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Markers of Metabolic Syndrome in Patients with Pituitary Adenoma: A Case Series of 303 Patients

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ABSTRACT

To assess the demographic characteristics and hormonal status of patients who presented to our clinic with pituitary adenoma and to demonstrate the presence, prevalence, and relationship of metabolic syndrome parameters in these patients. The study included 303 patients with known or newly diagnosed pituitary adenoma and 52 age- and sex-matched healthy controls. The patients were classified into 3 groups; acromegaly (ACRO) (n = 54),prolactinoma (PRLoma) (n = 163), and non-functional adenoma (NFA) (n = 86). in 55.6 % (n = 172) and 52 % (n = 163) of the patients, respectively. The waist circumference of all patients ($p < 0.001$) and body mass index (BMI) of patients with PRLoma ($p = 0.03$) and ACRO ($p < 0.001$) were found to be significantly higher than in the controls. The HbA1c, insulin and HOMA-IR values were significantly higher in the ACRO and PRLoma groups, whereas the insulin and HOMA-IR values were significantly higher in the NFA group compared with the control group ($p < 0.001$ and $p < 0.001$, respectively). When the 3 patient groups were compared, waist circumference and BMI were significantly higher in the ACRO group than in the PRLoma group ($p = 0.04$ and $p = 0.03$, respectively). . In patients developing pituitary failure after treatment, age, waist circumference, plasma glucose, low-density lipoproteins and triglyceride values were significantly increased when compared with those without pituitary failure after treatment ($p < 0.001$). In our study, it was found that there was increased metabolic and cardiovascular risk in functional pituitary adenoma and NFA.

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Introduction

Pituitary adenoma is the most common type of pituitary disorder [1]. An adenoma is a benign tumor of the anterior pituitary. Although it accounts for 10–15 % of all intracranial masses, its prevalence is approximately 16.7 % based on results from autopsy series and magnetic resonance (MR) imaging studies [2]. Pituitary adenomas can be listed according to their incidence as follows: prolactinoma (40–57 %), non-functional adenomas (NFA; 28–37 %), growth hormone-secreting adenomas (8–16 %), adrenocorticotropic hormone (ACTH)-secreting adenomas (1–2 %), and thyroid-stimulating hormone (TSH)-secreting adenomas (1 %) [3].

The primary action of prolactin (PRL) is to induce and maintain lactation. However, recently, the metabolic effects of PRL have started to be recognized, including prenatal and postnatal pancreas islet cell development and insulin secretion, food intake and weight gain, and enhancement of lipolysis through the modulation of adipokine release (leptin, adiponectin and interleukin-6). It has been suggested that PRL elevation leads to hyperinsulinemia, insulin resistance, endothelial dysfunction, and metabolic syndrome through the above-mentioned mechanisms [4–7].

Increased hepatic gluconeogenesis and glycogenolysis, decreased peripheral glucose consumption, increased hepatic and peripheral insulin resistance, and dyslipidemia are detected due to growth hormone (GH) over-secretion in patients with acromegaly (ACRO). It was shown that there is impaired carbohydrate metabolism in more than 50 % of patients with ACRO [8–10] in addition

to elevated glycated hemoglobin (HbA1c), insulin and fibrinogen levels [11, 12]. There is emerging evidence that triglycerides (TG) and low-density lipoprotein (LDL) particles are known to be atherogenic, and that GH and insulin-like growth factor 1(IGF-1) values are correlated to LDL-C [13].

There are limited data regarding increased cardio-metabolic risk in non-functional adenoma (NFA) [14]. In this study, we aimed to assess whether there was an increase in metabolic risk in patients with functional and non-functional adenoma.

Patients and Methods

Study population

This was a prospective, single-center study. The study included 303 patients with known or newly diagnosed pituitary adenoma between 2016 and 2018, and 52 age- and sex-matched healthy controls. All metabolic parameters were studied in the patients and controls. The study was approved by Institutional Ethics Committee (Approval No.: 59/2.12.2016).

Study protocol

In all patients, symptoms at diagnosis, time of diagnosis, surgical status, diameter of adenoma at diagnosis, and medication were recorded. In addition, anthropometric and laboratory measurements were also performed. Blood measurements, physical examination findings, weight (kg), height (cm), and waist circumference (cm) were recorded in all subjects. Body mass index (BMI; kg/m^2) was calculated. In all patients, final status of pituitary adenoma was evaluated through MR imaging.

Blood sampling

After 8 h of fasting, blood samples were drawn for metabolic parameters [glucose, insulin, HbA1c, lipid profile, and hormone parameters including PRL, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, testosterone, adrenocorticotropic hormone (ACTH), cortisol, free thyroxine (T4), thyroid-stimulating hormone (TSH), growth hormone (GH), and insulin like growth factor-1 (IGF-1)] between 08:00 and 09:00 AM. Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR): >2 fasting plasma insulin level (mIU/l) × glucose (mg/dl)/405 was considered as insulin resistance [15].

Biochemical and hormonal assessment

Fasting blood glucose was measured using a DXC 800 analyzer with glucose oxidase hydrogen peroxide. Serum FSH, LH (mIU/ml), PRL (ng/ml), E2 (pg/ml), GH (ng/ml), IGF-1 (ng/ml), ACTH (pg/ml), cortisol (µg/dl), and total testosterone (ng/ml) levels were measured using a Unicel DxI 800 system immune analyzer (Beckman Coulter Ireland Inc., Galway, Ireland) with a chemiluminescent micro-particle immunoassay (paramagnetic particle, chemiluminescent immunoassay). Serum TSH (µIU/ml) and T4 (ng/dl) were measured using a DXI 800 immune analyzer (Beckmann Coulter Ireland Inc., Galway, Ireland) with an electrochemiluminescence immunoassay. Lipid parameters were measured using a T800 modular analyzer (Roche) with cholesterol esterase and glucose oxidase methods. HbA1c was measured using high-performance liquid chromatography. Insulin was analyzed on a Roche Hitachi Cobalt 600 system using an electrochemiluminescence immunoassay (ECLIA).

Statistical analysis

Data were analyzed using the IBM SPSS Statistics version 20.0 software (IBM Corp. released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). Categorical variables are summarized as number and percentage, whereas numeric variables are summarized as mean ± standard deviation (SD) and median (min-max) where appropriate. Categorical variables were compared using the Chi-square test. Normal distribution was assessed in numerical variables using the Shapiro–Wilk test. In the comparison of numerical variables between the groups, one-way analysis of variance (ANOVA) was used when assumptions were met, and the Kruskal–Wallis test was used when assumptions were not met. Bonferroni, Scheffe, and Tamhane tests based on the homogeneity of intra-group variances were used to perform binary comparisons for variables found to be significant in the Kruskal–Wallis ANOVA test. The Mann–Whitney U-test with Bonferroni correction was used for binary comparisons if assumptions were unmet. Pearson's correlation test was used to evaluate the relationship between numerical variables if assumptions were met, and Spearman's correlation was used if assumptions were not met. A p-value <0.5 was considered to be statistically significant.

Results

Demographic and biochemical parameters

The study included 309 patients with pituitary adenoma who were managed in our clinic between 2016 and 2018. Fifty-two age- and sex-matched healthy individuals were included as controls. Prolactinoma (PRLoma) was found in 52 % (n = 163), non-functional adenoma (NFA) in 27.8 % (n = 86), ACRO in 17.4 % (n = 54), and Cushing's disease was diagnosed in 1.9 % (n = 6) of the patients. Patients with Cushing's disease were excluded due to the limited number of patients. There were 223 women (62.8 %) and 132 men (37.2 %) in the study group. ▶ **Table 1** presents the biochemical and demographic characteristics for all groups.

When the sizes of the pituitary adenomas at diagnosis were assessed, the mean adenoma size was found to be significantly larger in the ACRO group (21.9 ± 10.4 mm) than in the PRLoma (14.2 ± 11.5 mm) and NFA groups (17.2 ± 14.1 mm) ($p < 0.001$). When stratified according to the pituitary adenoma size, it was found that the proportion of patients who presented with macro-adenoma (diameter > 10 mm) was higher than those who presented with micro-adenoma (diameter < 10 mm) [172 (55.6 %) vs. 137 (44.3 %)]. The proportion of patients who presented with macro-adenoma was significantly higher in the ACRO group than in the PRLoma group. Although no significant difference was detected between the NFA and ACRO groups, the number of patients with NFA who presented with macro-adenoma was higher than those with PRLoma.

There was no significant difference in disease duration and number of patients who underwent radiotherapy among the groups ($p = 0.015$ and $p = 0.3$). Pituitary surgery and subsequent pituitary failure was significantly more common in the ACRO group when compared with the PRLoma group ($p = 0.01$), but there was no sig-

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▶ **Table 1** Prolactinoma (PRLoma), non-functional adenoma (NFA), and acromegaly (ACRO) biochemical and demographic characteristics parameters.

	PRLoma (n = 163)	NFA (n = 86)	ACRO (n = 54)	p
Diameter of PA at the time of diagnosis (mm)	14.2 ± 11.5	17.2 ± 14.1	21.9 ± 10.4	**0 .00** * b,c
Last PA diameter (mm)	6.8 ± 6.4	7.9 ± 9.7	8 ± 6.8	0.5
Duration of disease (years)	5.1 ± 4.5	4.9 ± 4.8	6.1 ± 4.3	0.154
Macro-adenom /Micro-adenom (n, %)	75/88 (% 45.9/54.1)	50/ 36(% 57.1/42.9)	46/8 (% 89.6/10.4)	**0 .00** * b
Affecting the visual field (Yes /No) (n, %)	47/116 (% 28.8/71.2)	43/41 (% 51.2/48.8)	47/7(% 87/13)	**0.00** * b
Operation history (Yes/No) (n, %)	46/117 (% 28.2/71.8)	47/39 (% 54.8/45.2)	51/3 (% 94.3/5.7)	**0 .00** * b
Radiotherapy history (Yes/No) (n, %)	3/160 (% 1.8/98.2)	2/84 (% 2.3/97.7)	3/51 (% 5.6/94.4)	0.32
Current status (Active/inactive) (n, %)	27/134 (% 16.8/83.2)	29/55 (% 34.5/65.5)	14/40 (% 25.9/74.1)	**0.00** * a
Pituitary insufficiency (Yes/No) (n, %)	23/140 (% 14.1/85.9)	28/58 (% 32.6/67.4)	16/38(% 29.6/70.4)	**0.01** * b

PA: Pituitary adenoma. [a] PRLoma vs. NFA; [b] PRLoma vs. ACRO; [c] NFA vs. ACRO. * p < 0.001.

▶ **Table 2** Biochemical and demographic parameters of prolactinoma (PRLoma), non-functional adenoma (NFA), acromegaly (ACRO), and healthy control (HC) group.

	PRLoma (n = 163)	NFA (n = 86)	ACRO (n = 54)	HC (n = 52)	p
Age	40.0 ± 12.3	44.5 ± 15.3	44.4 ± 10.5	43.6 ± 12.1	0.06
Gender F/M (n, %)	114/49 (% 69.9/30.1)	49/37 (% 57/43)	28/26 (% 51.9/48.1)	32/20 (% 61.5/38.5)	0.55
Waist sircumference (cm)	100.5 ± 13.0	92.7 ± 13.9	106.2 ± 11.6	88.7 ± 12.1	**0.00** * b,c,f
BMI (kg /m2)	28.3 ± 5.4	28.3 ± 5.4	30.8 ± 5	25.9 ± 3.6	**0.00** * b,c,f
SBP (mmHg)	135.1 ± 10.1	131.9 ± 11.2	135.1 ± 11.0	125.6 ± 12.1	**0.00** * f
DBP (mmHg)	83.4 ± 8.3	84.1 ± 8.5	85.3 ± 9.0	81 ± 8.5	0.155
FPG (mg/dl)	101.59 ± 24.6	97.9 ± 19.5	153.11 ± 64	92.3 ± 11.0	**0.00** * b,d,f
HbA1c (mmol/mol)	38 ± 4.6	37 ± 3.6	50 ± 11.9	33 ± 1.9	**0.00** * b,c,d,f
Insulin (µU/l)	12.5 ± 8.9	8.6 ± 4.4	20.5 ± 14.7	5.9 ± 3.1	**0.00** * b–f
HOMA-IR	3.2 ± 2.7	2.1 ± 1.3	8.1 ± 8.0	1.2 ± 0.78	**0.00** * a–f
Total cholesterol (mg /dl)	204.1 ± 50.6	215.8 ± 70.8	218.8 ± 53.1	195.7 ± 38 .9	0.07
LDL (mg/dl)	144.7 ± 42.6	133.8 ± 37.4	157.9 ± 50.8	127.3 ± 35.3	**0.01** * d,f
HDL (mg /dl)	39.0 ± 11.3	42.6 ± 12.4	37.4 ± 9.7	40.2 ± 12.2	0.06
Triglycerides (mg /dl)	172.6 ± 114.9	176.6 ± 73.0	183.4 ± 97.8	143 ± 80	**0.03** * e

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; HbA1c: Glycated hemoglobin; HOMA-IR: Homeostatic Model Assessment of Insülin Resistance; LDL: Low-density lipoprotein; HDL: High-density lipoprotein. * p < 0.001; [a] PRLoma vs. NFA; [b] PRLoma vs. ACRO; [c] PRLoma vs. control; [d] NFA vs. ACRO, [e] NFA vs. control; [f] ACRO vs. control.

nificant difference between the ACRO and NFA groups. When assessed according to sex, the pituitary failure rate was higher among men than in women [17.3 % (n = 33) vs. 48.6 % (n = 53); p < 0.001] (▶ **Table 2**).

When assessed in terms of metabolic and biochemical parameters, it was seen that waist circumference was significantly increased in all 3 patient groups when compared with the controls (p < 0.001). No significant difference was found in diastolic blood pressure between the 3 patient groups and controls, whereas systolic blood pressure was significantly increased in the ACRO group compared with the controls (p < 0.001). HbA1c, insulin, and HOMA-IR values were significantly higher in the ACRO and PRLoma groups when compared with the controls (p < 0.001); only insulin and HOMA-IR values were significantly higher in the NFA group than in the controls (p < 0.001) (▶ **Table 2**). When metabolic syndrome parameters were assessed according to disease activity, it was seen that disease activity was positively correlated with waist circumference, systolic blood pressure, glucose, HbA1c, insulin, and HOMA-IR values (p < 0.001 r: 0.217).

Hormonal parameters

▶ **Table 3** presents hormonal parameters in the three patient groups. As expected, PRL levels were significantly higher in the PRLoma group compared with the other groups. Again, GH and IGF-1

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▶ **Table 3** Hormonal parameters of prolactinoma (PRLoma), non-functional adenoma (NFA), acromegaly (ACRO), and healthy control (HC) group.

	PRLoma (n = 163)	NFA (n = 86)	ACRO (n = 54)	HC (n = 52)	p
ACTH (pg/ml)	24.8 ± 32.4	22 ± 33.5	25 ± 15	29.8 ± 34	0.14
Cortisol (µg/dl)	7.4 ± 3.8	5.9 ± 3.9	6.9 ± 4.9	10.4 ± 4.0	**0.00** * a,c,e,f
GH (ng/ml)	1.565 ± 0.5	0.3 ± 0.61	14.1 ± 20.6	0.6 ± 0.7	**0.00** * b,d,f
IGF-1 (ng/ml)	149 ± 83	120.2 ± 81.1	324.7 ± 195.7	138 ± 33	**0.00** * b,d,f
LH (mIU/l)	5.6 ± 6.9	4 ± 9.2	4 ± 10	9.7 ± 13.7	0.093
FSH (mIU/l)	8.5 ± 14.5	12.3 ± 24	15 ± 18.5	17.2 ± 26.6	**0.00** * c,e
PRL (ng/ml)	312 ± 765	10.0 ± 9.6	14.5 ± 11.8	9.06 ± 0.4	**0.00** * **a–c**
TSH (mIU/l)	1.7 ± 1.1	1.3 ± 1	1.1 ± 0.9	1.8 ± 1	**0.00** * a,b,f
sT4 (ng/dl)	0.99 ± 0.81	0.97 ± 1.1	1.1 ± 0.9	1.0 ± 0.87	0.06
Total testosterone (ng/ml)	0.91 ± 0.97	1.1 ± 1.4	1.2 ± 2.8	1.4 ± 1.3	0.192

ACTH: Adrenocorticotropic hormone; LH: Luteinizing hormone; FSH: Follicle-stimulating hormone: PRL: Prolactin; TSH: Thyroid-stimulating hormone; sT4: Free thyroxine; GH: Growth hormone; IGF-1: Insulin-like growth factor. * $p < 0.001$. [a] PRLoma vs. NFA; [b] PRLoma vs. ACRO; [c] PRLoma vs. control; [d] NFA vs. ACRO; [e] NFA vs. control; [f] ACRO vs. control.

levels were found to be significantly higher in the ACRO group when compared with the other groups ($p < 0.001$). No significant difference was found in ACTH, LH, testosterone, and fT4 levels between groups, whereas cortisol levels were significantly lower in all 3 patient groups when compared with the controls ($p < 0.001$).The serum TSH level was significantly higher than in the ACRO group, whereas it was significantly lower in the NFA group when compared with the PRLoma group. In addition, FSH levels were found to be significantly lower in the NFA and PRLoma groups than in the controls ($p < 0.001$).

Discussion

In this study, we aimed to assess the demographic characteristics and hormonal status of functional and non-functional adenoma in patients who presented to our clinic with pituitary adenoma and to demonstrate the presence, prevalence, and relationship of metabolic syndrome parameters in these patients.

In our study, we demonstrated that PRLoma is the most common pituitary adenoma and is followed by nonfunctional adenoma (NFA).Additionally it was shown the mean adenoma size was found to be significantly larger in the ACRO group than in the others. Pituitary surgery and subsequent pituitary failure was significantly more common in the ACRO group when compared with the PRLoma group. In this study was seen that waist circumference was significantly increased in all 3 patient groups when compared with the controls. HbA1c, insulin, and HOMA-IR values were significantly higher in the ACRO and PRLoma groups when compared with the controls; only insulin and HOMA-IR values were significantly higher in the NFA group than in the controls. Furthermore, it was seen that disease activity was positively correlated with waist circumference, systolic blood pressure, glucose, HbA1c, insulin, and HOMA-IR values.

In the literature, there are only a few studies investigating whether there is a relationship between non-functional pituitary adenoma and metabolic syndrome. Doğan et al. found increased insulin resistance and androstenedione levels in 47 women with NFA when compared with healthy controls [14]. Again, Joustra et al., detected decreased HDL-C levels with increased TG levels and increased metabolic syndrome frequency in 145 patients with NFA who previously underwent treatment and achieved remission. The authors have attributed these metabolic abnormalities to hypothalamic dysfunction [15]. In our study population, it was found that metabolic parameters such as TG, insulin, and HOMA-IR levels were increased when compared with controls, but there was no significant difference in HDL-C levels in the NFA group. However, disease duration showed a positive correlation with TG levels in this group. The presence of a relationship between adenoma diameter and lipid parameters in the NFA group supports the correlation between atherosclerosis and adenoma size, compressive findings, and failure.

In our study, it was found that waist circumference, plasma glucose, serum LDL-C, and TG levels were significantly increased in patients with pituitary failure following treatment (surgery and/or radiotherapy) when compared with those showing no pituitary failure . When stratified according to sex, pituitary failure was found to be more common in our male patients, contrary to the literature. In our study, hypopituitarism following treatment seemed to be one of the reasons for the more frequent presence of impaired metabolic parameters in the ACRO group. GH deficiency develops more frequently in patients with ACRO treated with surgery and radiotherapy than in patients NFA who are treated in the same way. It is known that, in addition to the classic hormones, GH deficiency also leads to abnormal body composition (increased fat mass, decreased lean mass), reduction in bone mass density, and decreased quality of life, as well as increased cardiovascular risk [16].

On the other hand, it is also known that raised GH levels in patients with ACRO increases cardiovascular mortality and atherosclerosis through increases in gluconeogenesis and glycogenolysis, reduced peripheral glucose use, increased hepatic and peripheral insulin resistance, dyslipidemia, and hypertension [14, 17]. These findings were supported with our study, and in our study it was

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found that presence of impaired metabolic parameters were markedly increased in the ACRO group when compared with both controls and the PRLoma and NFA groups. In a controlled study, it was shown that increased insulin secretion continued to accompany glucose uptake in patients with ACRO, even in the presence of normal GH levels, thereby emphasizing that this may be due to either persistently enhanced pancreatic β-cell mass or persistent peripheral insulin resistance [18]. In other words, this suggests that glucose metabolism disorders may persist despite remission being achieved [11]. In our study, the ACRO group were not have active disease compared with the remaining two groups, thereby implying remission ($p > 0.05$).We think that that one should meticulously assess glucose metabolism and other metabolic parameters during follow-up, even in the event of stable remission.

It has been shown that functional pituitary adenomas confer increased atherosclerosis and cardiovascular risk In patients with ACRO, vascular resistance is increased due to GH and IGF-1, resulting in hypertension in clinical practice. There is a two-fold increase inmortality in patients with ACRO when compared with the general population and cardiovascular causes account for 60 % of the mortality in these patients [8].

In animal and human studies, increased body weight (particularly increased fat mass), elevated blood glucose and insulin resistance, decreased HDL-C, and elevated LDL-C and TG values were detected in patients with hyperprolactinemia, proposing that an impaired metabolic profile may contribute atherogenesis [19–21]. In our study, it was seen that waist circumference, BMI, insulin, and HOMA-IR values were significantly higher in the PRLoma group than in the controls; however, no significant difference was detected in blood pressure and lipid parameters.

This is the first study in the literature comparing metabolic parameters in patients with NFA, PRLoma and ACRO. The weakness of this study is that our patients were not newly diagnosed and included in the routine clinical follow-up. It may be more meaningful to look at the metabolic parameters of patients with hypophysis adenoma before and after treatment.

In conclusion, we have observed that ACRO and PRLoma could enhance the risk for cardiovascular disorders directly or through facilitatory process by revealing increased metabolic syndrome parameters. In addition, we also found increased metabolic and cardiovascular risk in NFA. It is unclear whether the risk is due to mass effect, post-treatment hormonal failure, or NFA itself. We think that novel, prospective, and randomized studies are needed in this field.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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