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ORIGINAL ARTICLE

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Metabolic profile differences in ACTH-dependent and ACTH-independent Cushing syndrome

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Abstract

Background: The most common etiologies of Cushing's syndrome (CS) are adrenocorticotropic hormone (ACTH)-producing pituitary adenoma (pitCS) and primary adrenal gland disease (adrCS), both of which burden patients with metabolic disturbance. The aim of this study was to compare the metabolic features of pitCS and adrCS patients.

Methods: A retrospective review including 114 patients (64 adrCS and 50 pitCS) diagnosed with CS in 2009–2019 was performed. Metabolic factors were then compared between pitCS and adrCS groups.

Results: Regarding sex, females suffered both adrCs (92.2%) and pitCS (88.0%) more frequently than males. Regarding age, patients with pitCS were diagnosed at a younger age (35.40 ± 11.94 vs. 39.65 ± 11.37 years, $p = 0.056$) than those with adrCS, although the difference was not statistically significant. Moreover, pitCS patients had much higher ACTH levels and more serious occurrences of hypercortisolemia at all time points (8 AM, 4 PM, 12 AM) than that in adrCS patients. Conversely, indexes, including body weight, BMI, blood pressure, serum total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides, fasting plasma glucose, and uric acid, showed no differences between adrCS and pitCS patients. Furthermore, diabetes prevalence was higher in pitCS patients than in adrCS patients; however, there were no significant differences in hypertension or dyslipidemia prevalence between the two.

Conclusions: Although adrCS and pitCS had different pathogenetic mechanisms, different severities of hypercortisolemia, and different diabetes prevalences, both etiologies had similar metabolic characteristics.

KEYWORDS

adrenal Cushing's, Cushing's syndrome, metabolic disturbance, pituitary Cushing's

1 | INTRODUCTION

Endogenous Cushing's syndrome (CS) is a rare endocrine disease characterized by endogenous glucocorticoid excess, with an estimated annual incidence of 2–3 cases per million.[1] As the name implies, patients affected with CS usually manifest a syndrome of systemic symptoms, including abdominal obesity, impaired glucose tolerance/diabetes, hypertension, hypokalemia, infections, dyslipidemia, and osteoporosis.[2] Increased morbidity and mortality among these patients have been attributed to the cardiovascular, thrombotic, metabolic, infectious, and musculoskeletal complications of the disease.[3]

Pathogenic mechanisms of endogenous CS can be divided into adrenocorticotropic hormone (ACTH)-dependent (accounting for about 70%–80% of cases, due

to a pituitary or other ectopic tumor) and ACTH-independent (accounting for about 20%–30% of cases, due to adrenal benign or malignant nodules, or adrenocortical hyperplasia) causes.[4,5] Although both ACTH-dependent and ACTH-independent CS result to endogenous hypercortisolism, ACTH levels of patients differ between the two types of CS. Specifically, ACTH levels are higher in ACTH-dependent CS patients, whereas ACTH levels are lower or can even be undetectable in ACTH-independent CS patients.[6] Aside from this difference, only a few studies have actually compared the demographic, clinical, and biochemical variables among patients with different CS etiologies.

In particular, the ERCUSYN Study Group reported that patients belonging in the adrenal CS (adrCS) group were older than those in the pituitary CS (pitCS) group. Hirsutism and diabetes prevalence in the ectopic CS (ectCS) group were also found to be higher than that in the adrCS and pitCS groups. Furthermore, pitCS patients reported more skin alterations, menstrual irregularities, and hirsutism than adrCS patients.[7] Another study reported that pitCS patients had a lower prevalence of hypertension, whereas no between-group differences in hypercortisoluria severity were observed.[8] Despite the findings of these studies, differences in the metabolic factors of the different etiologies of CS remain unclear.

Therefore, a retrospective study was performed to analyze and compare the metabolic features of pituitary CS (pitCS) and adrenal CS (adrCS) patients.

2 | METHODS

2.1 | Ethical approval

The study was conducted in accordance with the principles of the *Declaration of Helsinki*, and the study protocol was approved by the ethics committee of the Shandong Provincial Hospital. Due to this study's retrospective nature, the need for a written consent was waived.

2.2 | Subjects

CS patients who were admitted and diagnosed in Shandong Provincial Hospital, which is affiliated to the Shandong First Medical University, between October 2009 and October 2019 were recruited for the present study. Patients who fulfilled the following criteria were included in the study: (1) having a recorded biochemical data compatible with adrCS or pitCS diagnosis, as stipulated in the Endocrine Society Clinical Guidelines[9]; (2) having a diagnosis of overt CS, which was established by an expert endocrinologist at the time of presentation; and (3) having a diagnosis that was retrospectively ascertained by the study authors at the time of data collection based on the documented biochemical and imaging tests, as well as management and follow-up details. As a result, a total of 64 adrCS and 50 pitCS subjects were eligible in our study.

2.3 | Definition of variables

Hypertension was defined as having a diastolic blood pressure (DBP) ≥ 90 mm Hg, systolic blood pressure (SBP) ≥ 140 mm Hg, or if the patient was currently taking antihypertensive medications, as defined by the World Health Organization (WHO) in 1999.[10] Regarding diabetes, subjects with a fasting plasma glucose (FPG) level ≥ 7.0 mmol/L or those self-reported with diabetes were diagnosed with diabetes mellitus in this study.[11] Lastly, dyslipidemia was defined according to the current lipids levels at the time of the study or if the patient was using anti-dyslipidemia medications. Cut-off value for hypercholesterolemia was total cholesterol (TC) ≥ 5.2 mmol/L and/or low density lipoprotein-cholesterol (LDL-C) ≥ 3.4 mmol/L. Cut-off values for hypertriglyceridemia and low high density lipoprotein-cholesterolemia were triglyceride (TG) ≥ 1.7 mmol/L, and high density lipoprotein-cholesterol (HDL-C) < 1.04 mmol/L, respectively.[12]

2.4 | Statistical analysis

All statistical analyses were performed using the SPSS software 25.0 for Windows (SPSS Inc., Chicago, USA). Normally and non-normally distributed continuous variables were presented as means ± standard deviation (SD) and medians (interquartile range), respectively, whereas categorical variables were presented as numbers (percentage). Differences between two groups were tested using the independent two-sample t-test, Mann-Whitney test, and Chi-squared test. All statistical tests were two-tailed, and statistical significance was defined at $p < 0.05$.

3 | RESULTS

3.1 | Characteristics of the study population

As shown in Table 1, the population consisted of 114 participants, including 64 adrCS and 50 pitCS patients. In terms of sex, females were found to suffer more frequently in both the adrCs (92.2%) and pitCS (88.0%) groups. In terms of age, pitCS patients were diagnosed at a younger age (35.40 ± 11.94 vs. 39.65 ± 11.37 years, $p = 0.056$) as compared to adrCS patients, although the difference was not statistically significant. Furthermore, regarding ACTH levels, lower measurements were found in adrCS patients, whereas higher measurements in pitCS patients were observed at all time points (8 AM, 4 PM, 12 AM).

TABLE 1 Characteristics of the study population

Characteristics	AdrCS $n = 64$	pitCS $n = 50$	P	T	Regular
Age (years)	39.65 ± 11.37	35.40 ± 11.94	0.056	1.931	
Female	59 (92.2)	44 (88.0)	0.452	–	
ACTH8am (pg/mL)	1.14 ± 1.24	84.05 ± 40.86	0.001	−16.118	7.2–63.3
ACTH4pm (pg/mL)	1.01 ± 0.79	66.81 ± 42.82	0.001	−10.777	–
ACTH0am (pg/mL)	0.99 ± 0.73	82.26 ± 41.16	0.001	−13.556	–
Cor 8am (nmol/L)	577.14 ± 176.99	835.70 ± 282.82	0.001	−5.952	133–537
Cor 4pm (nmol/L)	559.22 ± 204.15	718.03 ± 295.91	0.001	−3.006	68.2–327.0
Cor 0am (nmol/L)	499.28 ± 175.94	709.88 ± 291.60	0.001	−4.114	–
FT4 (pmol/L)	13.88 ± 3.81	15.32 ± 3.57	0.092	−1.705	12–22
TSH (mIU/L)	1.33 ± 1.33	1.17 ± 1.04	0.559	0.587	0.27–4.20
ALT (IU/L)	34.44 ± 24.42	36.97 ± 27.72	0.641	−0.468	7–40
AST (IU/L)	22.80 ± 12.05	23.22 ± 11.47	0.850	−0.190	13–35
Cr (μmol/L)	56.33 ± 13.55	56.80 ± 16.29	0.868	−0.167	40–105

All data are expressed as mean ± standard deviation or n (%). ACTH: adreno-cortico-tropic-hormone; Cor: cortisol; FT4: free thyroxine; TSH: thyroid stimulating hormone; ALT: Alanine aminotransferase; AST: Aspartate transaminase; Crea: creatine.

Although serum cortisol levels were elevated significantly in both groups, the cortisol levels in pitCS patients were higher than that of adrCS patients (835.70 ± 282.82 vs. 577.14 ± 176.99 nmol/L at 8 AM, $p < 0.001$; 718.03 ± 295.91 vs. 559.22 ± 204.15 nmol/L at 4 PM, $p < 0.001$; 709.88 ± 291.60 vs. 499.28 ± 175.94 nmol/L at 12 AM, $p < 0.001$; respectively). Additionally, thyroid function (serum FT4 and TSH levels), liver function (serum alanine aminotransferase and aspartate transaminase levels), and renal function (serum creatine levels) tests showed no significant differences between the two groups.

3.2 | Metabolic profiles of adrCS and pitCS patients

In our study, the metabolic profiles of adrCS and pitCS patients were compared. As shown in Table 2, both body weight (67.67 vs. 72.88 kg, $p = 0.22$) and BMI (27.69± vs. 27.86 kg/m^2, $p = 0.91$) were similar between the two groups. Regarding blood pressure, no significant differences in either the SBP (143.39 vs. 145.58 mmHg, $p = 0.55$) or DBP (93.53 vs. 96.00 mmHg, $p = 0.45$) readings were found between the two groups. Regarding serum lipid profile, serum TC (6.06 vs. 5.83 mmol/L, $p = 0.41$), LDL-C (3.72 vs. 3.58 mmol/L, $p = 0.49$), HDL-C (1.49 vs. 1.46 mmol/L, $p = 0.77$), and TG (1.80 vs. 1.61 mmol/L, $p = 0.31$) levels were also similar between adrCS and pitCS patients. Furthermore, FPG (5.86 vs. 6.46 mmol/L, $p = 0.13$) and uric acid (UA) (293.53 vs. 309.46μmol/L, $p = 0.43$) levels had no significant differences between the two.

TABLE 2 Metabolic profile of the study population

Items	AdrCS $n = 64$	pitCS $n = 50$	P	T
Weight (kg)	67.67 ± 19.74	72.88 ± 10.75	0.221	−1.231
BMI (kg/m^2)	27.69 ± 6.85	27.86 ± 3.85	0.911	−0.112
SBP (mmHg)	143.39 ± 23.49	145.58 ± 20.39	0.553	−0.594
DBP (mmHg)	93.53 ± 16.04	96.00 ± 19.08	0.455	−0.750
TC (mmol/L)	6.06 ± 1.41	5.83 ± 1.22	0.408	−0.830
LDL-C (mmol/L)	3.72 ± 1.06	3.58 ± 0.94	0.490	0.693
HDL-C (mmol/L)	1.49 ± 0.32	1.46 ± 0.52	0.767	0.298
TG (mmol/L)	1.80 ± 1.08	1.61 ± 0.72	0.309	1.024
FBG (mmol/L)	5.86 ± 1.64	6.46 ± 2.33	0.125	−1.546
UA (μmol/L)	293.53 ± 106.60	309.46 ± 98.84	0.432	−0.789

All data are expressed as mean ± standard deviation. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; TC: total cholesterol; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; TG: triglyceride; UA: uric acid.

3.3 | Risk of metabolic disturbance in adrCS and pitCS patients

By definition, as shown in Table 3, both adrCS patients and pitCS patients were usually burdened with metabolic disturbance. Among the patients in our study, 83.33% had hypertension, 72.55% had high TC levels, 58.82% had high LDL-C levels, 9.80% had low HDL-C levels, 39.00% had high TG levels, and 35.96% had diabetes. However, on comparison of the two groups, only diabetes prevalence was higher in pitCS patients than

TABLE 3 Risk of metabolic disturbance of the study population

Items	AdrCS	pitCS	*P*	$\chi 2$
Hypertension	52 (81.25)	43 (86.00)	0.499	0.456
High TC	44 (74.58)	30 (69.77)	0.591	0.289
High LDL-C	33 (55.93)	27 (62.79)	0.487	0.483
Low HDL-C	4 (6.78)	6 (13.96)	0.229	1.448
High TG	22 (37.29)	17 (41.46)	0.674	0.177
Diabetes	17 (26.56)	24 (48.00)	0.018	5.601

All Data are expressed as n (%) for categorical variables. Pearson chi-squared test was used in the comparison for dichotomous variables. TC: total cholesterol; TG: Triglyceride.

that in adrCS patients. Additionally, no significant differences in hypertension or dyslipidemia prevalence were observed between the two groups.

4 | DISCUSSION

In this study, it was found that although pitCS patients had a higher diabetes prevalence and more serious occurrences of hypercortisolemia than adrCS patients, they had similar metabolic characteristics. To the best of our knowledge, this was the first study to focus on the metabolic differences between adrCS and pitCS patients.

The pituitary gland produces and secretes various hormones, including thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and ACTH, which have traditionally been seen as the regulators of single bodily processes, including endocrine functions.[13] Recently, some studies have reported that the pituitary hormones also played some additional roles in physiology. For example, the TSH receptor (TSHR) was found to be expressed on hepatocytes,[14] allowing TSH to regulate hepatic cholesterol and bile acid metabolism.[15,16] Another study showed that FSH could also regulate hepatic cholesterol metabolism, wherein its inhibition reduced serum cholesterol levels.[17] ACTH was also reported to act on osteoblastic MC2Rs, subsequently inducing vascular endothelial growth factor (VEGF) expression.[18] Therefore, it was possible that ACTH might also have some effects on the metabolic homeostasis.

Metabolic disturbance has been the most common complication for patients with Cushing's syndrome. A previous study showed that, aside from serious hypercortisolemia, ACTH levels differed in CS patients with different etiologies, wherein ACTH levels were higher in pitCS patients, while ACTH levels were lower or even undetectable in adrCS patients.[6] Contrarily, in this study, we did not find obvious metabolic differences between pitCS and adrCS patients. The possible reasons were as follows: (1) the effect of hypercortisolemia was too predominant, consequently masking the effect of ACTH; (2) the effect of ACTH on metabolic dysfunction was too weak; (3) the sample size was relatively small. Therefore, further experimental studies are needed to evaluate the metabolic effect of ACTH.

It was found in this study that serum cortisol levels in pitCS patients were higher than that of adrCS patients. This was consistent with a previous study, reporting that baseline serum cortisol and urinary cortisol levels were higher in pitCS patients, as compared to adrCS patients.[19] In contrast, another study found that there was no difference in cortisoluria severity between adrCS and pitCS patients.[8] One possible reason for this discrepancy was that they had a high proportion of adrenocortical carcinoma patients, which might have been associated with extremely high cortisol levels. Another reason was that the adrCS patients in their study might have had very stable cortisol production rates with high levels, possibly damaging the hypothalamic CRH-producing neurons, as compared to the high amplitude ACTH and cortisol secretions in pitCS patients.[20]

Diabetes prevalence was also found to be higher in pitCS patients than in adrCS patients, whereas no differences were found in blood pressures and lipid profiles. Contrary to our findings, no between-group differences in diabetes prevalence was reported in the ERCUSYN Study.[7] The reason for this discrepancy was probably associated with the retrospective nature of our study, as compared to the largely prospective pro-active data collection in the European registry.

Despite the findings of our study, certain limitations were noted. First, this study utilized retrospective data collection, which has an associated risk of missing data. As such, the population was probably not fully representative of all patients who were screened and diagnosed with CS during the study period. Second, we did not enroll CS patients with ectopic ACTH secretion in this study. Lastly, the lack of a 24-hour urinary free cortisol data limited the further explorations of cortisol levels in pitCS and adrCS patients.

In conclusion, metabolic disturbance was the most common complication in CS patients. Although adrCS and pitCS had different pathogenetic mechanisms, different occurrences of serious hypercortisolemia, and different diabetes prevalences, they had similar metabolic characteristics. Therefore, further experimental studies are needed to evaluate the metabolic effects of ACTH and to validate the present study's findings.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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