Review

Thieme

Metabolic Alterations in Patients with Pheochromocytoma

Authors
Zoran Erlic[1], Felix Beuschlein[1, 2]

Affiliations
1 Klinik für Endokrinologie, Diabetologie und Klinische Ernährung, Universitätsspital Zürich, Zürich, Switzerland
2 Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Munich, Germany

Correspondence
Prof. Felix Beuschlein, MD
Klinik für Endokrinologie,

Diabetologie und Klinische Ernährung
Universitätsspital Zürich
Rämistrasse 100
CH-8091 Zürich
Switzerland
Tel.: + 41/44/255 36 25, Fax: + 41/44/255 33 30
felix.beuschlein@usz.ch

ABSTRACT

Metabolic alterations in patients with hormonally active pheochromocytoma/paraganglioma (PPGL) have been described early on in the literature. The initial findings were related to disturbed glucose homeostasis and lipolysis activation, as well as elevated metabolic rates in affected patients. Similarly, from early autopsy reports, the presence of brown adipose tissue had been noted in PPGL patients. In more recent years, changes in body weight, fat mass and distribution have been analyzed in more detail in addition to activity of brown adipose tissue based on functional imaging techniques. Over the last decades, several larger case series and cohort studies have contributed towards the elucidation of possible mechanism contributing to these clinical observations. Herein, we summarize the clinical and experimental data regarding metabolic alterations and related clinical manifestations in PPGL patients.

Abbreviations

ADRA2A	alpha2A-adrenergic receptors
BAT	brown adipose tissue
BMD	bone mineral density
BMI	body mass index
CT	computed tomography
CTX	C-terminal telopeptide of type I collagen
DM	diabetes mellitus
FDG	fluordesoxyglucose
FFA	free fatty acids
HDL	high-density lipoprotein
IL	interleukin
ISI	insulin sensitivity index
IVGTT	intravenous glucose tolerance test
LDL	low-density lipoprotein
OGTT	oral glucose tolerance test
PET	positron emission tomography
PPGL	pheochromocytoma/paraganglioma
TNF	tumor necrosis factor
UCP1	uncoupling protein 1

Introduction

Adrenal pheochromocytoma and paragangliomas arising from the chromaffin cells of the adrenal glands and sympathetic paravertebral ganglia of the thorax, abdomen and pelvis, respectively, are hormonally active tumors secreting one or more catecholamines (epinephrine, norepinephrine and dopamine). In this article, we will use the term paraganglioma (PGL) for paragangliomas of the abdomen, pelvis and thorax. Paragangliomas arising from the parasympathetic ganglia in the neck and the skull-base, also called head and neck paragangliomas, are usually hormonally inactive and will not be part of this review [1].

One of the biggest challenges in the diagnostic work-up of patients with pheochromocytoma/paraganglioma (PPGL) is related to their diverse clinical presentation, mimicking many other clinical conditions. The clinical signs and symptoms of affected patients

Erlic Z, Beuschlein F. Metabolic Alterations in Patients with Pheochromocytoma … Exp Clin Endocrinol Diabetes 2019; 127: 129–136

129

has been widely described in the literature and mainly related to catecholamine excess affecting the cardiovascular system [2]. In this review article, we aim to focus on metabolic alterations and related clinical manifestations from clinical studies in PPGL patients. While less apparent by associated signs and symptoms, these metabolic features might well have additional impact on the morbidity and long-term outcome. More attention will be put on the retrieved clinical and experimental data of PPGL patients from these studies and less on additional explanation based on physiologic studies in human or animal models.

PPGL and Glucose Homeostasis

As catecholamine excess can be considered as the biochemical hallmark of PPGL manifestations it is not surprising that glucose homeostasis alterations can occur in affected patients. In fact, from physiologic studies it is well known that activation of alpha and beta adrenergic responses are involved in glycogen metabolism (decreased glycogenesis and increased glycogenolysis) and gluconeogenesis (increased gluconeogenesis) in the liver and in the regulation of insulin and glucagon release (decreased insulin and increased glucagon secretion) in the pancreas (reviewed in [3]).

PPGLs as a secondary cause of diabetes mellitus have been described already early on in the literature [4, 5]. In studies assessing the presence of diabetes mellitus in PPGL patients, the prevalence has been reported to vary between 21–37 % [6–14] (▶ **Table 1**). If studies are included where the presence of diabetes mellitus was not actively tested, the prevalence was lower (15-18 %) [7, 15, 16]. Although the correlation of PPGL with diabetes mellitus has been established for some time, the unawareness/underestimation of PPGL as a secondary cause of diabetes mellitus has been documented by several published case reports of long-term therapy-resistant diabetes mellitus and newly diagnosed diabetes mellitus with ketoacidosis or hyperglycaemia syndrome, in which the diagnosis of PPGL was only made later and rather incidentally [17–25]. Notably, in only rare instances, diabetes mellitus had been the sole clinical manifestation of PPGLs in those patients [26, 27]. In these published cases, diabetes mellitus either resolved or meliorated after surgical removal, confirming the proposed pathogenic role of catecholamine excess.

Evidence for impaired insulin secretion in PPGL patients

Both impaired insulin secretion and increased insulin resistance have been implicated as underlying causes of diabetes mellitus in PPGL patients (▶ **Table 1**) [18, 25, 28–37]. In fact, all published studies have identified a blunted insulin response towards oral glucose tolerance testing (OGTT) with a predominantly early phase secretion defect based on a delayed and lower insulin peak in comparison to postoperative testing and compared to normal subjects [18, 25, 28–32, 34, 35, 37]. The same impaired insulin secretion profiles could be documented following intravenous arginine or tolbutamide (sulfonylurea) administration, which are known stimuli for insulin secretion of the pancreatic beta cells [29–31, 33]. In addition, hyperglycemic clamp studies on 13 PPGL patients confirmed the preoperative impaired insulin secretory response to intravenous glucose stimuli, which normalized after successful tumor resection [37]. Interestingly, in some of these studies, improve-

ment of insulin secretion after OGTT or intravenous glucose tolerance test (IVGTT) could already be observed upon treatment initiation with alpha-adrenergic receptor blockers. This effect was only slightly further improved by the additional use of beta-adrenergic receptor blockers, suggesting a major pathogenic role in the alpha-adrenergic receptors stimulation of the pancreatic beta cells [29, 31, 32, 34]. In favor of this hypothesis, the alpha2A-adrenergic receptors (ADRA2A) of the pancreatic beta cells have been implemented as mediators for the inhibitory effects of catecholamines in early-phase insulin release [38]. In these recent pharmacological and genetic association studies both, pharmacological selective blocking of ADRA2A as well as specific genotypes of the ADRA2A coding gene, were associated with reduced insulin secretion.

Evidence for increased insulin resistance in PPGL patients

The notion that not only insulin secretion, but also insulin sensitivity could be compromised in these patients had been postulated already in early studies, by showing for example a less pronounced hypoglycemic response after intravenous insulin infusion in PPGL patients prior surgery [29]. In 2003, two hyperinsulinemic euglycemic clamp studies described a postoperative improvement of the insulin sensitivity index (ISI) [35, 36]. While the ISI calculation was slightly different between these two studies, in both instances ISI was proportional with the glucose infusion rate necessary to maintain euglycemia in the steady state. However, this improvement in insulin resistance could not be reproduced in a more recent study of 13 PPGL patients, where the ISI, calculated as in the former study by Wiesner et al. [36], was not different before and after PPGL removal [37]. Similarly, in two further case reports, the insulin resistance, expressed as either metabolic glucose rate in hyperinsulinemic euglycemic-clamp [25] or whole body insulin sensitivity index in OGTT [18], did not show a significant change before and after surgery. The hypothesis of the pathogenic role of catecholamines on insulin resistance is based on physiological and pharmacological studies with epinephrine and norepinephrine in humans and animal models, where unopposed hepatic glucose production during hyperglycemia, as well as decreased splanchnic and muscular glucose uptake has been documented (reviewed in [3]). However, it should be noted, that no similar studies have been performed in the context of PPGL patients. A further potential explanation for insulin resistance observed in PPGL patients bases on the presence of elevated free fatty acids in affected patients (discussed later in this review), with known effect on insulin resistance [3]. Further, an increase in adiponectin level has been observed in PPGL patients postoperatively, with lower preoperative levels [10, 39]. Adiponectin is secreted from adipose tissue and evidence suggests that elevated levels improve insulin sensitivity [3]. In contrast, the preoperative low adiponectin levels has not been confirmed in a different PPGL cohort [12]. Similarly, in some case reports a slightly increase of leptin levels, another hormone produced from the adipocytes enhancing insulin sensitivity, was documented after PPGL removal [40–42]. However, this finding has not been consistently reported and has not been observed in an additional study [43]. Furthermore, at this point it is not clear, whether the changes in the levels of adiponectin and leptin are due to direct or indirect actions of catecholamines.

130

Erlic Z, Beuschlein F. Metabolic Alterations in Patients with Pheochromocytoma … Exp Clin Endocrinol Diabetes 2019; 127: 129–136

▶ **Table 1** Summary of sample size and major outcomes.

	Total number of patients studied (sum or total number per study)	Method	Baseline*	After surgery**	Reference
PPGL and glucose homeostasis					
Frequency of diabetes mellitus (DM)	60	current DM treatment or fasting blood glucose ≥ 7 mmol/l	19/60 (31.2%)	1/55 (1.8%); no follow up data for 5 patients with DM at baseline	[6]
	153	current DM treatment or abnormal HbA1c or multiple random blood glucose ≥ 11.1 mmol/l	36/153 (23.5%)	6/145 (4.1%); no data about 8 patients with DM at baseline	[7]
	67	fasting plasma glucose ≥ 7 mmol/l or 2-h plasma glucose glucose ≥ 11.1mmol/l	21/67 (31.3%)	1/66 (1.5%); no data about 1 patient who died after surgery	[8]
	191	current DM treatment or fasting blood glucose ≥ 7 mmol/l on two occasions	68/191 (35.6%)	1/191 (0.5%)	[9]
	26	not specified	9/26 (34.6%)	5/26 (19.2%)	[10]
	176	plasma glucose ≥ 7 mmol/l on two occasions	51/176 (29%)	not available	[11]
	49	current DM treatment or fasting blood glucose ≥ 7 mmol/l on two occasions	18/49 (37%)	not available	[12]
	43	current DM treatment or HbA1c ≥ 6.5%	9/43 (21%)	4/43 (9.3%)	[13]
	17	current DM treatment or fasting blood glucose ≥ 7 mmol/l on two occasions	6/17 (35%)	1/17 (6%)	[14]
Total	782		237/782 (30.3%)	19/543 (3.5%)	
Insulin secretion studies	31	OGTT with glucose and insulin measurement	31/31 (100%) pathologic glucose tolerance with blunted insulin response	31/31 (100%) improved glucose tolerance and insulin secretion response	[18, 25, 28–32, 34, 35, 37]
	13	hyperglycemic clamp	preoperative impaired insulin secretion on glucose stimuli compared with after surgery		[37]
Total	44		44/44 (100%) improvement of insulin secretion after surgery		
Insulin resistance studies	5	hyperinsulinemic euglycemic clamp	improvement of ISI after PPGL removal		[35]
	10	hyperinsulinemic euglycemic clamp	improvement of ISI after PPGL removal		[36]
	13	hyperinsulinemic euglycemic clamp	no difference in ISI before and after PPGL removal		[37]
	1	hyperinsulinemic euglycemic clamp	no difference in metabolic glucose rate before and after PPGL removal		[25]
	1	OGTT with glucose and insulin measurement	no difference in whole body insulin sensitivity index before and after PPGL removal		[18]
Total	30		15/30 (50%) with improvement of insulin resistance after PPGL removal		
PPGL and lipid metabolism					
Free fatty acids (FFA)	36	fasting plasma FFA measurement	12/36 (33%) with elevated levels	0/36 (0%) with elevated levels	[29, 30, 34, 36, 37, 46–47]
Triglyceride	121	fasting triglyceride measurement	1/120 (0.01%) postoperative increase in fasting triglyceride levels		[10, 14, 36, 37, 40, 50]
LDL-cholesterol	70	fasting LDL-cholesterol measurement	without significant change pre- and postoperative		[36, 40, 50]
HDL-cholesterol	42	fasting HDL-cholesterol measurement	significant postoperative HDL-cholesterol decrease		[50]
	18	fasting HDL-cholesterol measurement	tendency towards HDL-cholesterol lowering after surgery		[40]
PPGL and body weight and body composition					
Body weight	377	anthropometric measurement (BMI)	significant weight gain after successful PPGL surgery		[10, 13, 14, 37, 40, 50, 53–54]
Fat mass	73	bio-impedance [14] and CT-based [50, 53] analysis	significant increase in body fat mass after successful PPGL surgery		[14, 50, 53]

* common column for descriptive outcomes of published case reports and cases series, the latter according to their reported statistical significance (no individual data available); ** follow-up time differs between studies and is not specified

Whether in addition to catecholamines other co-secreting hormones might play a pathogenic role has not yet been extensively studied. In one case report, the presence of diabetes mellitus had been postulated to be caused by a concomitant somatostatin co-secretion, but this hypothesis had not been studied prior to surgery in this patient [20].

Summarizing the yet published literature, PPGLs can be regarded as an established secondary cause of diabetes mellitus, with a relevant unawareness of this fact among practitioners. Clinicians should include PPGLs in the differential diagnosis in patients with newly diagnosed diabetes mellitus and consider biochemical screening if suggestive signs and symptoms are present such as paroxysmal spells, palpitation and headache as well as hypertension in lean and young patients. A defect in insulin secretion has been more consistently documented in PPGL patients and seems to play a major role in the pathogenesis of glucose intolerance in PPGL patients.

PPGL and Lipid Metabolism

The sympathetic nervous system is one of the major regulators of adipocyte function. Adipocytes are rich in different subtypes of adrenergic receptors and their expression seems to be regulated in a complex manner according to specific physiological needs [44]. One of the major short-term metabolic effects on adipocytes is the well-established beta adrenergic stimulation of lipolysis in these cells. A variety of further metabolic actions on adipocytes have been postulated, which among others might affect also lipid metabolism [45].

Free fatty acids

The presence of elevated levels of products from lipolysis has been widely documented in PPGL patients (▶ **Table 1**). One of the first studies demonstrated an elevation of free fatty acids (FFA) in PPGL patients (7 of 8 cases) that normalized both upon pharmacological treatment with alpha-adrenergic blockade and following surgery [46]. This initial observation was confirmed in several other case series in the past [29, 30, 34], but could not be established in more recent studies [36, 37]. In one case report, only combined alpha- and beta-adrenergic blockade and surgery, but not alpha-adrenergic blockade alone could normalize elevated FFA levels [47]. As mentioned in the introduction section and with reference to the known physiological mechanisms, the hypothesis behind the observation of elevated FFA in PPGL patients relies on predominant beta-adrenergic stimulation of lipolysis in adipocytes. However, impaired insulin secretion in PPGL patients might further contribute to this effect [48]. The latter might explain the normalization of FFA after alpha-adrenergic blockade in the study from Engelman et al. [46]. In this context the observation that glycerol levels were not consistently increased preoperatively in PPGL patients is of interest [29, 34, 47]. The reasons and mechanisms responsible for this effect, however, are not clear.

Cholesterol and triglycerides

In one case report, a female patient with concomitant familial combined hyperlipidemia and PPGL has been investigated in some detail before and after pharmacological and surgical treatment [49]. According to this report, a postoperative increase of total cholesterol and triglyceride levels was observed, enhanced during the preoperative combined alpha- and beta-adrenergic blockade, with concomitant decrease in HDL-cholesterol levels postoperatively. The postulated mechanism from the authors sees an increased activity of lipoprotein lipase and increased pre-treatment energy consumption, as was observed in the patient. No significant change in triglyceride [10, 14, 36, 37, 40, 50] and LDL-cholesterol levels [36, 40, 50] had been observed in later studies, while a significant postoperative decrease in HDL-cholesterol was noted in one study [50] and a tendency towards postoperative HDL-cholesterol lowering in another (▶ **Table 1**) [40]. A significant positive correlation between urinary norepinephrine levels and HDL-cholesterol was documented in one report [50]. The stimulatory effect of catecholamines on the lipoprotein lipase in presence of impaired insulin secretion could explain this effect [51]. However, the elevated HDL-cholesterol levels and increase of lipoprotein lipase activity in PPGL patients could also be considered as an indirect effect of catecholamines-induced thermogenic activation of adipocytes (discussed later in this review) [52].

In summary, the activation of lipolysis resulting in high levels of FFA is a common metabolic feature in PPGL patients. Alteration of cholesterol levels are less evident in these patients. The possible mechanism of higher HDL levels prior to surgery in PPGL patients merit further clarification.

PPGL and Body Weight and Body Composition

Weight gain following successful PPGL treatment

Weight gain after PPGL resection has been observed already in early clinical descriptions [5]. Likewise, significant weight gain after successful PPGL treatment has been confirmed in more recent cohort studies (▶ **Table 1**) [10, 13, 14, 37, 40, 50, 53, 54]. In a paper by Spyroglou et al. [13], a significant correlation of weight gain and preoperative urine normetanephrine concentration was observed in 43 PPGL patients and an effect of adrenalectomy on weight gain could be excluded by comparison with matched primary hyperaldosteronism patients, who underwent the same surgical procedure. However, the correlation of weight change with urine norepinephrine or plasma normetanephrine could not be solidified in this study. Further, in a recent study by An and colleagues [54], the preoperative urinary total catecholamine levels of 210 PPGL patients were negatively correlated with preoperative body mass index (BMI) and further positively correlated with the postoperative change in BMI. In contrast, no correlation between weight change and plasma norepinephrine levels before and after surgery were found in a different cohort of 42 PPGL patients [50].

One of the possible explanations for the observed weight change is the high metabolic rate present in PPGL patients compared with matched control populations, which decreases significantly following successful tumor removal [5, 14, 46, 49]. This could be due to the observed higher protein and fat oxidative metabolism relative to carbohydrate oxidation, as shown in a case report in one patient prior surgery [49]. Other explanations could include activation of brown adipose tissue (BAT) in PPGL patients (discussed later in this review), which is capable to turn free fatty acids and glucose in heat, thereby

132

Erlic Z, Beuschlein F. Metabolic Alterations in Patients with Pheochromocytoma … Exp Clin Endocrinol Diabetes 2019; 127: 129–136

dissipating energy [55]. The further hypothesis of tumor cachexia is possible, but not evident as in one large cohort study no association between change in metabolic rate and inflammatory cytokine (IL-1, IL-6 and TNF-alfa) was observed [14].

PPGL and fat mass

With bio-impedance measurements in one study and computed tomography (CT) based analysis in two additional studies, a significant increase in body fat mass has been documented following PPGL resection (▶ **Table 1**) [14, 50, 53]. The increase involved both, visceral and subcutaneous fat depots, which were found to be reduced in PPGL patients before treatment in comparison to patients with non-functional adrenal adenomas or normal controls [50, 53]. Notably, this reduced fat mass before surgery was independent from BMI, which was not different between PPGL subjects before surgery and controls. No significant correlation between changes in fractionated plasma catecholamines or metanephrines with fat mass change could be observed in these two studies [50, 53].

PPGL and brown adipose tissue (BAT)

Based on in vivo and in vitro studies, the autonomic nervous system is clearly involved in the activation of human brown adipose tissue (reviewed in [55]). The presence of BAT in PPGL patients had been noted very early in autopsy reports [56]. More recently, these observations were of particular clinical relevance, due to the increased numbers of functional imaging performed in these patients. BAT activity can be identified incidentally with different radiopharmaceuticals used in routine diagnostics, predominantly with ^{18}F-Fluorodeoxyglucose (FDG) [57, 58], and thus lead to false-positive results for example in the work-up of patients with malignant PPGL. It is not clear, if the prevalence of BAT in PPGL patients is higher than in the general population, since currently only data from functional imaging studies are available and its activation depends from different endogenous and exogenous factors [59]. In a retrospective analysis of 59 PPGL patients, 22 % had BAT visualization on ^{18}F-FDG positron emission tomography (PET)/CT scan, compared with 9.5 % in control subjects, although this difference was not statistically significant. For patients, who had concomitant imaging with further tracers (^{18}F-6-Fluorodopamine and ^{123}I-metaiodobenzylguanidine) no significant difference in BAT activity in PPGL patients and controls was seen, as well as between the tracers [57]. In the former study a significant correlation between plasma norepinephrine levels and BAT-activity in ^{18}F-FDG PET/CT scans was observed, while this was not the case for the other two tracers studied. In a distinct analysis of 14 PPGL patients, a significant correlation between BAT activity and high metanephrine levels (defined as elevated either normetanephrine or metanephrine plasma levels with upper two standard deviation as cut-off point) was documented [53]. Similar findings were obtained in a more recent investigation, where 31 % of 21 hormonally active tumors had BAT activity compared with none of the six hormonally silent tumors. In contrast, this study found no significant correlation between metanephrine levels and BAT activity [60]. In one further study, the prevalence of retroperitoneal BAT was estimated histologically in adjacent periadrenal adipose tissue after surgical removal [61]. In five of eight (62.5 %) PPGL patients BAT was present, compared to two of two (100 %) patients with non-functioning adrenal tumors,

15 of 32 (46.9 %) patients with aldosterone-producing adenoma, three of nine (33.3 %) patients with cortisol-producing adenoma and one of six (16.7 %) patient with secondary hypercortisolism; these differences, however, were not found to be statistically significant. Using the uncoupling protein 1 (UCP1) as marker of BAT, no influence of plasma metanephrines on UCP1 expression level could be identified.

Considering these data together, it is evident, that BMI and fat mass are decreased in patients with PPGL. In addition to the high metabolic rate and activation of lipolysis, the impact of brown adipose tissue for these effects remains uncertain, as well as the importance of catecholamine excess on its presence and activity.
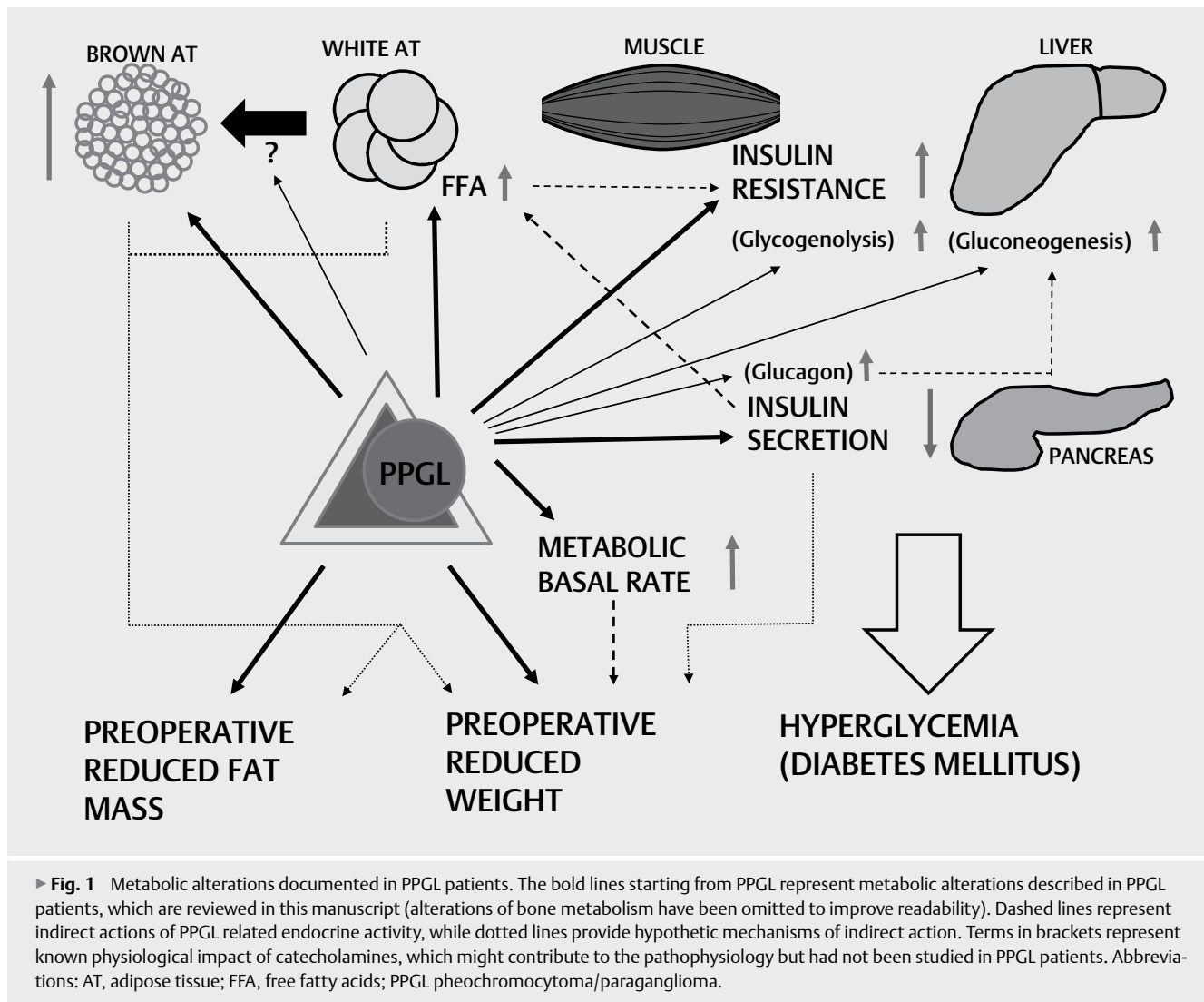
PPGL and bone metabolism

A possible role of the sympathetic nervous system on bone metabolism has been assessed in vitro and in animal models, which provided evidence for a negative effect of sympathomimetic activation on bone mass (reviewed in [62]).

In a retrospective clinical study, increased levels of the bone resorption marker C-terminal telopeptide of type I collagen (CTX) were observed in PPGL patients compared to controls (patients who were negative on PPGL screening). This initial increase was reduced following successful surgical treatment [63]. This finding could be confirmed in a larger cohort study, where CTX was higher in 31 PPGL patients compared to 280 patients with non-functioning adrenal adenoma [64]. In both studies, the bone formation parameters procollagen type 1 N propeptide [63] as well as bone-specific alkaline phosphatase [64], did not differ between PPGL patients and controls and were unchanged after tumor removal. In the study from Kim et al. [64], bone mineral density (BMD) analysis showed a decreased BMD at the lumbar spine level, but not at the proximal femur in PPGL patients compared to controls. Both, BMD at the lumbar spine as well as CTX levels were associated with urine metanephrine and normetanephrine levels, BMD negatively and CTX positively [64].

In summary, there is emerging evidence that catecholamine excess in PPGL patients might negatively influence bone mass. However, further studies are needed to analyze its impact on fracture risk and thus morbidity in these patients.

Conclusion and Perspectives

There is ample clinical evidence that glucose and lipid metabolism are compromised in PPGL patients and it is prudent to speculate that these findings might confer to the the increased cardiovascular risk observed in this patient population compared with matched hypertensive patients [65, 66]. Specific characteristics of PPGL patients in energy expenditure, weight, fat mass and body composition are well documented in the literature, while the underlying mechanism are not completely elucidated. It would be interesting for future studies to analyze in more detail the presence of BAT in this patient population with alternative methods, not only focusing on its activity. In general, physiological studies as well as adrenergic-receptor expression on the key metabolic organs provide a number of arguments towards the direct activity of catechola-

▶ **Fig. 1** Metabolic alterations documented in PPGL patients. The bold lines starting from PPGL represent metabolic alterations described in PPGL patients, which are reviewed in this manuscript (alterations of bone metabolism have been omitted to improve readability). Dashed lines represent indirect actions of PPGL related endocrine activity, while dotted lines provide hypothetic mechanisms of indirect action. Terms in brackets represent known physiological impact of catecholamines, which might contribute to the pathophysiology but had not been studied in PPGL patients. Abbreviations: AT, adipose tissue; FFA, free fatty acids; PPGL pheochromocytoma/paraganglioma.

mine excess for this change [55]. A summary of the described findings is illustrated in ▶ **Fig. 1**.

Still, it remains unanswered, whether all of the observed manifestations are directly caused by catecholamine excess, or whether some are indirect responses to an upstream metabolic alteration in PPGL patients or a physiological adaptation to the catecholamine stress. It would be interesting to study in detail whether patients with PPGLs of different hormonal characteristics (e. g. epinephrine or norepinephrine secretory tumors) could be characterized by different metabolic profiles due to different receptor affinities and distinct biological effects of the individual catecholamines. One important issue in future studies addressing this question is to correlate catecholamine and not metanephrine profiles with the investigated clinical or metabolic outcome. While metanephrines (e. g. plasma-free metanephrines) are markers with very good sensitivity and specificity for PPGL diagnosis, they are not biologically active. Thereby, in some of the studies from the recent literature, the incongruent or absent correlation of metabolic findings with tumor hormone activity might well depend on the fact that the correct marker for tumor secretory activity (catecholamines) were

not investigated in detail. Further, the known adrenergic receptor downregulations and desensitization in PPGL patients with longstanding catecholamine excess might have added another layer of complexity into the interpretation of associated metabolic effects. For these reasons, these observations are likely to differ from well appreciated effects described in physiological studies [67, 68]. Other possible causes of incongruent outcomes include the limited possibility to consider multiple other factors such as duration of disease, extent of catecholamine excesses, co-morbidities and concomitant medication use. Furthermore, it should be stressed, that the retrospective nature of most of the studies and the small number of included patients (that reflect in many instances case reports) further limits the power of statistic evaluations. Finally, the wealth of germline and somatic genetic findings in PPGL patients allows for future investigation of potential genotype/phenotype correlation also for metabolic alterations that might extent the prospect of precision medicine approaches. Only further clinical studies focused on this patient cohort will help us to elucidate these aspects, which due to the rarity of the tumor is not easy to achieve.

Conflict of Interest

No conflict of interest has been declared by the authors.

References

[1] Lenders JW, Duh QY, Eisenhofer G et al. Pheochromocytoma and paraganglioma: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2014; 99: 1915–1942

[2] Lenders JWM, Eisenhofer G, Mannelli M et al. Phaeochromocytoma. Lancet 2005; 366: 665–675

[3] Mesmar B, Poola-Kella S, Malek R. The physiology behind diabetes mellitus in patients with pheochromocytoma: A review of the literature. Endocr Pract 2017; 23: 999–1005

[4] Duncan LE, Semans JH, Howard JE. Adrenal medullary tumor (pheochromocytoma) and diabetes mellitus, disappearance of diabetes after removal of the tumor. Ann Intern Med 1944; 20: 815–821

[5] McCullagh EP, Engel WJ. Pheochromocytoma with Hypermetabolism: Report of Two Cases. Ann Surg 1942; 116: 61–75

[6] Stenstrom G, Sjostrom L, Smith U. Diabetes-Mellitus in Pheochromocytoma - Fasting Blood-Glucose Levels before and after Surgery in 60 Patients with Pheochromocytoma. Acta Endocrinol-Cop 1984; 106: 511–515

[7] Beninato T, Kluijfhout WP, Drake FT et al. Resection of Pheochromocytoma Improves Diabetes Mellitus in the Majority of Patients. Ann Surg Oncol 2017; 24: 1208–1213

[8] Pogorzelski R, Toutounchi S, Krajewska E et al. The effect of surgical treatment of phaeochromocytoma on concomitant arterial hypertension and diabetes mellitus in a single-centre retrospective study. Cent European J Urol 2014; 67: 361–365

[9] La Batide-Alanore A, Chatellier G, Plouin PF. Diabetes as a marker of pheochromocytoma in hypertensive patients. J Hypertens 2003; 21: 1703–1707

[10] Elenkova A, Matrozova J, Zacharieva S et al. Adiponectin - A possible factor in the pathogenesis of carbohydrate metabolism disturbances in patients with pheochromocytoma. Cytokine 2010; 50: 306–310

[11] Amar L, Servais A, Gimenez-Roqueplo AP et al. Year of diagnosis, features at presentation, and risk of recurrence in patients with pheochromocytoma or secreting paraganglioma. J Clin Endocr Metab 2005; 90: 2110–2116

[12] Isobe K, Fu L, Tatsuno I et al. Adiponectin and adiponectin receptors in human pheochromocytoma. J Atheroscler Thromb 2009; 16: 442–447

[13] Spyroglou A, Adolf C, Hahner S et al. Changes in body mass index in pheochromocytoma patients following adrenalectomy. Horm Metab Res 2017; 49: 208–213

[14] Petrak O, Haluzikova D, Kavalkova P et al Changes in energy metabolism in pheochromocytoma. J Clin Endocrinol Metab 2013; 98: 1651–1658 doi:10.1210/jc.2012-3625

[15] Chen YF, Hodin RA, Pandolfi C et al. Hypoglycemia after resection of pheochromocytoma. Surgery 2014; 156: 1404–1409

[16] Modlin IM, Farndon JR, Shepherd A et al. Phaeochromocytomas in 72 patients: Clinical and diagnostic features, treatment and long term results. Br J Surg 1979; 66: 456–465

[17] Lee H, Dominiczak AF, Jennings GLR et al. Case of chronic indolent pheochromocytoma that caused medically controlled hypertension but treatment-resistant diabetes mellitus. Hypertension 2017; 69: 740–746

[18] Erlic Z, Roost K, Tschopp O et al. Improvement of insulin secretion and oral glucose tolerance after pheochromocytoma removal: A case report. Endocrine Abstracts 2017, doi:10.1530/endoabs.49.EP104

[19] Sedhai YR, Reddy K, Patel D et al. Unusual case of pheochromocytoma presenting with diabetic ketoacidosis. BMJ Case Rep 2016; 2016:

[20] Hirai H, Midorikawa S, Suzuki S et al. Somatostatin-secreting Pheochromocytoma Mimicking Insulin-dependent Diabetes Mellitus. Intern Med 2016; 55: 2985–2991

[21] Lee IS, Lee TW, Chang CJ et al. Pheochromocytoma presenting as hyperglycemic hyperosmolar syndrome and unusual fever. Intern Emerg Med 2015; 10: 753–755

[22] Donckier JE, Rosiere A, Heureux F et al. Diabetes mellitus as a primary manifestation of multiple endocrine neoplasia type 2B. Acta Chir Belg 2008; 108: 732–737

[23] Isotani H, Fujimura Y, Furukawa K et al. Diabetic ketoacidosis associated with the pheochromocytoma of youth. Diabetes Res Clin Pr 1996; 34: 57–60

[24] Edelman ER, Stuenkel CA, Rutherford JD et al. Diabetic-Ketoacidosis Associated with Pheochromocytoma. Clev Clin J Med 1992; 59: 423–427

[25] Ishii C, Inoue K, Negishi K et al. Diabetic ketoacidosis in a case of pheochromocytoma. Diabetes Res Clin Pr 2001; 54: 137–142

[26] Tong C, England P, De Crespigny PC et al. Diabetes mellitus as the only manifestation of occult phaeochromocytoma prior to acute haemorrhage in pregnancy. Aust Nz J Obstet Gyn 2005; 45: 91–92

[27] Yamashita S, Dohi Y, Kinoshita M et al. Occult extraadrenal pheochromocytoma treated as diabetes mellitus. Am J Med Sci 1997; 314: 276–278

[28] Wilber JF, Turtle JR, Crane NA. Inhibition of Insulin Secretion by a Phaeochromocytoma. Lancet 1966; 2: 733

[29] Spergel G, Bleicher SJ, Ertel NH. Carbohydrate and Fat Metabolism in Patients with Pheochromocytoma. New Engl J Med 1968; 278: 803

[30] Brooks MH, Guha A, Danforth E et al. Pheochromocytoma - Observations on Mechanism of Carbohydrate Intolerance and Abnormalities Associated with Development of Goldblatt Kidney Following Removal of Tumor. Metabolis 1969; 18: 445

[31] Vance JE, Buchanan KD, Ohara D et al. Insulin and Glucagon Responses in Subjects with Pheochromocytoma - Effect of Alpha Adrenergic Blockade. J Clin Endocr Metab 1969; 29: 911

[32] Colwell JA. Inhibition of Insulin Secretion by Catecholamines in Pheochromocytoma. Ann Intern Med 1969; 71: 251

[33] Hamaji M. Pancreatic Alpha-Cell and Beta-Cell Function in Pheochromocytoma. J Clin Endocr Metab 1979; 49: 322–325

[34] Turnbull DM, Johnston DG, Alberti KGMM et al Hormonal and Metabolic Studies in a Patient with a Pheochromocytoma. J Clin Endocr Metab 1980; 51: 930–933

[35] Diamanti-Kandarakis E, Zapanti E, Peridis MH et al. Insulin resistance in pheochromocytoma improves more by surgical rather than by medical treatment. Hormones (Athens) 2003; 2: 61–66

[36] Wiesner TD, Bluher M, Windgassen M et al. Improvement of insulin sensitivity after adrenalectomy in patients with pheochromocytoma. J Clin Endocrinol Metab 2003; 88: 3632–3636

[37] Komada H, Hirota Y, So A et al. Insulin Secretion and Insulin Sensitivity Before and After Surgical Treatment of Pheochromocytoma or Paraganglioma. J Clin Endocrinol Metab 2017; 102: 3400–3405

[38] Gribble FM. Alpha2A-adrenergic receptors and type 2 diabetes. N Engl J Med 2010; 362: 361–362

[39] Okauchi Y, Ishibashi C, Shu K et al. Decreased Serum Adiponectin Level during Catecholamine Crisis in an Obese Patient With Pheochromocytoma. Intern Med 2017, doi:10.2169/internalmedicine.9089-17

[40] Bosanska L, Petrak O, Zelinka T et al. The effect of pheochromocytoma treatment on subclinical inflammation and endocrine function of adipose tissue. Physiol Res 2009; 58: 319–325

[41] Sakane N, Yoshida T, Mizutani T et al. Serum leptin levels in a patient with pheochromocytoma. J Clin Endocrinol Metab 1998; 83: 1400

Erlic Z, Beuschlein F. Metabolic Alterations in Patients with Pheochromocytoma … Exp Clin Endocrinol Diabetes 2019; 127: 129–136

135

[42] Wocial B, Ignatowska-Switalska H, Berent H et al. Do catecholamines influence the level of plasma leptin in patients with phaeochromocytoma? Br J Biomed Sci 2002; 59: 141–144

[43] Bottner A, Eisenhofer G, Torpy DJ et al. Lack of leptin suppression in response to hypersecretion of catecholamines in pheochromocytoma patients. Metabolism 1999; 48: 543–545

[44] Lafontan M, Berlan M. Fat cell adrenergic receptors and the control of white and brown fat cell function. J Lipid Res 1993; 34: 1057–1091

[45] Lafontan M, Barbe P, Galitzky J et al. Adrenergic regulation of adipocyte metabolism. Hum Reprod 1997; 12: (Suppl 1): 6–20

[46] Engelman K, Mueller PS, Sjoerdsma A. Elevated Plasma Free Fatty Acid Concentrations in Patients with Pheochromocytoma. Changes with Therapy and Correlations with the Basal Metabolic Rate. N Engl J Med 1964; 270: 865–870

[47] Krentz AJ, Hale PJ, Horrocks PM et al. Metabolic effects of pharmacological adrenergic blockade in phaeochromocytoma. Clin Endocrinol (Oxf) 1991; 34: 139–145

[48] Jocken JW, Blaak EE. Catecholamine-induced lipolysis in adipose tissue and skeletal muscle in obesity. Physiol Behav 2008; 94: 219–230

[49] Winocour PH, Masud T, Clark F et al. Lipid and lipoprotein metabolism in familial combined hyperlipidaemia during treatment of sporadic phaeochromocytoma: A case study. Postgrad Med J 1992; 68: 371–375

[50] Okamura T, Nakajima Y, Satoh T et al. Changes in visceral and subcutaneous fat mass in patients with pheochromocytoma. Metabolism 2015; 64: 706–712

[51] Pedersen SB, Bak JF, Holck P et al. Epinephrine stimulates human muscle lipoprotein lipase activity in vivo. Metabolism 1999; 48: 461–464

[52] Bartelt A, John C, Schaltenberg N et al. Thermogenic adipocytes promote HDL turnover and reverse cholesterol transport. Nat Commun 2017; 8: 15010 doi:10.1038/ncomms15010

[53] Wang QD, Zhang M, Ning G et al. Brown Adipose Tissue in Humans Is Activated by Elevated Plasma Catecholamines Levels and Is Inversely Related to Central Obesity. Plos One 2011; 6: doi:10.1371/journal.pone.0021006

[54] An Y, Reimann M, Masjkur J et al. Adrenomedullary function, obesity and permissive influences of catecholamines on body mass in patients with chromaffin cell tumours. Int J Obes (Lond) 2018, doi:10.1038/s41366-018-0054-9

[55] Bahler L, Molenaars RJ, Verberne HJ et al. Role of the autonomic nervous system in activation of human brown adipose tissue: A review of the literature. Diabetes Metab 2015; 41: 437–445

[56] Rona G. Changes in Adipose Tissue Accompanying Pheochromocytoma. Can Med Assoc J 1964; 91: 303–305

[57] Hadi M, Chen CC, Whatley M et al. Brown fat imaging with (18)F-6-fluorodopamine PET/CT, (18)F-FDG PET/CT, and (123)I-MIBG SPECT: a study of patients being evaluated for pheochromocytoma. J Nucl Med 2007; 48: 1077–1083

[58] Yeung HW, Grewal RK, Gonen M et al. Patterns of (18)F-FDG uptake in adipose tissue and muscle: a potential source of false-positives for PET. J Nucl Med 2003; 44: 1789–1796

[59] Paulus A, Lichtenbelt WV, Mottaghy FM et al. Brown adipose tissue and lipid metabolism imaging. Methods 2017; 130: 105–113

[60] Puar T, van Berkel A, Gotthardt M et al. Genotype-Dependent Brown Adipose Tissue Activation in Patients With Pheochromocytoma and Paraganglioma. J Clin Endocrinol Metab 2016; 101: 224–232

[61] Betz MJ, Slawik M, Lidell ME et al. Presence of brown adipocytes in retroperitoneal fat from patients with benign adrenal tumors: Relationship with outdoor temperature. J Clin Endocrinol Metab 2013; 98: 4097–4104

[62] Graham S, Hammond-Jones D, Gamie Z et al. The effect of beta-blockers on bone metabolism as potential drugs under investigation for osteoporosis and fracture healing. Expert Opin Investig Drugs 2008; 17: 1281–1299

[63] Veldhuis-Vlug AG, El Mahdiui M, Endert E et al. Bone resorption is increased in pheochromocytoma patients and normalizes following adrenalectomy. J Clin Endocrinol Metab 2012; 97: E2093–E2097

[64] Kim BJ, Kwak MK, Ahn SH et al. Lower Bone Mass and Higher Bone Resorption in Pheochromocytoma: Importance of Sympathetic Activity on Human Bone. J Clin Endocrinol Metab 2017; 102: 2711–2718

[65] Zelinka T, Petrak O, Turkova H et al. High incidence of cardiovascular complications in pheochromocytoma. Hormone and Metabolic Research 2012; 44: 379–384

[66] Stolk RF, Bakx C, Mulder J et al. Is the excess cardiovascular morbidity in pheochromocytoma related to blood pressure or to catecholamines? J Clin Endocr Metab 2013; 98: 1100–1106

[67] Ratge D, Wisser H. Alpha- and beta-adrenergic receptor activity in circulating blood cells of patients with phaeochromocytoma: Effects of adrenalectomy. Acta Endocrinol (Copenh) 1986; 111: 80–88

[68] Valet P, Damase-Michel C, Chamontin B et al. Platelet alpha 2- and leucocyte beta 2-adrenoceptors in phaeochromocytoma: effect of tumour removal. Eur J Clin Invest 1988; 18: 481–485