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Metabolic disorders during endogenous Cushing's syndrome: prevalence, associated factors, and outcome after remission

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Objective. The prognosis of Cushing's syndrome (CS) is related to a higher cardiovascular morbidity and mortality. This study aimed to determine the prevalence of metabolic disorders in patients with CS, the associated factors, and the rate of remission of these disorders after the remission from CS.

Methods. It is a retrospective study including 75 cases of CS followed up at the university hospital La Rabta of Tunis from 1987 to 2018. Clinical and paraclinical data were collected from medical files.

Results. The mean age of the patients was 44.1±18.9 years and the sex ratio was 0.39. At CS diagnosis, the frequencies of obesity, hypertension, diabetes, dyslipidemia, and metabolic syndrome were 52, 75, 43, 83, and 73%, respectively. The age, gender, body mass index, waist circumference, and baseline serum cortisol level were not associated with the presence of diabetes, hypertension or dyslipidemia. Forty-eight patients were operated on. At one year, 38 patients were in remission from CS. The remission rates of hypertension, diabetes, and dyslipidemia were respectively 58% ($p<0.001$), 76% ($p<0.001$), and 17% (NS).

Conclusion. Metabolic disorders were frequent during CS and their frequencies decreased after the remission from the syndrome.

Key words: Cushing's syndrome, obesity, hypertension, diabetes, dyslipidemia, remission

Cushing's syndrome results from a long-term exposure to excessive glucocorticoids (GC). Its major origin is a long-term treatment with GC. Endogenous CS is secondary to an excess of production of GC by the adrenal glands. The chronic excess of GC during CS causes a weight gain with a characteristic redistribution of fat from peripheral to central parts of the body and metabolic disorders such as hypertension, diabetes mellitus, and dyslipidemia. These cardiovascular risk factors are responsible for the increased mortality rate in patients with CS that is about twice to four times higher than that of matched controls (Etxabe and Vazquez 1994; Lindholm et al. 2001; Feelders et al. 2012; Dekkers et al. 2013).

The prevalence of these disorders and the rates of remission after remission from CS vary widely between studies.

The aim of this study was to determine 1) the prevalence of the metabolic disorders during endogenous CS and their risk factors and 2) the frequency of the remission of these disorders after the remission from CS.

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Patients and Methods

Ethics approval and consent to participate. All procedures performed in the studies involving human participants were in accordance with the ethical standards of the University Hospital La Rabta in Tunis and the ethical standards of the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics committee of La Rabta University Hospital, Tunis, Tunisia. Informed consent was obtained from all subjects or a parent and/or legal guardian if the subjects were under 18 years of age.

Study design. This is a retrospective study concerning 75 patients with endogenous CS followed up at the Endocrinology Department of the Rabta University Hospital in Tunis over a period of 32 years, from 1987 to 2018. The patients were 54 women and 21 men with a mean age of 44.1±18.9 years (14–88 years).

Data collection. The following data were collected from medical files: 1) the clinical parameters at CS diagnosis: age, gender, personal history of hypertension, diabetes, and dyslipidemia, weight, height, waist circumference (WC), systolic and diastolic blood pressure; 2) the results of biological investigations at CS diagnosis: kalemia, fasting plasma glucose (FPG), two hours after oral glucose tolerance test (OGTT) plasma glucose (2h-PG), total cholesterol (TC), triglycerides (Tg) and high density lipoprotein-cholesterol (HDL-c); 3) the etiology of CS and its treatment; and 4) the outcome of the metabolic disorders at one year of follow-up in the patients in remission from CS.

Diagnostic criteria. The diagnosis criteria were following: 1) the diagnosis of CS was made based on a non-suppressed serum cortisol (cortisol ≥50 nmol/l) after low-dose dexamethasone suppression test (two-day, 2 mg test); 2) hypertension was defined by the presence of known and treated hypertension or systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg; 3) the glucose metabolism abnormalities were defined according to the American Diabetes Association criteria (Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2004); 4) the dyslipidemia was defined by the presence of known and treated dyslipidemia or by the presence of an abnormality of at least one of the lipid parameters (TC ≥2.00 g/l, Tg ≥1.50 g/l and/or HDL-c <0.50 g/l regardless of gender); 5) the pure hypertriglyceridemia was defined as hypertriglyceridemia with a Tg (g/l)/TC (g/l) ratio ≥2.5; 6) the pure hypercholesterolemia was defined as hypercholesterolemia with Tg (g/l)/TC (g/l) ≤0.5; 7) the mixed dyslipidemia was defined by the presence of dyslipidemia with Tg (g/l)/TC (g/l) between 0.5 and 2.5; 8) the metabolic syndrome was defined according to the criteria of the International Diabetes Federation 2009 (Alberti et al. 2009); and 9) the remission from CS was diagnosed on the basis of a low baseline serum cortisol level (<138 nmol/l) and/or a non-suppressed serum cortisol level after low-dose dexamethasone suppression test (two-day, 2 mg test). Patients in remission from CS had either eucortisolism or adrenal insufficiency.

Statistical analysis. The analysis of the data was performed using statistical analysis software SPSS version 23. Chi-square test was used to compare percentages and failing that Fisher test was used. Student T test was used to compare means, failing that, non-parametric U Mann Whitney test for independent groups was used. For paired groups, Mac Nemar test was used to compare percentages. The difference was considered significant when $p<0.05$.

Results

The etiologies of CS were a Cushing's disease in 35 cases (47%), an adrenal adenoma in 26 cases (35%), bilateral adenomas in four cases (5%), an undetermined origin of adrenocorticotropic hormone (ACTH)-dependent CS in seven cases (9%), and a malignant corticosurrenaloma in three cases (4%). One case of stroke and one case of coronary artery disease were reported. No case of heart failure or lower limb arteriopathy was noted. Weight gain was reported in 32 cases (43%). It was estimated by 14 patients at a mean of 2.8±1.6 kg (1–7 kg). The mean body mass index (BMI) was 31.0±6.5 kg/m^2 (17.1–52.6 kg/m^2). Obesity was present in 39 cases (52%) and overweight in 25 cases (33%). The metabolic disorders are presented in Table 1.

Table 1
Prevalence and duration of metabolic disorders in patients with Cushing's syndrome

Parameter	Number of cases n (%)	Duration <5 years n (%)
Obesity	39 (52%)	–
Hypertension	56 (75%)	41 (73%)
Diabetes	32 (43%)	24 (75%
Dyslipidemia	62 (83%)	53 (85%)
Metabolic syndrome	55 (73%)	–

Table 2
Comparison of clinical parameters and baseline cortisol levels between patients with and those without diabetes

Parameter	With diabetes (n=32)	Without diabetes (n=43)	p-value
Age (years)	44.4±17.6	43.9±19.9	0.91
Female gender [n (%)]	22 (69)	32 (74)	0.58
Weight gain [n (%)]	15 (47)	17 (40)	0.52
Body mass index (kg/m^2)	32.4±7.5	30.0±5.6	0.12
Waist circumference (cm)	110±11	101±15	0.05
Baseline cortisol (nmol/l)	700±419	739±535	0.75

Data are presented as mean±SD.

Table 3
Comparison of clinical parameters and baseline cortisol levels between patients with and those without hypertension

Parameter	With hypertension (n=56)	Without hypertension (n=16)	p-value
Age (years)	44.9±19.1	39.7±17.3	0.36
Female gender [n (%)]	41 (73)	11 (69)	0.75
Body mass index (kg/m^2)	31.9±6.9	28.1±4.4	0.08
Waist circumference (cm)	107±16	100±18	0.18
Baseline cortisol (nmol/l)	653±339	976±802	0.21

Data are presented as mean±SD.

Table 4
Comparison of clinical parameters and baseline cortisol levels between patients with and those without dyslipidemia

Parameter	With dyslipidemia (n=62)	Without dyslipidemia (n=6)	p-value
Age (years)	44.5±18.6	35.8±18.3	0.27
Female gender [n (%)]	46 (74)	2 (33)	0.057
Body mass index (kg/m^2)	31.2±6.6	28.2±8.3	0.20
Waist circumference (cm)	106±14	99±23	0.20
Baseline cortisol (nmol/l)	731±502	593±284	0.78

Data are presented as mean±SD.

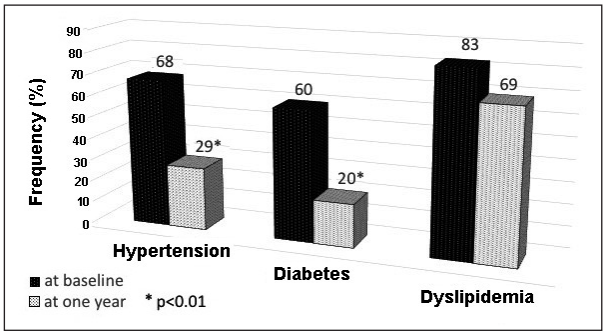


Figure 1. Outcome of the metabolic disorders in patients in remission from Cushing's syndrome at one year of follow up.

Diabetes was known in 17 patients. In 58 of other patients, FPG revealed seven cases of diabetes. Oral glucose tolerance test was performed in 31 cases and revealed diabetes in eight other cases, impaired fasting glucose (IFG) in seven cases, impaired glucose tolerance (IGT) in four cases and the association of IFG and IGT in five cases. Hypertension was known in 26 cases and diagnosed in 30 other cases. In the 56 hypertensive patients, serum potassium was <3.9 mmol/l in 21 cases (37%) and <3.5 mmol/l in 11 cases (20%). Dyslipidemia was known in 12 cases and was diagnosed in 50 other cases; it was a mixed dyslipidemia in 40 cases (80%) and a pure hypercholesterolemia in 10 cases (20%). The metabolic syndrome was present in 55 cases (73%).

Age, gender, BMI, WC, and baseline cortisol level were not associated with the presence of hypertension, diabetes nor dyslipidemia (Tables 2–4). Age, gender, and serum cortisol level were not associated with the presence of a metabolic syndrome. The frequency of the metabolic syndrome was significantly higher in patients over 30 years of age as compared to those younger than 30 years (84% vs. 44%, p=0.001).

Forty-eight patients were operated on. Adrenal surgery was performed in 19 patients and pituitary surgery in 29. Three patients died post-operatively. Thirty-eight patients were in remission from CS at the end of the first year of follow-up. These subjects achieved eucortisolism in 8 cases and had an adrenal insufficiency in 30 cases. The Figure 1 represents the frequencies of the metabolic disorders in patients in remission from CS at baseline and at one year of follow up. The frequencies of hypertension and diabetes significantly decreased after remission from CS. The rate of remission at one year was 58% for hypertension, 76% for diabetes, and 17% for dyslipidemia.

Discussion

We retrospectively studied metabolic disorders in 75 cases of CS. We assessed their prevalence before and after remissioning from CS and tried to determine the associated factors. The obesity frequency in patients with CS was higher than in the Tunisian general adult population (52% vs. 25.4%, p<0.001) (El Ati et al. 2012). The obesity prevalence in CS was between 32% and 41% in the literature (Mancini et al. 2004; Feelders et al. 2012). The mean BMI in our patients was 31.0 kg/m^2 compared to 26.9 kg/m^2 in the general adult population (El Ati et al. 2012). This has also been reported by other studies where the patients with endogenous CS had a higher BMI compared to subjects of equivalent age and

gender (Barahona et al. 2009; Valassi et al. 2011). This is explained by the effect of glucocorticoids on the regulation of fat differentiation and distribution and their central effect on appetite and eating behavior.

The hypertension frequency in our CS patients was higher than in the Tunisian general adult population (75% vs. 30%, p<0.001) (Elasmi et al. 2009; Marzouk-Aissi et al. 2012), as was the diabetes frequency (43% vs. 15%, p<0.001) (Elasmi et al. 2009). The prevalence of hypertension in CS varies between 55% and 85% in the literature (Etxabe and Vazquez. 1994; Mancini et al. 2004; Giordano et al. 2011; Valassi et al. 2011; Feelders et al. 2012; Li et al. 2020). In the literature data, the diabetes prevalence during CS varied between 20% and 47% (Biering et al. 2000; Arnaldi et al. 2004; Mancini et al. 2004; Resmini et al. 2009; Pivonello et al. 2010; Giordano et al. 2011; Mazziotti et al. 2011; Valassi et al. 2011; Feelders et al. 2012; Li et al. 2020). It should be noted that the measurement of FPG alone is insufficient for the diagnosis of diabetes in subjects with CS and OGTT is required. In fact, in the present study, eight over 15 cases of unknown diabetes were diagnosed by 2h-PG. In the study of Mancini et al. (2004), the two thirds of the diabetes cases were diagnosed by OGTT. This is explained by the fact that insulin resistance is the main mechanism involved. Diabetes has been described as the most important cardiovascular risk factor in CS and it was an independent risk factor for mortality, this was not the case for hypertension (Clayton et al. 2016).

In our study, the age, gender, BMI, WC, and baseline serum cortisol level were not significantly associated with the presence of hypertension or diabetes. However, WC was higher in patients with diabetes (p=0.05). An increase in the diabetes frequency with age was described in CS (Biering et al. 2000). Besides, a positive correlation between FPG and the degree of hypercortisolism has been observed (Mancini et al. 2004).

The frequency of dyslipidemia in our CS patients was 83% compared to 21% in the general Tunisian adult population (p<0.001) (El Ati et al. 2012) and 37% to 72% in the other studies on CS (Mancini et al. 2004; Giordano et al. 2011; Feelders et al. 2012; Li et al. 2020). It is noteworthy that the frequency depends on diagnostic criteria. In the present study, both TC, Tg and HDL-c were used for the diagnosis of dyslipidemia. Mixed dyslipidemia was the most frequent type (80% of the cases). We did not find any factor associated with the presence of dyslipidemia, even though female gender was more frequent in patients with dyslipidemia (p=0.057). The metabolic syndrome was present in 73% of our patients. The prevalence of the metabolic syndrome and its risk factors were not studied elsewhere.

The frequency of hypertension decreased after the remission from CS and reached that of the general population (29% vs. 30%, p=0.9) (Marzouk-Aissi et al. 2012). The remission rate of hypertension at one year was 58% in our study and varied between 32% and 75% in other studies (Faggiano et al. 2003; Gomez et al. 2007; Hassan-Smith et al. 2012; Li et al. 2020). The remission rate of diabetes at one year was 76% in our study and 40% in the study of Faggiano et al. (2003). This rate reached 79% at 44 months of follow up in the study of Sippel et al. (2008). The diabetes frequency after the remission from CS was close to that of the general adult population (20% vs. 15%, p=0.3) (Elasmi et al. 2009). The persistence of carbohydrate metabolism disorders after CS treatment has been described in other studies (Colao et al. 1999; Arnaldi et al. 2004; Feelders et al. 2012). The frequency of dyslipidemia remained higher than the general adult population (69% vs. 21%, p<0.001) one year after the cure of CS (Elasmi et al. 2009). In fact, the effect of the treatment of hypercortisolism on dyslipidemia seems to be mild (Colao et al. 1999; Bolland et al. 2011).

All studies showed a decrease in the prevalence of cardiovascular risk factors after the remission from CS. However, the risk for cardiovascular events remained high (Li et al. 2020). Patients treated for CS still have higher prevalence of coronary and carotid atherosclerosis with an increased mortality rate (Faggiano et al. 2003; Geer et al. 2012; Barahona et al. 2013; Li et al. 2020).

The limits of this study are the relatively limited number of cases and its retrospective pattern.

Conclusion

Obesity, hypertension, diabetes, and dyslipidemia were more frequent in patients with CS compared with the general adult population. The studied factors were not associated with the presence of these metabolic disorders. There was a significant decrease in the prevalence of hypertension and diabetes after one year of remission from CS. Large prospective studies are needed to determine the factors associated with the metabolic disorders and more importantly the predictive factors of remission of the metabolic disorders after the cure of CS.

Conflict of interest: *The authors declare no conflict of interest.*

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