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Research Article

Hypercorsolism and Metabolic Diseases: Clinical and Biochemical Features

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Abstract: There is an increasing evidence that defects of hypotalamic pituitary adrenal(HPA) axis leading to mild hypercortisolism may play a part in the etiology of the metabolic syndrome. This study includes 94 patients admitted in the department of endocrinology of hedi chaker sfax from 1990 to 2008 .All patients present defect of the HPA axis associated with metabolic abnormalities. We included in this data patients presenting at least two metabolic disoreders. In a retrospective comparative study our population was subdivided in three groups: Group1(G1) :32 patients (34%) with cushing syndrome(CS). Group 2 (G2) : 31 patients (33.6%) with subclinical cushing's syndrome (SCS). Group 3(G3) :31 patients (36.6%) with non functioning incidentaly discovred adrenal masses by non invasive abdominal imaging techniques (NFAI). The clinical evaluation and Biochemical measurement show that in CS positive correlations was found between plasma cortisol (8am) and diastolic blood pressure (DBP), 2h glucose concentration and diastolic blood pressure (P=0.05). In SCS, positive correlations were noted between plasma cortisol (8am), waist circumference, fasting glucose, 2h glucose concentration,TG and TC but without statistic significance. In NFAI, positive but non significant correlations were objected between plasma cortisol (8am) and waist circumference, systolic blood pressure (SBP) and DBP. Our study ,with its postive correlations ,allowed us to focus on the major role of chronic excess of glucocorticoid to induce severe metabolic disorders.

Keywords: Cushing syndrome, metabolic alteration , insulin resistance , cardiovascular risk.

INTRODUCTION

There is an increasing evidence that defects of hypotalamic pituitary adrenal(HPA) axis leading to mild hypercortisolism may play a part in the etiology of the metabolic syndrome. Several studies show that raised plasma cortisol concentration is associated with components of metabolic syndrome such as raised blood pressure, glucose intolerance ,dyslipedimia and abdominal obesity.

A modest excess of cortisol can be unapparent and prolonged and can predispose to metabolic alterations.

The purpose of the present study is to establish a correlation between these metabolic abnormalities and hypercortisolism in order to explain better the relationship between these entities.

SUBJECTS AND METHODS

This study includes 94 patients admitted in the department of endocrinology of hedi chaker sfax from 1990 to 2008. All patients present defect of the HPA axis associated with metabolic abnormalities . We included in this data patients presenting at least two metabolic disoreders. In a retrospective comparative study our population was subdivided in three groups:

Group1(G1) :32 patients (34%)(87.1% female) with cushing syndrome(CS). They presented clinical signs of hypercortisolism and failed to suppress cortisol levels after 1mg dexamethasone (DST) and after two-day 2-mg DST.

Group 2 (G2) : 31 patients (33.6%) (60%female) with subclinical cushing's syndrome (SCS).Theses patients had no clicnical signs of hormonal excess in the presence but they had at least

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two abnormalities in HPA function assessed by endocrine tests and they failed to achieve serum cortisol surpression after 4 mg of DST.

Group 3(G3) :31 patients (36.6%) (60% female) with non functioning incidentaly discovred adrenal masses by non invasive abdominal imaging techniques. Inclusion criteria were absence of specific signs and /or symptome of hormone excess, test of HPA axis function all normal and morphological aspect of the tumor suggesting the presence of a benign mass.

METHODS

The clinical evaluation concerns all patients : weight, body mass index (BMI) waist circumfirence (WC) systolic blood pressure (SBP) and diastolic blood pressure (DBP) were evaluated.

Biochemical measurement : diastolic blood pressure (TC), triglycerid (TG) and plasma glucose were evaluated in all patient. An oral glucose toleance test was performed according to world health organization criteria (75g glucose) if type two diabete was suspected.

The HPA axis was evaluated by at least two of the following explorations : plasma cortisol levels at 8am,16pm and 23pm, free urinary cortisol, overnight 1 mg DXM test and /or two days 2-mg DXT and determining of the ACTH. Serum cortisol and urinary free cortisol were determined in basal condition using a commercial RIA. Dynamic tests were performed in most cases.

Metabolic syndrome (MS): was objected in 81% of patients in accordance to the Adult.

Treatment Panel III criteria

WC >102cm for man and >88cm for women
BP >130/85
Serum glucose level >=1.1g/l(6.1mmol/l)
TG >=1.5g/l (1.7mmol)
HDL cholesterol <0.4g/l for man and <0.5 g/l for women

Statistical Analysis

Data ara expressed as mean. Statistical comparisons between groups were made by NOVA. Correlations were examined by Spearman analysis. The levels of statistical significance were set at P< 0.05.

RESULTS

The hormonal results are summarized in Table-1: the mean of cortisol level 8am, 16pm, 23pm and cortisol after 4mg DST are expressed for three groups**.** Plasma cortisol (8am) exceeded the normal range in 19 patients in G1, 16patients in G2 and 4 patients in G3. Compared with SCS and non functional AI, patients with SC had significantly higher plasma cortisol 8am, 16pm and 23pm levels. A statistically significant difference was found also in cortisol after 4mg DST wich was higher in CS than in SCS and non functioning AI.

Glucose intolerance was detected in 28 patients (87.5%) CS, 19 (59.3%) SCS and 20(64.5%) non functioning AI. Serum fasting glucose levels were significantly higher in CS and SCS than non fonctioning AI (P=0.04). Oral glucose tolerance test digonosed 12 patients with type 2 diabetes mellitus (8 patients with CS and 4 patients with SCS) (Fig-1)

Triglycirid mean values were elevated in 21 patients of G1 (65.6%), 13 patients of G2 (41.9%) and 13patients of G3 (41.9%). Fasting triglycirid concentration levels were higher in CS than in SCS and non functioning AI but no significant difference was found (P=0.06) (Fig-2).

Concerning the total cholesterol levels ,they were abnormal in 23 patients of G1 (71.8%) 22 patients of G2(70.9%) and in 15 patients of G3(48.3%) with statistically significant diffrence of the mean value betwwen three groups (P=0.002)

Blood pressure (Table-2).

SBP and DBP mean values were higher in CS comparing to SCS and AI, this result was without statistically significant difference for the SBP (P=0.11) and with significant difference for DBP (P=0.019)

Anthropometric measurement (Table-2)

Our data shows that CS were overweight, had the highest body mass index and highest waist circumference with a difference statistacally significant comparing to G2and G3 (P=0.02).

Over weight was more frequent in NFAI (G1= 32.2% ; G2 =29% ; G3 =58%) and obesity was more frenquent in CS (62.5%).

Waist to hip ratio was more elevated in CS than SCS and NFAI.

In CS positive correlations was found between plasma cortisol (8am) and DBP , 2h glucose concentration and TC (P=0.05).

In SCS, positive correlations were noted between plasma cortisol (8am), waist circumference, fasting glucose, 2h glucose concentration, TG and TC but without statistic significance.

In NFAI, positive but non significant correlations were objected between plasma cortisol (8am) and waist circumference, SBP and DBP.

Table-1: Hormonal Evaluation

	CS(G1)	SCS(G2)	Non functioning AI (G3)	P value
Cortisol 8am(ng/ml)	317.4	271.2	175	0.001
Cortisol 16pm(ng/ml)	231.3	145	75.5	0.04
Cortisol 23pm(ng/ml)	163.4	126.5		0.3
Cortisol after 4mg DST(ng/ml)	196.8	71.1	15	0.001

Table-2: Anthropometric and blood pressure in the three groups

	CS	SCS	NFAI	P value
SBP(mmHg)	152	143	145	0.11
DBP(mmHg)	91.2	83.5	80.7	0.019
Weight(kg)	81.4	77.1	71.8	0.05
BMI(kg/m2)	32.75	28.5	28.35	0.02
Waist circumference(cm)	109.5	102.3	99.2	0.005
Waist to hip ratio	0.97	0.93	0.94	0.4

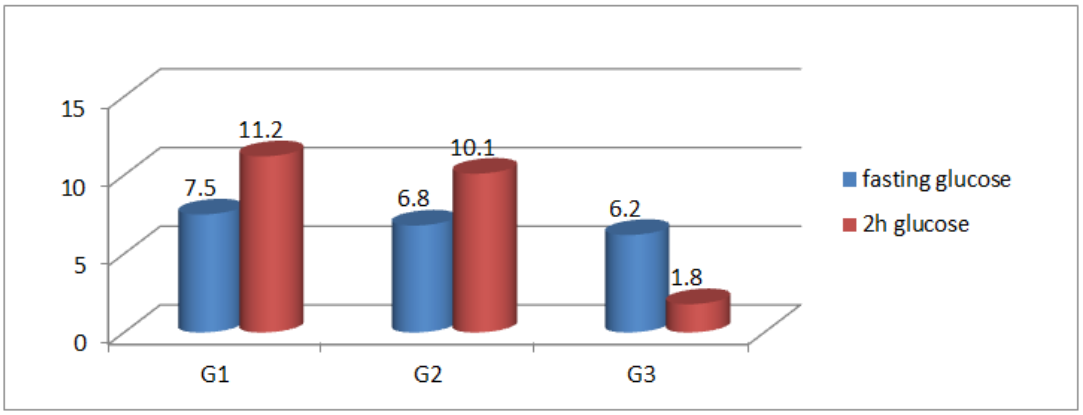

Fig-1: Glucose Metabolisme

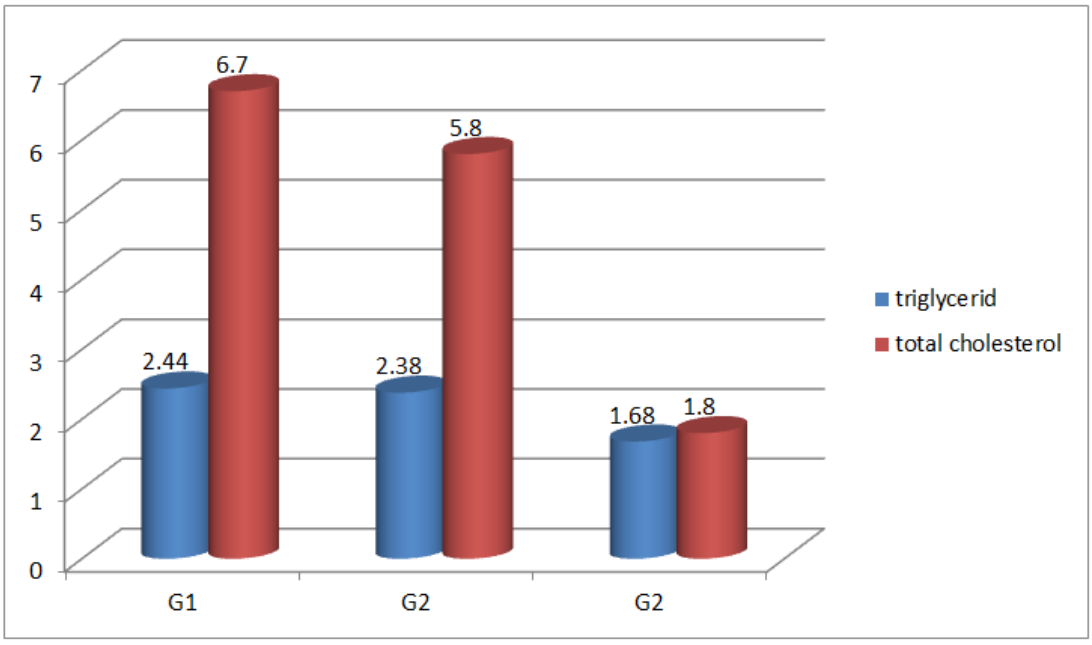

Fig-2: Lipids Metabolisme

DISCUSSION

Few studies have evaluated the relationship between hypercortisolism and metabolic disorders comparing patients with CS, SCS and NFAI.

Chronic glucocorticoid excess has been suggested to induce metabolic alterations that may be correlated with the degree of hypercortisolime [1]

SCS is an entity in itself and more common than CS with an estimated prevalence of about 8/10000 in general population [2].

Chiodini and al were the first to demonstrate that this prevalence is higher in patients with severe and multiple metabolic disease.

Glucose Metabolisme

Several data described a high prevalence (61%) of abnormal glucose tolereance in NFAI which is suitable to our results . The prevalence was lower than that observed in CS that's why we suggest that even patients with NFAI should have a screening for glucose intolerance. The exact mechanism with the insulin resistance in NFAI has not been yet clarified but it is possible that the adenomae had an intratumorol secretory capacity which can cause an insulin resistance .In their comparative study tauchmanova and al demonstrated that fasting glucose is more raised, with a significant difference, in patients having SCS than those with NFAI [10]. Phillips in 1998 and Word in 2003 [11] demonstrate that fasting glucose and 2h glucose changing levels were strongly correlated with a free cortisol (8am) such correlations were noted in our data with SCS and CS.

Type 2 diabetes is more frequent in SCS(30%) than in NFAI (10-15%) with a significant difference [3-9], this is comfirmed in our study where 12 cases with type 2 diabetes were noted (8 with CS and 4 with SCS) (P=0.04).

Lipid Metabolism

It seems that the liver is the essential site of action of the glucorticoide were it plays an essential role in the lipids metabolism. In hypercortisolism there is an increase in triglycerid and total chlesterol levels. The mechanism of these changes is probably multifactorial. Many authors have evaluated lipid profile abnormalities associated with hypercortisolim. Prevalance of abnormal lipid values varied between 50 and 70% in SCS and reached 28% in NFAI. Terzolo *et al*., [12] noted higher means level of TG in SCS than in CS and NFAI but no correlation was found between TG or TC and hormonal variables . Garrapa *et al.*, [13] noted in their comparative study a higher mean levels of TG and TC in CS than in NFAI. Rifat *et al.,* [14] noted the same results between SCS and NFAI but without significant difference.P barat *et al.*, demontrated the existance of positive correlation between cortisol (8am) and TC as well as the rate of TG. These findings are confirmed again in our data and this is thanks to the large number of patients in each group comparing to other study.

Blood Pressure

There is a large range of literature on the profound effects of glucocorticoid which cause arterial hypertension(HTA) throught several mechanisms. There is good evidence that cortisol excess was correlated with the hypertension but not in all studies. HTA was observed in 61 to 91% in CS, in 63 to 75% in SCS and in 42% in NFAI probably because of the high prevalance of metabolic syndrome in the total population [15. A positive correlation between cortisol level and hypertension was established for the first time in 1991 Soszynski and al [16] than by Phillip and al in 1998 [11] these results were found in our study. Our analyses showed for the first time positive correlations between plasma cortisol level after 4mg DST and both SBP and DBP in CS and SCS .

Anthropometric Data

Glucorticoid play a key role in the fat masses function and distribution. In fact cortisol augments directly or indirectly the total mass of adipose tissue and redistributes it from peripheral to central depots [17]. Even the presence of an adrenal incidentaloma has been associated with an increased incidence of overweight and obesity similar to overt CS [18]. Prevalence of obesity is related to hypercortisolism degree. It was noted in 90% of CS in 40% of SCS and in 30% of NFAI .Judith andwithitworth noted in his data that patients with CS had higher BMI and waist to hip ratio than matched controls . In the same study cortisol level correlated positively with BMI and waist circumference .Garapa *et al.*, [13] showed that patients with CS had significantly high waist circumference and waist to hip ratio than in SCS and in NFAI .Correlations between abdominal fat and hypercortisolism have been found, although there is considerable controversy in the literature .Weigensberg MJ *et al*., [19] noted that abdominal fat developement correlate significantly with cortisol 8h in normal patients but no correlation with waist circumference. These controversies are also noted in our study. Indeed, positive correlations between hypercortisolism and the anthropometric parameters were objected only in SCS ans NFAI these results are because patients with adrenal incidentaloma even in the absence of sign or symptom of hypercortisolim can show a wide and almost continuous spectrum of cortisol hypesecretion ranging from normality of the HPA axis to various degree of cortisol excess over the physiological daily production rate .

CONCLUSION

Our study ,with its postive correlations ,allowed us to focus on the major role of chronic excess of glucocorticoid to induce severe metabolic disorders . The current data allow us to hypothesize that the subtle autonomous cortisol secretion of incidental adenoma may cause an acquired condition of insulin resistance in normoglycemic and non obese subjects . We kicked up for the first time the predictive value of cortisol after 4mg DST in determining risk and severity of the metabolic abnormalities which increase the global cardiovascular risk and mortality.The treatment of both

hypercortisolime and cardiovascular risk factors is a requirement .

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