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GLUCOSE METABOLISM IN PATIENTS WITH SUBCLINICAL CUSHING'S SYNDROME

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Abstract

This clinical review will summarize the avail- able data regarding the effect of either physiological or increased glucocorticoid concentrations on glucose metab- olism and insulin-sensitivity, in order to clarify the role, if any, of subclinical Cushing's syndrome (SCS), a status of altered hypothalamic–pituitary–adrenal axis secretion in the absence of the classical signs or symptoms of overt cortisol excess, in patients with adrenal incidentalomas (AI) and diabetes mellitus type 2. Focusing on patients with SCS associated to AI, while there is convincing evidence in the literature that even a mild hyper cortisolemia is associated with alterations of glucose metabolism, evidence is insuffi- cient to conclude that the simple correction of chronic, even mild, hypercortisolism can completely revert metabolic, mainly glycemic alterations. At the same time, considering the variability of the prevalence of Cushing's syndrome in patients with diabetes mellitus type 2 reported in the litera ture, no agreement does exist whether screening for CS can be useful and recommended in those patients.

Introduction

Subclinical Cushing's syndrome (SCS) is defined as a status of altered hypothalamic–pituitary–adrenal (HPA) axis secretion in the absence of the classical signs or symptoms of overt cortisol excess [1–4]. The interest in SCS is due to its high prevalence in some patient's cate- gories, as those with adrenal incidentalomas (AI). Although SCS by definition is not associated with signs and/or symptoms specific to overt cortisol excess, such as purple striae, easy bruising, proximal muscle weakness, and plethora [5], some evidence suggests that this condition may lead to long-term consequences of cortisol excess that are similar to those present in overt Cushing's syndrome (CS), like gluco-metabolic alterations [4].

This clinical review will summarize the available data regarding the effect of either physiological or increased glucocorticoid concentrations on glucose metabolism and insulin-sensitivity, in order to clarify the role, if any, of subclinical hypercortisolism in patients with AI and dia- betes mellitus type 2.

Glucocorticoids and glucose metabolism

Glucocorticoid hormones (GCs) are produced in the adre- nal cortex under the control of the HPA axis and act at different target tissues by binding two different intracel- lular receptors, the glucocorticoid receptor (GR) and the mineralcorticoid receptor (MR) [6]. On the other hand, it is well known that the effects of GCs vary considerably between subjects, due to a different sensitivity, which is at least partially, genetically determined [7, 8]. Moreover, other factors that modulate the biological effects of GCs in target tissues has been recognized: among them, the 11b-hydroxysteroid dehydrogenase (11b-HSD) enzymes, which interconvert cortisol and its inactive metabolite cortisone, are of particular interest: 11b-HSD type 1, which is pre- dominantly expressed in liver and adipose tissue, amplifies local GC action by conversion of cortisone to cortisol, whereas 11b-HSD type 2, which is mainly expressed in the kidney, reduces GC-induced effects by converting cortisol to cortisone [9].

In humans, blood glucose levels are determined mainly through the balance between insulin-dependent glucose production and muscle glucose utilization. GCs are so named based on their actions on carbohydrate metabolism, namely on insulin-dependent processes [10–13]. In partic- ular, the effect of GC includes increased hepatic glucose production, decreased insulin-dependent glucose uptake into peripheral tissues, breakdown of muscle and fat to provide additional substrates for glucose production, and inhibition of insulin

release from pancreatic b cells [10, 11]. The mechanisms by which GCs achieve these effects are multifactorial, as demonstrated by in vitro and in vivo studies [10–13].

At hepatic level, GCs increase endogenous glucose production both directly and indirectly, the latter by antagonizing insulin's metabolic actions, through a number of proposed mechanism. Specifically, GCs increase glu- coneogenesis stimulating specific rate-limiting enzymes (e.g., phosphoenolpyruvate carboxykinase, and glucose-6- phospahatase), favoring the availability of free fatty acids and aminoacids, facilitating metabolite transport across the mitochondrial membranes, and finally potentiating the effects of other glucoregulatory hormones, such as gluca- gons and epinephrine [10, 11]. Finally, a role for the nuclear peroxisome proliferator-activated receptor-alfa (PPAR)-a in facilitating the GC-induced gluconeogenesis has recently been reported [14], and very recent studies have shown that the nuclear liver receptor LXRb plays a pivotal role in the development of GC-related hypergly- cemia, at least in mice [15].

At peripheral levels, namely in skeletal muscle tissue that accounts for 80% of insulin-induced glucose disposal, GCs reduce the insulin-mediated glucose uptake either by directly interfering with several components of the insulin signaling cascade or modulating protein and lipid metab- olism. In particular, in animal models, GCs have been reported of being able to reduce the expression and phos- phorylation of insulin receptor substrate (IRS)-1, phos- phatidylinositol 3-kinase (PI3-K), and protein kinase B (PKB)/Atk, and to reduce the migration of glucose trans- porter GLUT-4 to cell surface [10, 11]. To date, few data do exist regarding the effects of GC on insulin signaling in humans, while a reduction in glycogen synthesis rates has been reported [11]. Moreover, GCs inhibit protein syn- thesis by reducing transport of aminoacids into the muscle, stimulate muscle proteolysis by activating a number of proteolytic systems (e.g., muscle ring finger-1 and Atrogin- 1 protein), and induce adipose lipolysis, resulting in an increase of aminoacids, nonesterified fatty acids and tri- glycerides, which, in turn, interfere with IRS-1- and PI3-K- mediated insulin signaling, as demonstrated in animal models [11].

In addition to their effects on insulin sensitivity, GCs also inhibit insulin secretion from pancreatic b-cells, as demonstrated in animal models, by reducing the glucose uptake through the suppression of GLUT-2 expression and glucokinase, the glucose oxidation by enhancing inward repolarizing K? currents, which limit calcium influx,

decreasing protein kinase's A and C activation [11]; finally, GCs decrease insulin biosynthesis by reducing ATP/ADP ratio, inducing b cells apoptosis directly and indirectly, through lipotoxicity due to elevated plasma concentration of free fatty acids [11, 16]. In humans, GCs exert an acute inhibitory effects on insulin secretion in vitro and in vivo, while strong evidence about an inhibitory effects on b cell after chronic hypercortisolism is currently lacking [11, 17]. Central actions of GCs may enhance vagal stimulation of insulin secretion [18].

The balance of all the above mentioned effects of GCs is important in determining whether insulin resistance is accompanied by compensatory hyperinsulinemia or hyperglycemia, and may explain in part why only some patients with hypercortisolism develop glucose intolerance [19, 20].

Subclinical Cushing's syndrome in patients with AI: focus on glucose metabolism derangement

The majority of the studies regarding the diagnosis and the treatment of SCS have been focused on series of patients with AI, clinically unapparent adrenal masses serendipi- tously found by abdominal imaging procedures for unre- lated diseases, that are thought to be present in up to 1–9% of adults, with a higher prevalence in elderly subjects [21– 29]. SCS is estimated to be present in 5–30% of patients with AI [1–4, 30–34].

The variability in the prevalence of SCS in this group of patients depends on differences in the inclusion criteria, study design, work-up protocols, and mainly diagnostic criteria of SCS [1–4, 34].

The diagnosis of SCS is a challenge for clinicians due to several causes. First, it includes a heterogeneous spectrum of clinical phenotype that mainly depends on the variability of cortisol secretion that is distributed continuously from apparently non-functioning adrenal adenomas to overtly cortisol-producing adenomas, as well as on peripheral cortisol sensitivity [1–4]. As a consequence, the identification of subtle signs of cortisol excess depends mainly on the personal practice of the physician, and may, therefore, be overlooked by those with less expertise with hypercortisolemic patients [4]. Second, no gold standard diagnostic tests to identify abnormal cortisol levels exist. In fact, although the 1-mg dexamethasone test (DST) is considered the most valuable test to screen for SCS, diagnosing SCS by arbitrary cortisol cutoffs at DST leads to unavoidable mistakes in classifying some patients, being cortisol secretion a continuum from completely normal to clearly increased levels and highly variable in the same individual [4]. Moreover, the reliabilities of other sug- gested

markers of HPA axis activity for the diagnosis of SCS, including high midnight serum cortisol level, low serum ACTH levels, high 24-h urinary free cortisol and low serum DHEAS levels, are low in SCS [4].

Despite diagnostic difficulties, several studies have demonstrated that a chronic, albeit slight, cortisol excess is able to induce the classic metabolic and cardiovascular complications of overt CS, such as arterial hypertension, obesity, or diabetes mellitus [5, 19, 20], together with bone disorders, like osteoporosis and fragility fractures [5, 35]. Unfortunately, all these comorbidities are very frequent in the elderly population, and they cannot be considered as specific features of SCS, which are, as above mentioned, more frequent in the elderly. However, there is still scarce information regarding the long-term detrimental effects, if any, of SCS [4].

Focusing on glucose metabolism, while an increased prevalence of impaired glucose tolerance or diabetes has been described at the diagnosis in patients with SCS, compared with non-functioning adenomas or controls [30, 32–34, 36, 37], these data were not confirmed by other studies that have reported a similar prevalence of impaired glucose metabolism in SCS than in the overall series of AI as well as in the general population [31, 38–43]; some of these studies suggest a particular role of aging in the development of unfavorable metabolic outcome [43] (Table 1). The variability in the prevalence of glucose metabolism impairment in SCS may depend on variability of method used; in fact, in some studies, fasting glucose and fasting insulin have been evaluated [30, 36, 39], while in others, the diagnosis has been performed by an oral glucose tolerance test [33, 34, 37, 40, 42, 43] that has been considered the gold standard test in CS [19, 20]. In fact, more than one half of patients with endogenous CS and diabetes were shown to have normal fasting glucose [19, 20]. Glycated hemoglobin, very recently added among the tools used for the diagnosis of diabetes mellitus, may be even more helpful in the clinical setting of SCS because this parameter is an integrated measure of glucose homeostasis, although its use in patients with SCS is not yet a standard practice [19, 20].

The results of these studies suggest that chronic mild hypercortisolism, such as in SCS, may be associated with the clinical phenotype of the insulin resistance syndrome or that, as an alternative hypothesis, AI may itself be an unrecognized manifestation of the metabolic syndrome. In fact, it has been shown that insulin is mitogenic, being able to stimulate adrenal cortex cell proliferation and tumor formation in a time and in a dose-dependent matter, without affecting cortisol synthesis [44]. In a recent study, Muscogiuri et al. [45] demonstrated a direct correlation between insulin resistance, evaluated by hyperinsulinemic euglycemic

clamp, and the size of the mass, in patients with clinically non-functioning AI, suggesting that clini- cally undetectable hypercortisolism may cause insulin resistance and compensatory hyperinsulinemia, responsible itself for tumor growth.

Normalization of hypercortisolism is the first step for the achievement of metabolic control in patients with overt or subclinical CS. Contrary to adrenal overt CS, where adre- nalectomy is the therapeutic gold standard, surgical approach might be proposed to patients with SCS, although long-term prospective studies assessing the metabolic outcome of patients with SCS and their follow-up are limited, with results sometimes discordant. In particular, whether patients with SCS should benefit from adrenalec- tomy is still a matter of debate, with the effect of adre- nalectomy on glucose metabolism impairment being controversial [31, 46–52].

A number of underpowered studies have reported an improvement in hyperglycemia and insulin sensitivity in patients with SCS after adrenalectomy, compared to those without SCS [31, 46–52]. In a case–control study, Erbil et al. [48] compared the outcome of adrenalectomy between 28 patients with overt CS and 11 patients with SCS: they found that diabetes mellitus improved more frequently among patients with the subclinical syndrome. Tsuiki et al. [50] followed up 20 patients with SCS for 15–69 months: 10 of them were submitted to adrenalec- tomy, and the remaining patients were managed conser- vatively. Of the total patients, eight patients benefited from surgery in terms of better control of hyperglycemia, whereas half of the non-operated patients showed wors- ening of their clinical conditions, while the others remained unchanged. Toniato et al. [51] carried out a prospective study in which 45 patients with SCS were randomly selected for surgery (n = 23) or conservative management (n = 22); mean duration of follow-up was about 8 years. They found that diabetes mellitus normalized or improved in about 2/3 of patients in the surgical group; on the other hand, some worsening of diabetes was noted in conserva- tively managed patients. Interestingly, Chiodini et al. [52] published a retrospective controlled study on 108 patients followed up for 18–48 months, in which adrenalectomy was recommended to all patients with SCS and to all patients without SCS but with mass size [4 cm or size increasing by [1 cm during the follow-up. Adrenalectomy improved glucose levels not only in patients with SCS, but also in patients without SCS, compared with patients treated conservatively.

All these studies suggest that laparoscopic adrenalec- tomy appears more beneficial than conservative manage- ment for patients with SCS. This conclusion should be viewed with caution because of some methodological shortcomings of the studies, including the lack of a formal comparison between the patients who were

operated and those who were not and the fact that medical treatment of associated clinical conditions was not standardized between groups.

On the other hand, other studies have reported no changes in glucose metabolism after adrenalectomy [40, 42]. Sereg et al. [40] carried out a retrospective uncon- trolled study, in which 47 out of 125 patients with clinically non-functioning adrenal adenomas underwent adrenalectomy, whereas 78 patients were followed up conservatively; these patients were re-assessed after a mean follow-up time of about 9 years. The frequency of impaired glucose tolerance or diabetes mellitus did not significantly differ between patients treated and not treated with adrenalectomy. We recently published a prospective study on 118 patients followed up for 1–10 years reporting

that adrenalectomy did not improve glucose levels in patients with SCS (n = 6), compared with patients treated conservatively (n = 10) or patients who underwent adre- nalectomy for non-functioning adenomas (n = 6) [42]. In all, the follow-up studies did not show a clear beneficial effect of surgery on glucose metabolism in SCS, but it has to be pointed out that adrenalectomy was not recommended for treatment of SCS, which was diagnosed only in a minority of patients submitted to surgery. These results also suggest that clinical improvement after adrenalectomy was not restricted to patients with SCS, casting some doubts on a cause-and-effect relationship. Moreover, it has to be pointed out that medical treatment was not standardized across the different groups in the different studies.

Based on the controversial data about the effect of adrenalectomy on glucose metabolism in SCS patients, the recent AME Position Statement on AI [29] did not make any recommendation on this point, stating that ‘‘data are insufficient to make any recommendation for or against surgery in patients with SCS.’’ Similarly, the AACE/AAES Medical Guidelines [53] for the management of AI repor- ted likewise that, in patients with SCS, until further evi- dence is available regarding the long-term benefits of adrenalectomy, ‘‘surgical resection should be reserved for those with worsening of hypertension, abnormal glucose tolerance, dyslipidemia, or osteoporosis (recommendation with a low level of evidence).’’ Moreover, the NIH state- of-the-science statement [21] suggested that ‘‘either adre- nalectomy or careful observation is a treatment option for patients with subclinical autonomous glucocorticoid hypersecretion.’’

Thus, the discordant results of above detailed studies, summarized in Table 2, seem to preclude any stringent recommendation of adrenalectomy for the management of glucose impairment in SCS.

Data from high-quality large prospective randomized trials are lacking to guide the optimal management of metabolic alterations of SCS and to indicate the superiority of a surgical or a non-surgical approach. These studies should include both surgically treated and adequately medically treated patients with and without SCS and should provide for an adequate follow-up period of observation.

Alternatively to adrenalectomy, drugs improving insulin sensitivity, such as metformin, or drugs increasing insulin secretion, such as sulfanylureas and miglitinides, could be used as second-line therapy in patients with SCS, and insulin analogs should be used if hyperglycemia is not corrected by oral hypoglycemic agents [20], although studies evaluating, in a comparative way, the best medical treatment of impaired glucose metabolism are lacking. Moreover, as insulin resistance and cardiovascular risk persist after correction of hypercortisolism, as demon- strated in patients with overt CS [19, 20], adequate treat- ment of concomitant diabetes and other comorbidities is mandatory also in patients with SCS.

In the past few years, aberrant cortisol responses to several stimuli due to the expression of aberrant receptors on adrenal cells have been reported in patients with SCS associated to bilateral incidentalomas [54]. Because these aberrant receptors may be specific pharmacological targets for controlling cortisol secretion, their detection deserves particular interest and some therapeutical protocols have been developed [20].

Subclinical Cushing's syndrome in patients with diabetes mellitus type 2

It is well known that diabetes mellitus represents a major determinant of the basal tone of the HPA axis, with an increased activity of HPA axis being reported in the pres- ence of chronic complications as well as a bad glycemic control [55–57].

Conversely, chronic hypercortisolism might cause dia- betes mellitus itself [19, 20]. In fact, CS is commonly complicated with an impairment of glucose metabolism, which is often clinically manifested as diabetes mellitus, prevalence of which varies between 20 and 50% [19, 20]. On the other hand, from 1996 various studies have shown a prevalence of unsuspected CS, mainly a SCS, in patients with type 2 diabetes, ranging from 0 to 9.4%, although a surgical improvement was attained in a minority of cases [58–67].

The method of screening was the 1-mg DST in all the cases except in at least two studies, where night salivary cortisol was used [64, 67]; moreover, the studies had a dif- ferent experimental design, as the diabetic population stud- ied differed across the studies (Table 3). In particular, several studies included patients with

clinical features making more likely a diagnosis of hypercortisolism, either hospitalized [58, 60, 61, 64] or outpatients [65–67], while only in one study [63] adult patients with newly diagnosed diabetes mellitus not selected for clinical characteristic were studied.

In a retrospective study on 90 diabetic patients with BMI > 25 and HbA1c > 9% Leibowitz et al. [58] found that about 3% of patients had a definitive diagnosis of SCS. In a prospective study on 200 overweight patients with poorly controlled type 2 diabetes, Catargi et al. [60] reported 2% prevalence of SCS. In a prospective case– control study, Chiodini et al. [61] reported a prevalence of 9.4% in a group of 294 overweight/obese patients with poorly controlled diabetes compared with 189 controls. Recently, Taniguchi et al. [64] found a 2.6% prevalence of SCS in a sample of 77 inpatients with type 2 diabetes.

However, the prospective study of Reimondo et al. [63] recently showed partially different results, as 1% of 100 consecutive patients with newly diagnosed diabetes was found to have a pituitary-dependent CS; in this study, a different population of patients with newly diagnosed diabetes mellitus, not selected for any clinical character- istic, were evaluated, with half of them with an acute presentation requiring emergency admission.

All these above mentioned studies indicate that a sys- tematic screening of hypercortisolism in the diabetic population might be useful and recommended.

On the other hand, the conclusions of at least three other studies [65–67], similarly conducted in patients with an elevated ‘‘a priori’’ probability of hypercortisolemic, were opposite. In fact, the authors did not find any case of SCS in their group of diabetic patients, and so they concluded that widespread screening of for CS in type 2 diabetic population is unjustified.

Two main issues are key to the justification of large- scale screening of CS. First, is occult CS associated with a more severe metabolic and cardiovascular disease? Second, does its cure have a beneficial impact on the outcome of patients? These issues remain mostly undefined by the available studies, because of the small number of diabetic patients found to have CS and submitted for specific treatment. In addition, none of the previous studies repor- ted on long-term data after successful treatment of occult CS. Discrepant results were reported as to the first point [60, 61], although amelioration of diabetes control has been reported in the few patients who attained remission of hypercortisolism [60, 61, 63].

In summary, the results of these studies do not allow us to make definitive conclusion on the utility of the screening for CS in patients with diabetes mellitus, and no consensus does exist, at present, on this topic as well as on the timing of such screening.

Conclusions

Based on the data above reported, although there is convincing evidence in the literature that even a mild hyper- cortisolemia is associated with alterations of glucose metabolism, it is our opinion that evidence is insufficient to conclude that the simple correction of chronic, even mild, hypercortisolism can completely revert metabolic, mainly glycemic alterations. Focusing on patients with SCS asso- ciated to AI, it is not, at present, clarified whether surgery is preferable to a nonsurgical approach to improve glyce- mic control. Until data from high-quality prospective studies will become available, we should recommend sur- gery to younger patients with SCS and to patients who present comorbidities potentially linked to cortisol excess, of recent onset, difficult to control or progressively deteriorating.

At the same time, considering the variability of the prevalence of Cushing's syndrome in patients with diabetes mellitus type 2 reported in the literature, no agreement does exist whether screening for CS can be useful and recom- mended in those patients. For all the above mentioned reasons, along with the associated high costs and workload, it appears that a nationwide screening program for occult CS in all patients with type 2 diabetes is not worthy. At the

same time, it is our opinion that an hormonal screening with 1-mg DST may be recommended only in diabetic patients with clinical features making more likely a diagnosis of CS, like difficult-to-treat diabetes associated with clinical comorbidities potentially linked to hypercortisolism.

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Table 1 Studies reporting prevalence of impaired glucose tolerance (IGT) or diabetes mellitus (DM) at diagnosis in series of at least 10 patients with adrenal incidentalomas

Studies [reference]	Patients (*n*)	SCS prevalence (%)	IGT prevalence (%) SCS vs. non-functioning or controls	DM prevalence (%) SCS vs. all patients
Rossi [30]	65	18.4	17 vs. 12	41.8 vs. 24
Mantero [31]	1,004	9.2	Similar	Similar
Terzolo [32]	41	100	36 vs. 14	5 vs. 0
Tauchmanovà [33]	126	22.2	28.6 vs. not reported	35.7 vs. not reported
Emral [36]	70	5.7	–	50 vs. 34.3
Bernini [38]	115	20	Similar	Similar
Terzolo [39]	210	17.9	–	13.5 vs. 26.2
Sereg [40]	125	10.4	–	23 vs. 23
Vassilatou [41]	77	26	–	20 vs. 22.8
Giordano [42]	118	14	19 vs. 15	19 vs. 15
Comlekci [43]	1,376	10.9	Similar	Similar

Table 2 Studies reporting the outcome of adrenalectomy (ADX) in series of at least 10 patients with adrenal incidentalomas

Studies [reference]	Operated patients (*n*)		Outcome
	With SCS	Without SCS	
Rossi [30]	5	13	ADX improved glucose vs. no change in controls
Midorikawa [46]	4	8	ADX reduced insulin resistance
Bernini [47]	6	9	ADX improved glucose in SCS and non-functioning
Emral [36]	3	7	ADX improved glucose in SCS vs. no change in non-functioning
Erbil [48]	11	–	ADX improved DM in 33%
Mitchel [49]	9	24	ADX improved glucose tolerance in all SCS
Tsuiki [50]	10	–	ADX improved DM in 80% vs. worsening in 60% of controls
Toniato [51]	23	–	ADX improved DM in 38% vs. worsening in 30% of controls
Sereg [40]	5	42	No difference in the frequency of DM between operated and controls
Giordano [42]	6	6	ADX did not improve DM vs. non-functioning
Chiodini [52]	25	30	ADX improved FG with or without SCS vs. controls

Table 3 Studies reporting the prevalence of SCS in series of at least 10 patients with diabetes mellitus

Studies [reference]	Patients (*n*, characteristics)	SCS prevalence (%) Diagnostic criteria
Leibowitz [58]	90 (BMI > 25, HbA1c > 9%)	3.3 UFC (>70 nmol/day), Nugent (>140 nmol/l), Liddle 2 and 8 mg
Catargi [60]	200 (BMI > 25, HbA1C > 8%)	2.0 Nugent (>60 nmol/l), ACTH h 8 (>2–14 pmol/l), F h 8 (>200–700 nmol/l), F h 24 (>71 nmol/l), UFC (20–100 μg/24 h), DST iv 4 mg (>27–66 nmol/l), imaging studies
Chiodini [61]	294 (BMI ≥ 19 and < 50, HbA1C 9.6%) 189 controls	9.4 (2.1 in controls) Nugent (>50 nmol/l) twice + one of the following criteria: a) UFC > 165.6 nmol/day b) ACTH > 2.2 pmol/l c) F24 > 207 nmol/l or DST + CRH test > 38.6 nmol/l
Reimondo [63]	100 (newly diagnosed)	1.0 Nugent (>110 nmol/l) twice, Liddle 2 mg, UFC, F24, ACTH, CRH test, MRI imaging
Taniguchi [64]	77 (BMI = 25, HbA1C = 10.4%)	2.6 NSC (>138 nmol/l), 0.5 mg DST (>83 nmol/l), ACTH (>10 pg/ml), imaging studies
Newsome [65]	171 (BMI > 25)	0 Nugent test (>50 nmol/l), UFC, imaging studies
Gagliardi [66]	106 (BMI > 25, waist > 80 or 94 cm, HbA1C > 8%)	0 NSC (>138 nmol/l), Nugent (>50 nmol/l), UFC (>350 nmol/24 h)
Mullan [67]	201 (BMI > 25, HbA1C > 7%, hypertension) 79 controls	0 NSC (>10 nmol/l), Nugent (>60 nmol/l), Liddle 2 mg, UFC

F Cortisol, *UFC* urinary free cortisol, *DST* dexamethasone test, *NSC* nocturnal salivary cortisol