that norepinephrine infusion leads to rapid free fatty acid mobilization and the development of subsequent fatty liver in dogs (44). Additionally, studies in a mouse model and human liver tissue have shown that elevated norepinephrine levels promote fibrosis progression via α 1-adrenergic receptor activation (45, 46). Due to missing data on liver fat content in the individuals included in our study, metabolic dysfunction associated steatotic liver disease/metabolic dysfunction associated steatohepatitis could not be analyzed. We were also unable to exclude other primary etiologies, such as drug-induced liver injury, on an individual level. However, further research is warranted to explore potential associations between plasma (nor)metanephrines secreted by PPGLs, liver health, and insulin resistance.

This persistent metabolic disruption emphasizes the need for long-term monitoring of glucose metabolism in patients post-PPGL resection since they may be at an increased risk for developing chronic hyperglycemia. In contrast to other studies, we did not observe an influence of PPGL on cholesterol levels or BMI in our cohort (47, 48). This lack of effect may be attributable to the high percentage (25%-30%) of patients in our study who were taking statins for primary prevention.

Strengths and Limitations

A key strength of our study is the inclusion of a large cohort of patients with both a current diagnosis and follow-up after resection of PPGL. This study represents the first subanalysis of the ProsPheo trial, highlighting the importance of obtaining long-term data in patients with this relatively rare disease. This allows for a comprehensive analysis of metabolic outcomes over time. Additionally, we used a control group where hyperaldosteronism, hypercortisolism including mild autonomous cortisol secretion (MACS), and catecholamine-producing PPGL, were excluded. This group was slightly older, which would theoretically increase the prevalence of prediabetes and diabetes. Furthermore, a retrospective cohort study from 2016 found that patients with nonfunctioning adrenal adenomas had a significantly higher risk of developing diabetes compared to those without adrenal tumors (adjusted relative risk = 1.87; 95% CI: 1.17-2.98) (49). Both factors further strengthen the validity of our findings.

However, our study has some limitations. First, our reliance solely on HbA1c to assess glucose metabolism may not fully capture the complexity of glucose regulation in these patients. We did not collect information on lifestyle behaviors, such as diet and physical activity, which could significantly influence the risk of glucose intolerance. Moreover, the inclusion of patients with genetic disorders that might potentially inherently increase the risk of glucose metabolism disturbances may have introduced a confounding factor. Due to the small number of

patients with *SDHB* PVs in our study cohort, we were unable to analyze any correlations between glucose regulation and this specific variant. However, the ongoing ProsPheo trial is expected to address this and related questions.

Conclusions

In summary, our study provides evidence that disturbances in glucose metabolism persist for several years following the resection of PPGL, suggesting a long-term metabolic impact, independent of active catecholamine secretion. Given that impaired glucose metabolism is a significant cardiometabolic risk factor, these findings emphasize the importance of ongoing metabolic monitoring in these patients. Nevertheless, the long-term cardiovascular outcomes in patients with resected PPGLs remain poorly understood.

Further data from the ProsPheo study will provide additional insights into the long-term effects of (metastatic) PPGL or a history of PPGL on cardiometabolic risk factors and the occurrence of cardiovascular events, offering a more complete understanding of the risks faced by these patients. Additionally, longitudinal data of the ProsPheo study will help to clarify the effects of (preexisting) chronic hyperglycemia and insulin resistance on the risk of PPGL development or recurrence.

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Disclosures

The authors have nothing to disclose.

Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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