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Metabolic parameters in patients with prolactinomas: a case-control study

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Anna Sophia Posawetz

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unter der Anleitung von

Priv.-Doz. Dr.med.univ. PhD. Verena Theiler-Schwetz

Univ.-Prof. Dr.med.univ. Barbara Obermayer-Pietsch

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Graz, am 24.07.20 *Anna Sophia Posawetz eh.*

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Zusammenfassung

Einleitung: Das Prolaktinom ist ein gutartiger Tumor der Hypophyse, der zu erhöhten Prolaktinwerten im Blut führt. Am häufigsten findet man ihn bei Frauen in der zweiten bis fünften Lebensdekade. Die klassischen Symptome nebst Galaktorrhoe werden durch Hypogonadismus (Amenorrhoe, Infertilität, Libido- und Potenzverlust, etc.) oder Masseneffekte ausgelöst. Als first line Therapie wird Cabergolin, ein Dopamin-Rezeptor-Agonist verabreicht. Neben Hyperprolaktinämie und Hypogonadismus wurden bei betroffenen Patientinnen und Patienten auch abnorme metabolische Parameter beobachtet. Diese verbessern sich im Laufe einer Therapie mit Dopamin-Agonisten. Die Studienlage ist jedoch noch spärlich und inkonklusiv. Das Ziel dieser Studie ist, Parameter des Lipid- und Glukosestoffwechsels von unbehandelten Patientinnen und Patienten mit Prolaktinom mit einer Kontrollgruppe zu vergleichen und zu beobachten, ob eine Behandlung mit Cabergolin zu einer Verbesserung der Parameter des Lipid- und Glukosestoffwechsels führt.

Methoden: In diese Fall-Kontroll-Studie wurden 21 Prolaktinom-Patienten und 30 gesunde Kontrollen eingeschlossen. Sie wurden zwischen 2014 und 2019 in der Ambulanz der Klinischen Abteilung für Endokrinologie und Diabetologie der Universitätsklinik für Innere Medizin in Graz rekrutiert. Bei der Erstdiagnose und nach Behandlungsbeginn wurden der Body Mass Index (BMI) sowie Parameter des Lipid- und Glukosestoffwechsels (Low-density lipoprotein, LDL, High-density lipoprotein, HDL, und Gesamtcholesterin, Triglyzeride, glykiertes Hämoglobin HbA1c, Nüchternglukose) erhoben. Weiters wurden auch Hypophysenhormonwerte und die Knochendichte untersucht.

Ergebnisse: Das LDL Cholesterin war mit 130 mg/dl (107 – 147,5) bei unbehandelten Prolaktinom-Patientinnen und Patienten signifikant erhöht verglichen mit 94,5 mg/dl (80 – 127,5) in der Kontrollgruppe (p=0,030). Nach einer Korrektur und Anpassung der Ergebnisse ans Körpergewicht, waren keine weiteren Lipidparameter signifikant verändert. Überdies konnte keine Abnahme der Knochendichte festgestellt werden. Nach Therapiebeginn zeigte sich eine signifikante Reduktion des mittleren Gesamtcholesterins von initial 214,50 mg/dl (±38,32) auf 196,89 mg/dl (±40,62). Die LDL Cholesterin Werte sanken signifikant von 135,72 mg/dl (±35,65) auf 119,56 mg/dl (±35,61) nach der Behandlung mit

Cabergolin (weicht vom initial beschriebenen LDL-Wert ab, da im Follow-up ein Patient ausgeschlossen werden musste). Weiters wurde bei Männern ein signifikanter Anstieg des Gesamttestosterons von 1,28 ng/ml (±0,63) auf 2,44 ng/ml (±1,03) ($p<0,001$) und des freien Testosterons von 6,09 ng/ml (±2,73) auf 9,64 ng/ml (±4,21) ($p=0,006$) festgestellt.

Conclusio: Zusammenfassend konnte ein Unterschied zwischen neudiagnostizierten Prolaktinom-Patientinnen und -Patienten und Kontrollen im LDL Cholesterin, jedoch nicht im Glukose-Stoffwechsel und in der Knochendichte gefunden werden. Nach einem Median von 14 Wochen Behandlung mit Cabergolin, verbesserten sich die LDL Cholesterin- und die Gesamtcholesterin-Werte signifikant, das freie und das Gesamttestosteron lagen wieder im Normalbereich. Die Fall-Kontroll-Studie erlaubt keinen Rückschluss auf Kausalität dieser Beobachtungen. Eine adäquate Kontrolle der Hyperprolaktinämie sollte angestrebt werden um das metabolische Profil betroffener Patientinnen und Patienten zu verbessern.

Schlüsselbegriffe: Prolaktinom, Hyperprolaktinämie, metabolische Parameter, Lipid Metabolismus

Abstract

Introduction: Prolactinomas are benign tumours of the pituitary gland causing hyperprolactinaemia. They occur most often in women between the second and fifth decade. Presenting symptoms are mostly due to hypogonadism or mass effect. The first line therapy is treatment with cabergoline, a dopamine agonist, inhibiting the anterior pituitary function. Only in resistant prolactinomas surgery or radiotherapy should be carried out. Other than symptoms associated with hyperprolactinemia or hypogonadism, an adverse metabolic profile has been described in prolactinoma patients, seemingly improving during cabergoline therapy. The available studies are, however, inconclusive. The aim of this study is to compare lipid and glucose parameters in treatment-naïve prolactinoma patients to healthy controls and to examine whether an improvement in these parameters can be observed after dopamine agonist therapy.

Methods: In this case control study 21 patients with micro- and macroprolactinomas and 30 healthy controls were included. They were recruited between 2014 and 2019 at the outpatient clinic of the Division of Endocrinology and Diabetology, Department of Internal Medicine, Medical University of Graz, Austria. At baseline and at follow-up metabolic parameters including low density lipoprotein LDL, high density lipoprotein HDL, total cholesterol, triglycerides, glycated haemoglobin HbA1c and fasting glucose as well as the BMI were collected. Additionally, pituitary hormone levels and bone mineral density were investigated.

Results: The LDL cholesterol was significantly higher in untreated prolactinoma patients with 130 mg/dl (107 – 147,5) compared to 94,5 mg/dl (80 – 127,5) in controls (p=0,030). After adjustment for bodyweight, none of the other metabolic parameters showed a significant difference. Furthermore, no difference in bone mineral density could be found. At follow-up, total cholesterol decreased significantly from 214,50 mg/dl (±38,32) to 196,89 mg/dl (±40,62). There was also a significant decrease in LDL cholesterol levels from 135,72 mg/dl (±35,65) initially to 119,56 mg/dl (±35,61) after treatment with cabergoline (different to initially reported LDL, due to the fact that one patient had to be excluded for follow-up analysis). Furthermore, a significant increase in total testosterone from 1,28 ng/ml (±0,63) to 2,44 ng/ml (±1,03) (p<0,001) and free testosterone from 6,09 ng/ml (±2,73) to 9,64 ng/ml (±4,21) (p=0,006) were found.

Conclusion: In conclusion, a difference between untreated prolactinoma patients and controls in LDL cholesterol, however not in glucose metabolism and bone mineral density could be found. After a median of 14 weeks, LDL cholesterol and total cholesterol had significantly improved. Free and total testosterone were restored to normal range. Conclusions on causality cannot be drawn from our data. However, our findings highlight the necessity to monitor metabolic parameters in patients with prolactinoma.

Key words: prolactinoma, hyperprolactinaemia, metabolic parameters, lipid metabolism

Glossary and abbreviations

ACTH	adrenocorticotropic hormone
BMD	bone mineral density
BMI	body mass index
CIMT	carotid intima media thickness
CT	computer tomography
DXA	dual energy x-ray absorptiometry
FSH	follicle-stimulating hormone
fT3	free triiodothyronine
fT4	free thyroxine
GH	growth homone
GnRH	gonadotropin-releasing hormone
Hb	haemoglobin
HbA1c	glycated haemoglobin
HDL	high density lipoprotein
HGH-axis	human-growth-hormone-axis
HPA-axis	hypothalamic-pituitary-adrenal-axis
LDL	low density lipoprotein
LH	luteinizing hormone
LPL	lipoprotein lipase
MEN-1	multiple endocrine neoplasia Type 1
MRI	magnetic resonance imaging
NFA	non-functioning pituitary macroadenomas
PRL	prolactin
RR	riva rocci, blood pressure

TG	triglycerides
TRH	thyrotropin-releasing hormone
TSH	thyroid-stimulating hormone
VLDL	very low density lipoprotein

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1. Introduction

1.1 Prolactinoma

1.1.1 Definition, Epidemiology

Prolactinomas, accounting for 45% of all pituitary tumours, are typically benign. These secretory adenomas develop from lactotroph cells and cause hyperprolactinaemia in affected patients (1,2).

Prolactinomas occur more often in female patients, especially in young adults. The peak incidence is between the second and fifth decade, where also the gender gap is the largest, with a female to male ratio peaking at 14,5:1. The prevalence is about 100 per million inhabitants, although recent data suggest it might be about four times higher (3,4).

1.1.2 Aetiology

The question of aetiology has not been fully answered. There are several counterarguments against the hypothesis, that prolactinomas occur due to a decrease in dopamine inhibition. Based on the observation that nearly all prolactinomas are monoclonal, the mutation hypothesis suggests that one cell is transformed by genetic alterations and subsequently proliferates abnormally, thereby accumulating more mutations, possibly leading to a malfunction of the dopamine receptor (5). Furthermore, 22% of patients with a multiple endocrine neoplasia I, consisting of parathyroid adenomas, enteropancreatic tumours and anterior pituitary tumours, present with a prolactinoma. The cause of MEN-1 is an autosomal dominant disorder located on chromosome 11 (3,6).

1.1.3 Classification

Prolactinomas are classified according to their diameter. Microadenomas are less than 1 cm and macroprolactinomas over or equal to 1 cm in their largest diameter. Usually, the levels of prolactin parallel tumor size. Levels around 100-150 µg/l can be found in microprolactinomas and levels over 250 µg/l in macroprolactinomas (7). Typically, more microadenomas are found in female and macroprolactinomas in male patients (8). Giant prolactinomas with a diameter ≥ 4cm are rare (1-5% of all prolactinomas). They are histologically and clinically similar to macroprolactinomas with prolactin levels over 1000 µg/l and might show aggressive and invasive behaviour. They occur 9 times more often in men than in women. Their response to

medical treatment is good, however sometimes surgery and radiotherapy are needed (9).

Pituitary tumours are typically adenomas, although about 140 carcinomas have been described in the literature. It is assumed that they develop from adenomas and transform slowly. A therapy-resistant invasive macroprolactinoma should raise suspicion for malignancy. Symptoms due to mass effects are common. The discovery of metastases ensures the diagnosis. They are typically in the central nervous system or arachnoidal tissue. Mostly, malignant prolactinomas require additional radiotherapy, although after the onset of metastases the overall survival only ranges around one year (10,11).

1.1.4 Symptoms

Most symptoms prolactinoma patients present with are caused by the elevated levels of prolactin. One of them is galactorrhoea. It is defined as a bilateral milky secretion of the mammary gland that occurs outside of pregnancy. It can be classified into three categories: degree one is one drop, degree two are several drops and degree three is spontaneous secretion (12). Furthermore, prolactin inhibits the secretion of GnRH, which is defined as a secondary hypogonadotropic hypogonadism (13). This leads to a decreased secretion of LH and FSH. FSH is needed to aromatize androgens to oestrogens in women. Moreover, hyperprolactinaemia leads to low progesterone levels. In the environment established by those effects, it is not possible for the follicle to undergo a normal development in the ovary. Oligorrhoea, amenorrhoea and infertility are the consequences. In mammals, this state is desired throughout lactation. Hyperprolactinaemia is responsible for 20% of cases of secondary amenorrhoea (12,14). The abnormal LH pulsatility is restored completely when the prolactin levels normalize (15). In men, the decreased amount of LH leads to low levels of testosterone and the reduction of FSH causes problems in spermatogenesis. 16% of men present with erectile dysfunction and 11% with oligospermia (16). Further symptoms are decreased libido and impaired sperm motility and quality. The results of long-term hypogonadism are reduced body hair and muscle mass, gynaecomastia and galactorrhoea, leading to an impaired quality of life as well as osteoporosis (13,16,17).

Headache is a symptom of prolactinomas, that is typically ipsilateral to the tumour and often presents as a trigeminal cephalalgia. However other headache phenotypes are also possible. There is a correlation between the intensity of the pain and the size of the tumour, indicating a mechanical cause of the headache. It is assumed that due to mass effects pain-sensitive structures are compressed (18).

Mild anaemia (<11g/dl) has been found in a third of men with prolactinomas. It is linked to macroprolactinomas. It has been reported that low testosterone levels lead to a deficiency in haematopoiesis, due to lower erythropoietin production. The anaemia improves when prolactin and testosterone levels normalize. Furthermore, it has been observed that anaemia is more often found in men presenting with prolactinoma-induced pituitary dysfunction, such as hypothyroidism and central adrenal insufficiency (19).

Prolactinomas are associated with lower bone mass. About a third of all prolactinoma patients show radiological vertebral fractures, which is significantly more than the normal population. These patients also have a lower BMD T-score and a longer disease duration compared to prolactinoma patients without fractures. Patients under treatment have a lower risk for fractures. For men, the hormonal status does not influence the prevalence significantly. For women, it could be proven that prolactinoma patients of higher age, after the menopause, and those with strongly elevated prolactin levels show a higher prevalence of radiological fractures (20,21).

Prolactinomas also occur in children, the youngest patient reported was two years old. Pubertal delay can be observed in both boys and girls. Boys suffer more often from neuro-ophthalmologic symptoms, such as headaches, and girls from hormonal dysfunctions such as amenorrhea. Gynaecomastia is normal in puberty in up to 60% of healthy adolescents, therefore this symptom is not always attributable to hyperprolactinaemia (22).

Gender differences in symptoms have been reported. Women more frequently suffer from weight gain and galactorrhea, whereas men often show higher serum levels of prolactin and a larger tumour size. It is not proven yet whether there is a difference between the pathogenesis of prolactinoma in men compared to women. Possibly the discreet symptoms in men at the beginning lead to a delayed diagnosis,

compared to women who suffer from amenorrhea and infertility during reproductive age (1,8).

1.1.5 Differential diagnoses

Physiological causes of hyperprolactinemia include pregnancy, lactation, breast stimulation, stress, coitus and exercise (23).

Apart from prolactinomas, there are also mixed secreting pituitary tumours, the most common of them growth-hormone and prolactin co-secreting adenomas. In a study of 1166 patients with a pituitary adenomas undergoing surgery, 2,2% had a mixed GH/PRL adenoma (24). There are two different types: either mixed adenomas with PRL producing as well as GH producing cells or mammosomatotroph adenomas, containing cells that produce both hormones (25,26). There has also been a case report of a patient initially presenting with a prolactinoma which later transformed into a mixed PRL/GH secreting tumour with monomorphous cells, producing both hormones (27). The simultaneous hypersecretion of prolactin and ACTH in an adenoma has also been observed (28), as well as a case of a mixed PRL, GH and ACTH producing pituitary macro-adenoma (29).

Hyperprolactinaemia has often been found in patients suffering from liver cirrhosis. Recent studies show, however, that, in contrary to a former belief, liver cirrhosis does not cause elevated prolactin levels. They rather result from associated co-morbidities or drug-intake (30). A similar observation could be made in patients with renal insufficiency, in which case hyperprolactinaemia can often be explained by medication affecting prolactin secretion in combination with a decreased renal clearance of prolactin. Only 18,3% of renal patients without drug-intake present with mild hyperprolactinaemia below 100 µg/l (31).

Thyrotropin releasing hormone (TRH) has been proven to stimulate not only thyroid stimulating hormone (TSH) but also prolactin. Primary hypothyroidism, resulting in compensatory high levels of TRH and TSH, thus results in elevated prolactin levels in 39% of hypothyroid patients (32).

Furthermore, the compression of the pituitary stalk leads to disruption of the dopamine transport to the pituitary, resulting in hyperprolactinaemia, because dopamine is the main inhibiting hormone of prolactin. This is called the stalk effect and can be caused by non-secretory tumours of the pituitary, cysts, or other sellar

lesions. Transsphenoidal surgery and removal of the lesion can normalize serum prolactin levels (33,34).

Another diagnostic pitfall is macroprolactinaemia. The biologically active monomeric form of prolactin weighs 23kDa. Macroprolactin has a molecular weight of over 100 kDa and very low receptor affinity and is therefore inactive and clinically irrelevant. However, it interferes with most immunoassays, leading to the misdiagnosis of hyperprolactinaemia. This should be kept in mind in cases of elevated prolactin, especially when patients do not present with typical symptoms of hyperprolactinaemia and the MRI is inconspicuous (35). Of all blood samples showing hyperprolactinaemia in a routine screening, up to 26% have increased concentrations of macroprolactin (36). In order to distinguish between the two molecules, polyethylene glycol can be added to the serum (37).

A possible cause for hyperprolactinaemia are adverse reactions of anti-dopaminergic therapeutic drugs. A French study with a duration of 15 years investigated new onset hyperprolactinaemia after initiation of medical treatment according to drug classes. Nearly a third of all cases of hyperprolactinaemia were caused by neuroleptics and a little less by neuroleptic-like drugs. Antidepressants were the third biggest cause and a small amount was due to H2-receptor antagonists (38). The increase of prolactin during treatment with neuroleptics is well proven (39). Two drug classes that are less well known to cause hyperprolactinemia are prokinetics, such as domperidone (40) as well as antihypertensives such as methyldopa (41).

1.1.6 Diagnosis

In order to establish the diagnosis of a prolactinoma, elevated serum prolactin levels have to be proven. The sample should be obtained without venepuncture stress. The levels are considered elevated if they are above 25µg/l. Differential diagnoses should be ruled out (42). In order to do so, it is advised to conduct an exact anamnesis to explore the symptoms and carry out a pregnancy test for women in child-bearing age. The use of medication, known to be causing hyperprolactinemia, has to be excluded (43). If possible, those drugs should be discontinued for three days and the levels of prolactin remeasured afterwards (42). Furthermore, to rule out renal failure and primary hypothyroidism, it is advised to measure serum creatinine and TSH. During the physical examination particular attention should be

payed to signs of hypogonadism, hypothyroidism, renal failure and visual field defects (43). A pituitary MRI helps to prove the presence of a macro- or microadenoma and to exclude other sellar or parasellar lesions (44).

Furthermore, the levels of macroprolactin have to be measured, especially in asymptomatic patients, in order to exclude the diagnostic pitfall of macroprolactinaemia. Moreover, if the serum levels do not mirror tumour size, prolactin measurement should be repeated after dilution of the sample to rule out falsely low prolactin levels. This so-called hook effect occurs when the second antibody of the immunoassay does not bind to the same prolactin molecule as the first antibody, but instead to the excess prolactin in the serum (42).

1.1.7 Therapy

The aim of prolactinoma treatment is to reduce the tumor size and to normalize serum prolactin levels. The symptoms caused by these two effects represent the indications for therapy. They have been listed by Gillam et al. (45).

Mass effects	Effects of hyperprolactinemia	Relative indications
• Hypopituitarism • Visual field defects due to pressure on the optic chiasm • Cranial nerve deficits • Headaches	• Hypogonadism • Amenorrhea or oligomenorrhea • Infertility • Impotence • Osteoporosis or osteopenia	• Bothersome hirsutism • Bothersome galactorrhea

Table 1 Indications for therapy (5)

Usually, macroprolactinomas meet these criteria and furthermore tend to grow, resulting in the requirement of therapy. As for asymptomatic patients, there is no absolute need for treatment. It has been proven that microadenomas rarely (7%) grow. Therefore, only regular follow-up examinations are necessary, as tumour enlargement is usually accompanied by an elevation of serum prolactin levels (45).

1.1.7.1 Pharmacological therapy

Dopamine inhibits anterior pituitary function via its receptor subtype D2 (46). Therefore, dopamine agonists are recommended as a first line treatment in patients

with prolactinoma by the Endocrine Society. The preferred medication is cabergoline (42).

When comparing cabergoline and bromocriptine concerning their potential to restore normoprolactinemia and treat amenorrhea, cabergoline not only achieves better results but also shows a lower frequency of adverse events (47). Cabergoline restores serum levels in 92% of microadenomas and 77% of macroadenomas. In 67% of the patients, tumour size could also be reduced. Moreover, in 70% of the cases of bromocriptine intolerance or resistance, patients responded to cabergoline (48).

The initial dose of cabergoline is 0,25 to 0,5 mg per week and is being increased to a weekly maintenance dose of 0,25 to 3,0 mg (2). The most common side effect of cabergoline is nausea and might be accompanied by vomiting (35%). Further possible adverse events are headaches, dizziness and vertigo. On seldom occasions, also diarrhoea, somnolence, paraesthesia and dyspnoea can occur. However, less than 3% of patients discontinue their therapy because of side effects (49).

The withdrawal of therapy was investigated in patients where normoprolactinaemia could be restored, the tumour had shrunk significantly and did not invade critical areas. After a period of two to five years after discontinuation of treatment, no patient showed an enlargement in tumour mass. In 31%-36% of patients hyperprolactinaemia reoccured, more frequently in patients with macroadenoma. However, the serum levels were significantly lower than at baseline (50). Therefore, after a successful treatment with dopamine agonists for at least two years, it is recommended to attempt the reduction or withdrawal of the medication under observation and with follow-up examinations (42).

1.1.7.2 Surgery

If a patient shows no significant improvement after the standard dose of a dopamine agonist, it is advised to treat these resistant prolactinomas with the highest tolerable dose, before attempting surgery. If the surgery needs to be carried out, a transsphenoidal approach is recommended (42).

The most common complications of surgery include infarction, haemorrhage, fluid and electrolyte abnormalities, hypopituitarism, thrombotic disorders such as deep

vein thrombosis, transient diabetes insipidus and epistaxis. Hospitals with a larger caseload and high-volume surgeons achieve better outcomes with less complications and a shorter postoperative stay (51,52).

An American study shows that 67% of patients intolerant of medication and 36% of patients with a dopamine agonist resistance restored normal prolactin levels after surgery. The remaining patients needed additional medication (53). Analyzing prolactin levels separately in terms of tumor size, they are evidently better for microprolactinomas (85% remission) compared to macroprolactinomas (31% remisson) (54). Concerning long-term outcome, a third of the patients with initial normoprolactinaemia after surgery showed recurrent hyperprolatinaemia years later (55). Likewise, microprolactinomas show better results with a temporary relapse of 13,7% and a permanent one in only 4,5% of patients between 15 and 21 years after surgery (56).

1.1.7.3 Radiotherapy

If surgery shows no success or patients suffer from an aggressive malignant or invasive prolactinoma, radiation therapy is recommended (42). Further indications are resistance or intolerance of dopamine agonists with the aim to decrease dose or duration of medical therapy and the tendency of the tumour to grow (43,57).

The general risks of cranial radiotherapy such as cerebrovascular accidents, soft tissue reactions, neurological dysfunctions or the long-term induction of intracranial malignomas exist, as well as the specific complication of radiation-induced hypopituitarism (45).

After a conventional fractional radiotherapy, only 34% of patients restore normal prolactin levels. However, patients undergoing radiotherapy have the most resistant prolactinomas with the aim of radiotherapy being a decrease in tumour size or the control of mass effects (45). The second approach is a stereotactic radiosurgery. Normoprolactinemia could be restored in 80% of patients after irradiation with a Leksell gamma knife. However, a major part of these patients needed additional dopamine agonist therapy. 97% of the adenomas did not grow further or even decreased in size (57).

1.2 Metabolism

The following chapter will specify relevant parameters of adverse metabolic profiles and associations to prolactinomas.

1.2.1 The relevance of an adverse metabolic profile

The metabolic syndrome is a combination of major and emerging risk factors, leading to atherosclerotic cardiovascular disease (58). The National Cholesterol Education Program Expert Panel of the United States suggested a table for the clinical identification of the metabolic syndrome, that is listed below. At least three of these criteria have to be fulfilled (59).

Risk Factor	**Defining Level**
Abdominal Obesity *Men* *Women*	Waist Circumference >102 cm >88 cm
Triglycerides	≥150 mg/dL
HDL cholesterol *Men* *Women*	 <40 mg/dL <50 mg/dL
Blood pressure	≥130/≥85 mmHg
Fasting glucose	≥110 mg/dL

Table 2 Definition of the metabolic syndrome

People with the metabolic syndrome have a 2-fold increased risk for atherosclerotic cardiovascular disease, a 5-fold increased risk for type 2 diabetes and a 2-3-fold higher risk for coronary heart disease (58).

Concerning the first risk factor, obesity, waist circumference has been chosen as a defining level, because it correlates better with metabolic risk than body mass index does (59). The BMI is defined by the Word Health Organisation as the weight in kilograms divided by the square of the height in metres (kg/m^2). A BMI over 25 is considered overweight and over 30 obese. It does, however, not distinguish between weight due to elevated muscle mass or fat (60). In contrast, waist

circumference focuses on abdominal obesity. It is measured between the bottom of the rib cage and the iliac crest. Whether excess fat is likely to lead to complications, depends on where it is. Visceral adipose tissue is a larger threat compared to subcutaneous fat. Through imaging techniques such as magnetic resonance imaging (MRI) and computer tomography (CT) it could be proven that waist circumference correlates best with high visceral fat (61). An elevated waist to hip ratio (>1.0 in men and >0.85 in women) indicates relative accumulation of abdominal fat. However, it can be misleading, especially regarding the progress over time, because the ratio can remain unchanged, even if the waist circumference has increased. Therefore, waist circumference alone is recommended as a measurement (60,61).

Moving on to the second criteria, triglycerides, they are the storage form of fatty acids in the adipose tissue, the latter accounting for 12% of the body weight. They are ingested with food or can be produced by the liver. In the blood system, they are transported as lipoproteins, because as lipophilic substances they cannot be dissolved in blood (62). Elevated triglyceride levels are most often found in people with the metabolic syndrome, but can also be caused by genetic disorders. They are an independent risk factor for coronary heart disease and therefore are considered atherogenic (59).

The third criterion, HDL, relates to lipoproteins. They transport triglycerides, phospholipids, cholesterol, cholesterol ester, and vitamins. The lipoproteins are classified according to diameter, the largest being chylomicrons, which are the transport form in the lymph system. They are followed by very low density lipoproteins VLDL, low density lipoproteins LDL and high density lipoproteins HDL being the smallest. The purpose of the first three is to provide the peripheral tissue with triglycerides and cholesterol. Cholesterol is used to build cell membranes or to synthesize steroid hormones and glycosides. They then shrink in size and are converted to the next denser form. The problem considering atherosclerosis is excess LDL, which accumulates in the intima of the blood vessels, where it oxidizes and is absorbed by macrophages, leading to the generation of atherosclerotic plaques. HDL, however, is responsible for reverse cholesterol transport, bringing excess cholesterol from peripheral tissues back to the liver, where it can be

eliminated through the production of bile acids. Therefore, high HDL blood levels are considered atheroprotective (62).

As for blood pressure, the systolic pressure is the best predictor for stroke and coronary heart disease, whereas the difference between systolic and diastolic pressure predicts heart failure and total mortality (63).

The last criterion, elevated fasting glucose, may indicate diabetes mellitus. This parameter is measured after 8 hours without caloric intake. For a reliable diagnosis of diabetes mellitus, further tests such as glycated haemoglobin (HbA1c) or oral glucose tolerance test are necessary. Type 2 diabetes accounts for 90-95% of all diabetes forms; most patients are obese (64). The disease is caused by insulin resistance, a secretory deficiency of the pancreatic β-cells, apoptosis of β-cells and thereby a decreased insulin secretion. The main symptom hyperglycaemia causes micro- and macroangiopathy (63). Not only is diabetes frequently associated with other atherogenic diseases, but it is also an independent risk factor. 55% of diabetic patients die because of a heart attack. Myocardial ischaemia is mostly painless due to diabetic neuropathy. Also cardiac insufficiency is much more frequent in diabetic patients (63,65).

1.2.2 Prolactinoma and metabolism

Prolactinoma patients often present with an adverse metabolic profile. Several studies undermining this thesis and presenting the current state of research will be outlined below.

Starting with the topic of obesity, a retrospective study was conducted in Israel, comparing prolactinoma patients with patients with non-functioning pituitary macroadenomas (NFA). Prolactinoma patients had significantly higher weight and often presented with recent weight gain. During treatment, 70% of the prolactinoma patients lost weight (mean change -8,3 kg), whereas this effect could not be observed in NFA patients. When analysing only male patients whose prolactin levels had normalized during therapy, a total of 90% also showed weight loss (66). Furthermore, another study approached the risk factor obesity by comparing body fat in men with prolactinoma to healthy controls by using a whole body dual energy x-ray absorptiometry (DXA). Newly diagnosed patients had higher total body fat compared to patients under treatment and to controls. The fat percentage showed

a positive correlation with prolactin and a negative correlation with androgen levels (67). Another study analysing non-obese premenopausal women with prolactinoma also confirmed the positive association between prolactin levels and total body fat. The body fat in patients with normalized prolactin levels due to dopamine agonist therapy was similar to healthy controls (68). However, in a cohort of 22 prolactinoma patients, there was no significant decrease in BMI after a six-month treatment (69). In order to find an explanation, several studies in rats were conducted. After elevated prolactin levels had been induced, rats tended to increase their food intake and gain body weight. Treating them with dopamine agonists lead to the opposite effect. The findings indicate, that prolactin might influence thalamic systems that regulate appetite (70).

A study focusing of the prevalence of the metabolic syndrome, showed that the syndrome was found significantly more often in patients with prolactin levels above the median compared to patients with lower levels. After a 60 month treatment, the prevalence sunk from 28% to 5% of patients (71). Ciresi et al. compared metabolic parameters of prolactinoma patients and showed a significant improvement in laboratory parameters and waist circumference after a 12-month treatment with cabergoline, BMI did not change significantly, however. The authors suggested that the improvement of metabolic parameters might be due to the effect of dopamine agonist treatment per se, rather than restoration of normoprolactinaemia. Undermining this hypothesis is the fact that the higher the doses of cabergoline were, the better the laboratory findings (72). In various studies comparing the metabolic parameters of prolactinoma patients before and after treatment with dopamine agonists for periods of 6, 12 or 60 months, a decrease in fasting glucose (69,71), fasting insulin (71,72), HbA1c (72) and the HOMA-IR (homeostasis model assessment insulin resistance), a parameter of insulin resistance, could be shown (69,71–73). Regarding lipid parameters, total cholesterol (71,73,74), triglyceride levels (69,71,72) and LDL levels (69,71–74) decreased significantly, whereas HDL levels increased significantly (71–73). A similar study with a shorter observational period of 12 weeks of treatment only showed a reduction of insulin concerning metabolic parameters. However, inflammatory markers decreased during the short-term-therapy (75).

Addressing the topic of insulin resistance, a possible mechanism could be that prolactin has been found to stimulate insulin and suppress adiponectin, a hormone that is produced by adipocytes, improving insulin sensitivity in the peripheral tissue (70). The question why elevated prolactin levels lead to an adverse metabolic profile also has not been fully answered yet. One of the theories focuses on how prolactin influences adipose tissue metabolism. The lipoprotein lipase is an enzyme that splits triglycerides from lipoproteins in order to make free fatty acids available for different tissues (76). During lactation, prolactin physiologically reduces LPL activity in the adipose tissue and enhances it in the mammary gland to produce breast milk. Four different isoforms of prolactin receptors were found in the subcutaneous abdominal tissue. Elevated prolactin levels have been shown to reduce the LPL activity in this area in a direct fashion (77). An imbalance in LPL activity leads to difficulties in insulin action, body weight and body composition (76).

Furthermore, concerning the topic of cardiovascular health, a parameter investigated in many studies is the carotid intima media thickness (CIMT). This marker is measured through ultrasound. It shows signs of preclinical atherosclerosis and helps to predict cardiovascular outcome (78). Jiang et al. found CIMT to be increased in prolactinoma patients, compared to healthy controls. Furthermore, there was a positive correlation with the levels of prolactin (79). Arslan et al. confirmed these results, also finding CIMT to be significantly higher in hyperprolactinaemic patients (78). Inancli et al. studied the development of the CIMT after a 6-month treatment with dopamine agonists. The thickness decreased significantly and independently from serum prolactin levels (73). A possible explanation for this phenomenon lies in the detection of prolactin receptors in atherosclerotic plaques. They are present in the macrophages, where the inflammatory response takes place, enhancing the process of inflammation and thereby leading to atherosclerosis (80).

A recent and extensive retrospective study included over 2000 prolactinoma patients and over 10.000 matching healthy controls. It compared the cardiovascular outcome after a period of observation of 6 years. The incidents that counted as a primary outcome were myocardial infarction, angina pectoris, stroke, transient ischaemic attack and heart failure. While the incidence rate in females was nearly

identical, the adjusted incidence rate ratio in males was 1,94. This implies a nearly doubled risk for cardiovascular incidents in men with prolactinoma (81).

1.3 Research question

The aim of this study is to investigate whether prolactinoma-induced hyperprolactinemia is associated with an adverse metabolic profile. Furthermore, we aim to examine whether these parameters improve after treatment with a dopamine-agonist. The relevance is based on the fact that adverse metabolic parameters are associated with a higher risk for cardiovascular events leading to increased mortality. Therefore, medical treatment of prolactinoma could be relevant even if the patients are free of symptoms.

The main hypotheses are:

- Main hypothesis: Prolactinoma patients prior to treatment have impaired glucose and lipid metabolism as compared to controls.
- In detail: Patients have higher levels of LDL, total cholesterol, triglycerides, HbA1c, fasting glucose, and lower levels of HDL compared to controls.
- Further hypotheses: Untreated prolactinoma patients show lower bone density in comparison to healthy controls.
- Parameters of glucose and lipid metabolism improve after restoration of normoprolactinaemia by dopamine agonist treatment.

This research questions are equally relevant for both men and women.

2. Methods

2.1 Study Design

This thesis was designed as a case-control study. Patients with a newly diagnosed prolactinoma as well as healthy controls were recruited at the outpatient clinic of the Division of Endocrinology and Diabetology, Department of Internal Medicine, Medical University of Graz, Graz, Austria. Metabolic and laboratory parameters were determined in all participants. Moreover, metabolic parametes were reanalyzed at first follow-up after initiation of dopamine agonist treatment.

All patients asked for participation in the study signed an informed consent prior to any study-related procedure. The ethics committee of the Medical University of Graz approved of the study. In an additional amendment, the ethics committee approved of the retrospective use of follow-up data for comparison in prolactinoma patients.

2.2 Recruiting of patients

The process started in 2014 and continued until spring 2019. 27 patients with a newly diagnosed prolactinoma and 30 controls could be recruited at the outpatient clinic of the Division of Endocrinology and Diabetology. They signed a written informed consent prior to any study-related procedures.

2.3 Inclusion and exclusion criteria

Men and women (pre- and postmenopausal) with an untreated prolactinoma were included. The diagnosis was made according to the criteria of the clinical guidelines of the Endocrine Society, namely clinical signs of hyperprolactinaemia, elevated levels of prolactin as well as a tumour in the pituitary gland proven by an MRI scan. The control group consisted of men and women (pre- and postmenopausal), that did not meet any exclusion criteria. Those were the presence of any disease of the pituitary gland, hypo- or hyperthyroidism, coronary heart disease or peripheral or central artery occlusive disease. Moreover, the exclusion criteria relevant for both groups were ongoing oestrogen, gestagen, anti-diabetic or cholesterol-lowering therapy. Furthermore, prolactinoma patients were excluded in case of mixed secreting tumours or hypogonadism due to other reasons to avoid an influence of sex hormones on metabolic parameters.

2.4 Data collection and evaluation

The data necessary for the thesis were acquired from medical records from the primary and follow-up examination, as well as the results from the blood samples on both occasions. In addition, the participants for the study underwent a bone density measurement and their metabolic parameters were examined.

2.5 Study parameters

Anthropometric data included height (cm), bodyweight (kg), waist and hip circumference (cm), blood pressure (mmHg) and heartrate (bpm). Afterwards, BMI (kg/m^2) and waist to hip ratio were calculated.

Patients were asked for clinical symptoms of hyperprolactinaemia including restriction of the visual field, gynecomastia and galactorrhoea. Men were additionally asked for decreased libido and erectile dysfunction and women for amenorrhoea.

Furthermore, the size of the pituitary tumour was determined according to MRI scan. The size was specified as the largest diameter in cm. Adenomas of the size of < 1cm were classified as microprolactinomas and those ≥ 1cm as macroprolactinomas.

Regarding the routine blood samples, the following values were relevant for our analysis: haemoglobin Hb (g/dl), glucose (mg/dl), glycated haemoglobin HbA1c (mmol/mol), cholesterol (mg/dl), high density lipoprotein HDL (mg/dl), low density lipoprotein LDL (mg/dl) and triglycerides (mg/dl). Endocrine parameters included: prolactin (ng/ml), thyroidea stimulating hormone TSH (µU/ml), free thyroxine fT4 (pmol/l), free triiodothyronine fT3 (pmol/l), luteinizing hormone LH (mIE/ml), follicle stimulating hormone FSH (mIE/ml), oestrogen (pg/ml, only female patients), testosterone (ng/ml, only male patients) and free testosterone (ng/ml, only male patients).

During the primary examination and with the help of the obtained laboratory parameters, all patients were analysed in terms of hypogonadism, hypothyroidism, insufficiency of the HGH-axis (= human growth hormone) or of the HPA-axis (= hypothalamic-pituitary-adrenal-axis).

In addition, parameters of osteodensitometry were included in this thesis (i.e. bone mineral density BMD and the T-value of the vertebral column, the femoral neck and the total hip). The T-value expresses the standard deviation above or below the BMD of the young adult mean of the same sex.

2.6 Statistical Analysis

Descriptive statistics were used to describe baseline characteristics. The Shapiro-Wilk Test was used to check for normal distribution. In case of normal distribution, parameters are presented as mean value and standard deviation. They are marked with the superscript number 1. If one or both variables are not normally distributed, they are presented as median and interquartile range. They are indicated by the

superscript number 2. Nominally scaled data are described by means of absolute and relative frequency.

The first part of the study compares newly diagnosed patients to healthy controls. For normally distributed variables an unpaired t-test was used. For the others, the Mann-Whitney-U-Test was used. The second part of the study compares baseline and follow-up values in patients with prolactinoma. The normally distributed variables were analysed using a paired t-test and the others using a Wilcoxon rank-sum test.

When comparing between groups, ANCOVA analysis was performed and adjustments for bodyweight carried out, due to the significant difference in bodyweight between study groups. Concerning the parameters oestrogen, testosterone and free testosterone, men and women were analysed separately. A p-value of 0,05 was considered statistically significant. The programme SPSS 23.0 was used to perform the analysis.

3. Results

3.1 Characterization of patients and controls

3.1.1 Quantitative data

In the present study we included 27 patients with prolactinoma. Six patients were excluded, three due to a screening failure, two due to a statin therapy, one patient due to a previously started cabergoline therapy, so that in total 21 patients remained in our analyses. It must be mentioned that 5 of the patients received a deviating dose of cabergoline of our standard operating procedure due to extremely high or only slightly elevated levels of prolactin. Nevertheless, they were included in the evaluation of the follow-up examination. The control group consisted of 30 patients.

3.1.2 Anthropometric and metabolic parameters

The mean age of the patients was 39,9 (±17,4) years and of the controls 37 (±10,9) years. In the patient cohort there were 7 female (33,3%) and 14 male (66,7%) patients, whereas the control group consisted of 17 female (56,7%) and 13 male (43,3%) patients. There was a significant difference in bodyweight between groups (median weight of patients: 90 kg (69,5 – 99,5) and the median weight of controls: 70 kg (55,5 – 84)). As a result, the BMI differed significantly between groups,

although there was no considerable difference in height. We found no significant difference in mean waist to hip ratio, blood pressure and mean heartrate. All of the above, as well as the p-values, are listed in Table 3.

	Patients	**Controls**	**p-value**
Age[1] (years)	39,9 (±17,4)	37 (±10,9)	0,465
Gender	33,3% f; 66,7%m	56,7% f; 43,3% m	
Bodyweight[2] (kg)	90 (69,5 – 99,5)	70 (55,5 – 84)	**0,019**
Height[1] (cm)	175,4 (±8,6)	173,8 (±9,7)	0,531
BMI[2] (kg/m^2)	27,5 (22,4 – 33,5)	22,9 (21 – 26,6)	**0,020**
Waist to hip ratio[1]	0,89 (± 0,12)	0,86 (±0,06)	0,348
RR syst[1] (mmHg)	129 (±21)	129 (±17)	0,978
RR diast[1] (mmHg)	84 (±15)	84 (±13)	0,893
Heartrate[1] (bpm)	69 (±13)	68 (±11)	0,856

Table 3 Anthropometric and metabolic parameters
1: Mean and standard deviation
2: Median and interquartile range

3.1.3 Prolactinoma specific data

Of the 21 prolactinoma patients, 42,9% were diagnosed with a microadenoma and 57,1% with a macroadenoma. The maximum diameter was used to compare the size of the tumour. The median was 1,1cm (0,73 – 2,28).

19% of the patients had normal pituitary function. 66,7% had partial hypopituitarism with affection of one axis only, 9,5% (n = 2) had partial hypopituitarism with affection of two axes, and 4,8% (n = 1) with affection of three axes. In detail, patients with a single hormonal insufficiency had hypogonadism, those with two affected axes had hypogonadism and GH insufficiency or hypothyroidism. One patient had hypogonadism, hypothyroidism and central adrenal insufficiency. In summary, 81% of the patients suffered from hypogonadism.

9,5% of the patients stated to have had a restriction of their visual field. Also 9,5% of the patients had noticed gynaecomastia. Nearly a quarter of the patients (23,8%) suffered from galactorrhoea. Decreased libido was reported by 38,1% and erectile dysfunction by 33,3% of the patients. Concerning women, 42,9% had secondary amenorrhoea.

3.2 Comparison of endocrine parameters

The following paragraph describes endocrine parameters in patients and controls examined at baseline. The results can be found in detail in Table 4.

As expected, there is a large difference in the levels of prolactin (median of 247,7 ng/ml (105,1 – 722,55) in patients versus 9,6 ng/ml (7,68 – 12,63) in controls). The only value where no significant difference could be measured was TSH. Concerning the thyroid gland however, there were deviations in the fT4 and fT3 status, showing a decrease in thyroid hormones in prolactinoma patients. Nevertheless, they were still in the normal range. When analysing sex hormones, it can be reported that the patients' levels of LH were lower (3,6 mIE/ml (1,75 – 5,09)) than those of healthy controls (6,28 mIE/ml (3,82 – 10,28)). The same applies to FSH levels, which were 3,37 mIE/ml (2,51 – 6,07) in prolactinoma patients and 5,84 mIE/ml (3,66 – 7,87) in controls. Furthermore, comparing the oestrogen levels of the female study participants, those of the patients were significantly lower 63 pg/ml (±47,2) than those of the controls 137,77 pg/ml (±83,86). Moreover, the testosterone levels of the male patients were significantly lower (1,28 ng/ml (±0,63)) than in controls (3,75 ng/ml (±1,40)). The same results were shown for levels of free testosterone. Both free and total testosterone levels in prolactinoma patients were below the normal range.

	Patients	**Controls**	**p-value**
Prolactin[2] (ng/ml)	247,7 (105,1 – 722,55)	9,6 (7,68 – 12,63)	**p<0,001**
TSH[1] (yU/ml)	1,9 (±0,7)	2,0 (±0,8)	0,594
fT4[2] (pmol/l)	13,4 (12,45 – 14,65)	15 (13,75 – 16,26)	**0,023**
fT3[1] (pmol/l)	4,1 (±0,66)	4,88 (±0,7)	**p<0,001**
LH[2] (mIE/ml)	3,6 (1,75 – 5,09)	6,28 (3,82 – 10,28)	**0,001**

FSH[2] (mIE/ml)	3,37 (2,51 – 6,07)	5,84 (3,66 – 7,87)	**0,004**
oestrogen (f) [1] (pg/ml)	63 (±47,2)	137,77 (±83,86)	**0,039**
Testosterone (m)[1] (ng/ml)	1,28 (±0,63)	3,75 (±1,40)	**p<0,001**
Free Testosterone (m)[1] (ng/ml)	5,60 (±2,65)	16,76 (± 4,48)	**p<0,001**

Table 4 Comparison of endocrine parameters
1: Mean and standard deviation
2: Median and interquartile range

3.3 Comparison of metabolic parameters

The main question of this thesis is to investigate whether prolactinoma patients without medical treatment have adverse glucose and lipid parameters compared to healthy controls. The results are presented below.

Concerning haemoglobin values, no significant difference could be found between the study groups. Furthermore, glucose levels did not differ between groups (88 mg/dl (85,5 – 95,5) in prolactinoma patients versus 89 mg/dl (85,5 – 92,75) in controls). The same was true for the HbA1c values (34 mmol/mol (32,25 – 35,75) in prolactinoma patients versus 33 mmol/mol (31 – 34,25) in controls).

However, we found significantly higher levels of cholesterol in prolactinoma patients (214 mg/dl (187 – 228,5)) as compared to healthy controls (185,5 mg/dl (165,5 – 212,75)). Mean HDL cholesterol in patients was significantly lower (55,95 mg/dl (±16,70)) than in controls (68,5 mg/dl (±14,78)). As for LDL cholesterol, prolactinoma patients had significantly higher levels compared to controls (130 mg/dl (107 – 147,5) versus 94,5 mg/dl (80 – 127,5)). Regarding triglycerides, no difference could be found between groups. Detailed results are shown in Table 5.

	Patients	**Controls**	**p-value**
Hb[1] (g/dl)	13,79 (±1,15)	14,25 (±1,36)	0,204
Glucose[2] (mg/dl)	88 (85,5 – 95,5)	89 (85,5 – 92,75)	0,916

HbA1c[2] (mmol/mol)	34 (32,25 – 35,75)	33 (31 – 34,25)	0,083
Cholesterol[2] (mg/dl)	214 (187 – 228,5)	185,5 (165,5 – 212,75)	**0,026**
HDL[1] (mg/dl)	55,95 (±16,70)	68,5 (±14,78)	**0,007**
LDL[2] (mg/dl)	130 (107 – 147,5)	94,5 (80 – 127,5)	**0,002**
TG[2] (mg/dl)	84 (62– 159)	66,5 (53,75 – 101)	0,066

Table 5 Comparison of metabolic blood values
1: Mean and standard deviation
2: Median and interquartile range

As the prolactinoma patients in our study had significantly higher bodyweight, an impact on the aforementioned outcomes had to be ruled out. After adjustment for body weight, we found no significant difference in total cholesterol (p=0,149) and HDL cholesterol (p=0,083) between groups. However, after adjustment for body weight, LDL cholesterol values stayed significantly higher in prolactinoma patients (p=0,030).

3.4 Comparison of bone mineral density (BMD)

In the following paragraph, the results of the bone mineral density measurement will be presented. The relevant parameters for the analysis are in each case BMD and the T-value of the lumbar vertebral column, the femoral neck and the total hip. A T-value below -1,0 is considered osteopenic and a T-value below -2,5 indicates osteoporosis (82). However, no significant difference between patients and controls could be found. Table 6 shows the exact numbers.

	Patients	**Controls**	**p-value**
Vertebral column BMD[1]	1,18 (±0,16)	1,18 (±0,15)	0,837
Vertebral column T-value[1]	-0,32 (±1,37)	0,28 (±1,18)	0,930
Femoral neck BMD[1]	0,98 (±0,11)	0,99 (±0,15)	0,714
Femoral neck T-value[1]	-0,46 (±0,88)	-0,26 (±1,24)	0,532
Total femur BMD[1]	1,00 (±0,12)	1,00 (±0,16)	0,771

Total femur T-value[1]	-0,46 (±0,97)	-0,28 (±1,25)	0,597

Table 6 Comparison of bone density
1: Mean and standard deviation

3.5 Results of the follow-up examination

All prolactinoma patients came for a routine follow-up after the initiation of cabergoline treatment. The duration period until the follow-up examination varied, with a median of 14 weeks (6,5 – 19). For one patient it was not necessary to receive a therapy, therefore the total number of patients included in this part of the analysis is 20.

As anticipated, the levels of prolactin were significantly lower than at the time of diagnosis and were mostly within the normal range at follow-up (with a median of 11,55 ng/ml (7,6 – 30,4)). There was no significant change in the levels of LH. However, the levels of FSH increased and showed a mean value of 4,83 mIE/ml (±2,20) at follow-up. The oestrogen levels of the female patients did not change relevantly. Nevertheless, analysing male patients, an elevation of both testosterone from 1,28 ng/ml (±0,63) to 2,44 ng/ml (±1,03) and free testosterone from 5,60 ng/ml (±2,65) to 9,64 ng/ml (±4,21) could be shown. The mean values were within normal range at follow-up in contrast to the baseline. The same applies to pituitary function. Only 42,1% of the patients had hypopituitarism at the time of the follow-up examination versus 81% at baseline. All were hypogonadal, none had hypothyroidism, GH deficiency or central adrenal insufficiency. This means, that 53,3% of the patients with hypogonadism at baseline showed no change at follow-up, while the other half had regained pituitary function.

	N	**Baseline**	**Follow-up**	**p-value**
Prolactin[2] *(ng/ml)*	20	271,70 (117,9 – 7,89)	11,55 (7,6 – 30,4)	**p<0,001**
LH[2] *(mIE/ml)*	19	2,96 (1,74 – 4,87)	3,98 (2,64 – 5,23)	0,171
FSH[1] *(mIE/ml)*	19	3,60 (±1,85)	4,83 (±2,20)	**0,023**
oestrogen (f)[1] *(pg/ml)*	5	47,66 (±40,95)	61,76 (±39,18)	0,318

Testosterone (m)[1] (ng/ml)	14	1,28 (±0,63)	2,44 (±1,03)	**p<0,001**
Free testosterone (m)[1] (ng/ml)	9	6,09 (±2,73)	9,64 (±4,21)	**0,006**

Table 7 Endocrine parameters at follow-up
1: Mean and standard deviation
2: Median and interquartile range

Concerning haemoglobin, the levels stayed the same. When analysing metabolic parameters, as was expected, there was no change in glucose and HbA1c values, they were still within the normal range. However, regarding the adverse cholesterol levels at baseline (214,50 mg/dl (±38,32)), the results at follow-up demonstrated a reduction to a mean level of 196,89 mg/dl (±40,62). Concerning HDL, the data provides no evidence of a significant change. LDL decreased significantly to 119,56 mg/dl (±35,61), suggesting an improved metabolic profile. The levels of triglycerides stayed within the normal range (84,5 mg/dl (60 – 168,25)).

	N	**Baseline**	**Follow-up**	**p-value**
Hb[1] (g/dl)	18	13,98 (±1,12)	13,98 (±1,39)	0,962
Glucose[2] (mg/dl)	17	88 (85,5 – 95,5)	87 (82 – 91,5)	0,191
HbA1c[2] (mmol/mol)	3	33 (30 – 33)*	32 (29- 33)*	0,157
Cholesterol[1] (mg/dl)	18	214,50 (±38,32)	196,89 (±40,62)	0,180
HDL[2] (mg/dl)	18	56 (39,5 – 70,5)	50 (40,5 – 64)	0,798
LDL[1] (mg/dl)	18	135,72 (±35,65)	119,56 (±35,61)	**0,014**
TG[2] (mg/dl)	18	98 (78,5 – 183,25)	84,5 (60 – 168,25)	0,142

Table 8 Metabolic parameters at follow-up
1: Mean and standard deviation
2: Median and interquartile range
**shows the range of values, due to the low case number*

4. Discussion

In line with most published data, we found evidence of impaired lipid metabolism in untreated patients with prolactinoma and an amelioration after initiation of cabergoline therapy.

Firstly, BMI was found to be elevated in untreated prolactioma patients compared to healthy controls, as also reported by Naliato (67,68). An explanation for this phenomenon is the possible influence of prolactin on thalamic systems regulating appetite and resulting in increased food intake, as shown in mice (70). Prolactin was furthermore found to be secreted by the adipose tissue and to suppress adipokines such as adiponectin and possibly leptin (83). Animal studies have confirmed a loss of weight gain and improvement of hyperlipidaemia after treatment with dopamine agonists (84). A decrease in BMI in prolactinoma patients after being treated with bromocriptine has also been reported (85).

The significant difference between cholesterol levels of people with and without hyperprolactinaemia, as well as the normalization of those levels under dopamine agonist treatment, has been shown in many studies and is in accordance with our findings (69–74). While the detailed results of the different studies varied, LDL was the one parameter that was most consistently found to improve after treatment, and it also showed significant decrease in this study. It supports the hypothesis, that this parameter is the first to improve and that only continued use of dopamine agonists might lead to amelioration of further metabolic parameters.

While total cholesterol was restored to the normal range, an improvement of HDL cholesterol could not be found. All of these findings parallel those of a previous study conducted by the Department of Endocrinology and Diabetology at the Medical University of Graz (86). It was designed as a retrospective study comparing the laboratory parameters of 55 prolactinoma patients before and after receiving dopamine agonists. Triglycerides were also investigated in this retrospective study and in line with the data presented here, no change was noted.

Past studies have shown that an excess of prolactin leads to an impaired glucose metabolism and worsens insulin resistance by stimulating insulin secretion and β-cell proliferation (87). Fasting glucose and HbA1c have also been investigated in this study and, as well as in our previous study, no significant changes could be

found, neither between prolactinoma patients and controls, nor after the initiation of treatment. Reasons for lacking effects on glucose metabolism might be the short duration of observation and the good glucose profile to begin with, demonstrated by the low number of patients with diabetes mellitus.

Concerning the topic of hypogonadism, nearly 50% of all hypogonadal prolactinoma patients could restore normal gonadal function after a median of 14 weeks. In detail, the mean oestrogen level of women did not change, which is in contrast to our previous findings, where also oestrogen improved significantly. In the previous study, however, the median period to follow-up was 9 months. The mean free testosterone and total testosterone in men, however, shifted from hypogonadal to normal range. This could also play an important role in body composition. A study monitoring testosterone deprivation while prostate cancer therapy found not only an increase in fat mass and a decrease in lean body mass, but also an elevated serum insulin (88). Treating males older than 65 with testosterone patches and initiating testosterone replacement in hypogonadal men both leads to an increase in muscle mass and a decrease in fat mass (89,90).

The results of BMD analysis in our study showed no significant difference between BMD of prolactinoma patients and controls. This is contrary to most findings in other studies, describing bone loss in women with prolactinoma, that seems to be linked to amenorrhea (17) and a prevalence of osteopenia in 56% of male prolactinoma patients (91). However, the improvement of hypogonadism alone, independent from the prolactin levels, enhances bone mass in males (92).

Results confirming an adverse metabolic profile also raise the question whether prolactinoma patients have an increased cardiovascular risk. The data in this filed is inconclusive. Toulis et al. conducted a retrospective study with over 2000 prolactinoma patients and found a nearly doubled rate for cardiovascular incidents in males (81). On the contrary, in a collective of 3232 participants of the Framingham Heart Study, no association between prolactin and cardiovascular risk factors was found. It must be mentioned that all of the participants had prolactin levels within the normal range, however (93). Nontheless, in light of a possibly elevated cardiovascular risk profile in prolactioma patients, we suggest monitoring glucose and lipid metabolism in affected patients.

Certain limitations of our data have to be acknowledged including the design as a case-control study with a retrospective analysis of follow-up data. In addition, the number of patients analyzed is small and our data are prone to statistical type I errors due to multiple testing without correction. Our statistical analysis approach is, however, supported by the fact that our analysis plan was a priori designed and that all analyses were hypothesis driven. The main strengths are, however, age-matched controls and the standardized treatment and follow-up of all patients. The significant impact of cabergoline treatment on prolactin and testosterone levels underlines the validity of our data.

5. Conclusion

The results of the case-control based study show that prolactinoma patients have higher LDL values than healthy controls. Furthermore, after receiving cabergoline treatment, LDL levels are significantly lower than at baseline. In addition, cholesterol levels significantly decreased after initiation of treatment. This adverse metabolic profile highlights the necessity to monitor lipid metabolism in patients with prolactinoma. Further studies should investigate possible pathophysiological mechanisms linking prolactin, lipid metabolism and cardiovascular health. Adequate control of hyperprolactinaemia is relevant even if the patients are free of symptoms, in order to lower their cholesterol levels and thereby reduce a possible risk of cardiovascular complications.

Appendix

Blood value	**Normal range**	**Unit**
Prolactin	2,1 – 17,7	ng/ml
TSH	0,10 – 4,00	yU/ml
fT4	9,5 – 24,0	pmol/l
fT3	3,0 – 6,3	pmol/l
LH	1,24 – 8,62	mIE/ml
FSH	1,27 – 19,26	mIE/ml

oestrogen (f)	See Table 10	pg/ml
Testosterone (m)	2,41 – 8,30	ng/ml
Free Testosterone (m)	6,69 – 54,69	ng/ml
Hb	13,0 – 17,5	g/dl
Glucose	70 - 100	mg/dl
HbA1c	20 - 42	mmol/mol
Cholesterol	- 199	mg/dl
HDL	41 -	mg/dl
LDL	100-130*	mg/dl
TG	- 149	mg/dl

Table 9 Normal range of laboratory parameters according to the Division for Endocrinology and Diabetology, Department of Internal Medicine, Medical University of Graz
**normal range may differ due to risk profile*

Cycle phase	**Normal range of oestrogen in pg/ml**
Follicular phase	- 160
Follicular phase 2nd – 3rd day	- 84
Periovulation +/- 3 days	34 - 400
Luteal phase	27 - 246
Postmenopause untreated	- 30
Postmenopause treated	- 93
Oral contraception	- 102

Table 10 Normal range of oestrogen according to cycle phase

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