DIAGNOSIS OF ENDOCRINE DISEASE

Prevalence of hypercortisolism in type 2 diabetes patients: a systematic review and meta-analysis

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Abstract

Objective: Type 2 diabetes (T2D) and Cushing's syndrome (CS) share clinical characteristics, and several small studies have recorded a high prevalence of hypercortisolism in T2D, which could have therapeutic implications. We aimed to assess the prevalence of endogenous hypercortisolism in T2D patients.

Design: Systematic review and meta-analysis of the literature.

Methods: A search was performed in SCOPUS, MEDLINE, and EMBASE for original articles assessing the prevalence of endogenous hypercortisolism and CS in T2D. Data were pooled in a random-effect logistic regression model and reported with 95% confidence intervals (95% CI).

Results: Fourteen articles were included, with a total of 2827 T2D patients. The pooled prevalence of hypercortisolism and CS was 3.4% (95% CI: 1.5–5.9) and 1.4% (95 CI: 0.4–2.9) respectively. The prevalence did not differ between studies of unselected patients and patients selected based on the presence of metabolic features such as obesity or poor glycemic control ($P = 0.41$ from meta-regression). Imaging in patients with hypercortisolism ($n = 102$) revealed adrenal tumors and pituitary tumors in 52 and 14% respectively.

Conclusions: Endogenous hypercortisolism is a relatively frequent finding in T2D, which may have therapeutic implications.

Introduction

Type 2 diabetes (T2D) is a common disease (prevalence ≈ 9%) (1) characterized by insulin resistance and a relative β-cell dysfunction. The clinical picture includes hyperglycemia, obesity, hypertension, and hyperlipidemia. Despite a multimodality treatment approach, T2D patients carry a significant risk for cardiovascular morbidity and mortality (2).

Cushing's syndrome (CS) due to endogenous hypercortisolism, on the other hand, is a very rare condition with an annual incidence of 2–3 per million

(3, 4) and is characterized by hyper-secretion of cortisol as a consequence of either pituitary or adrenal neoplasia, as well as ectopic ACTH-producing tumors. The classic features of overt CS include truncal adiposity, hypertension, dyslipidemia, and diabetes (5). CS is associated with long-term multi-morbidity and an increased mortality risk (6, 7, 8).

Evidently, T2D and CS share many clinical characteristics, and some patients diagnosed with T2D could represent incipient or subclinical CS. A review from

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2012 recorded a wide scatter in the prevalence of CS in T2D ranging between 0 and 9.4% based on 11 studies using different biochemical criteria (9). Proper identification of such patients may have important clinical implications as CS may be curable by surgery, whereas T2D is a chronic disease requiring lifelong medical treatment. However, many unresolved issues remain and it is presently unknown whether it is justifiable to screen for CS in T2D.

The aim of this study is to perform a systematic review and meta-analysis on the prevalence and clinical characteristics of endogenous hypercortisolism in T2D patients.

Methods

Eligibility criteria

Cross-sectional studies and cohort studies assessing the prevalence of hypercortisolism or CS in T2D patients were eligible for inclusion. Eligible articles should present data on hypercortisolism based on at least two of the following biochemical tests: midnight salivary cortisol, midnight serum cortisol, overnight dexamethasone suppression test (1 or 2 mg), low-dose 48-h dexamethasone suppression test, or 24-h urinary free cortisol (10). The definition of a positive test was based on cut-off values used in included articles. The prevalence of hypercortisolism was defined as the number of positive tested patients divided by the total number of tested patients. The prevalence of CS as defined and provided by each article was also extracted.

Inclusion of articles was restricted to articles in English and to articles that included at least ten T2D patients to minimize the risk of selection bias. Articles containing the following populations were also excluded: pregnant women, intensive care patients, and patients receiving corticosteroid treatment. If an article presented data from different study groups in one paper, these groups were assessed for eligibility separately. In case of data from one cohort being published more than once, the article with most complete data was included. Articles that were irretrievable online were requested by contacting the authors.

Search strategy and study selection

We searched three electronic databases, SCOPUS, MEDLINE, and EMBASE, from inception until September 2014. Search terms included controlled vocabulary and keyword searches for (type 2 diabetes) AND (Cushing's syndrome) OR (Cushing's disease) OR (subclinical Cushing's syndrome) OR (hypercortisolism). The search string is available from the corresponding author upon request. Two reviewers independently screened titles and abstracts of articles and reviewed the full text of any title or abstract deemed potentially eligible. Reviewers resolved disagreements by discussion.

Data extraction

Two reviewers independently extracted the following data from included publications: year of publication, number of T2D patients, gender distribution, tests and cut-off values used, results from additionally performed imaging tests (pituitary or adrenal imaging). We extracted the number of T2D patients with hypercortisolism as defined above. In a second step, we extracted the prevalence of CS as defined and reported by the individual studies. Studies were classified according to screening algorithm (i.e., application of different tests in a predetermined sequence).

Risk of bias assessment

With regard to risk of bias assessment, we considered the following design features to be potentially relevant: inclusion and sampling of T2D patients, determination of exposure status (diabetes mellitus), and determination of outcome (hypercortisolism). As we defined eligibility as adequate definition used to determine diabetes and adequate definition for hypercortisolism (see above), all studies could be considered as carrying a low risk of bias. With regard to selection of patients, we considered a low risk of bias, if T2D patients were not selected for testing because of a high pre-test probability of having CS, and if the use of glucocorticoid use was ruled out explicitly.

Statistical analysis

For all studies, we used the number of patients tested positive for hypercortisolism or CS (numerator) and the total number of patients (denominator) to estimate the prevalence of hypercortisolism. Meta-analysis was performed using the STATA *metaprop* command. A random-effects model was used by default given the expected heterogeneity. Meta-regression was performed using an exact likelihood approach (11). Pooled percentages and 95% CIs (confidence interval) were reported for each endpoint. Stata version 12.0 (Statacorp) was used for all analyses.

Results

Study selection and study characteristics

The initial search identified 247 unique publications. By assessment of references of key articles, two additional articles were found. After screening titles and abstracts, 32 publications were considered potentially relevant and subjected to full-text review. Reasons for exclusion are shown in Fig. 1. Finally, 14 articles reporting on the prevalence of hypercortisolism in T2D patients were included.

Study characteristics are summarized in Table 1. Included studies were published between 1996 and 2012. Of the 14 studies, 11 were cohort studies (12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22) and three were case–control studies (of which only data on the group with T2D patients were considered) (23, 24, 25). The 14 study groups contained a total of 2827 T2D patients, none of whom was treated with corticosteroids in any form. No study excluded patients using antidiabetic drugs. The reported mean age of the patients ranged from 53.5 to 63 years, mean BMI of the patients ranged from 25.0 to 34.5 kg/m^2, and mean HbA1c ranged from 7.7 to 12.2%. As regards first-step screening, 13 studies used biochemical testing and one study (22) used abdominal CT scan; nine studies were based on inclusion of outpatients, (13, 14, 15, 17, 20, 21, 22, 23, 24) 4 studies on inpatients (12, 16, 19, 25), and one on both inpatients and outpatients (18).

Methods used to determine hypercortisolism

All studies used a screening algorithm, the composition of which, however, differed considerably between the different studies. The tests most often used as first-step screening were 1 mg overnight dexamethasone
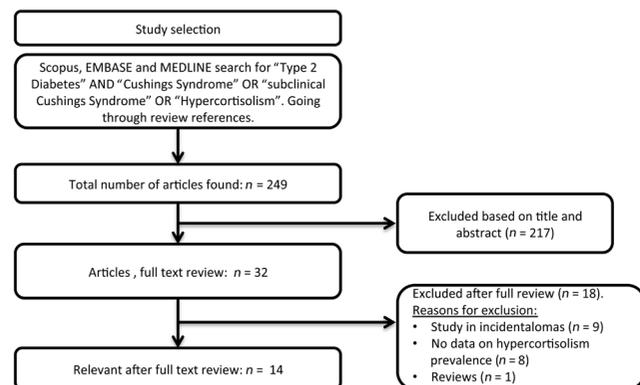

Figure 1
Flow chart of study selection.

Table 1 Characteristics of included studies.

Study	Number of diabetic participants (%)	Male/ female	Number of patients with hypercortisolism (%)	MSC (%)	MPC (%)	OD (%)	LDDST (%)	ACTH elevated (%)	UFC (%)	Pituitary adenoma (%)	Adrenal adenoma (%)	Ectopic adenoma (%)	Number of patients with CS (%)
1 (14)	90 (100)	26/64	3 (3.3)			4 (4.4)	3 (3.3)	0 (0)	3 (3.3)	2 (2.2)	1 (1.1)	0 (0)	3 (3.3)
2 (12)	200 (100)	49/151	17 (8.5)	2 (1)	17 (8.5)	52 (26)			17 (8.5)	3 (1.5)	8 (4)	0 (0)	4 (2)
3 (25)	289 (100)	124/165	35 (12.1)			51 (17.6)		5 (1.7)	8 (2.7)	4 (1.4)	21 (7.1)	2 (0.7)	27 (9.3)
4 (24)	141 (100)	141/0	4 (2.8)	28 (19.9)			4 (2.8)	3 (2.1)	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)
5 (21)	103 (100)	34/69	8 (7.8)	12 (11.7)		29 (28.2)	1 (0.9)	2 (1.9)	0 (0)	1 (0.9)	4 (3.9)	0 (0)	0 (0)
6 (18)	100 (100)	67/37	1 (1)		1 (1)	5 (5)	1 (1)	1 (1)	1 (1)	1 (1)	0 (0)	0 (0)	1 (1)
7 (17)	171 (100)	102/69	1 (0.6)			31 (18.1)			3 (1.8)	0 (0)	0 (0)	0 (0)	1 (0.6)
8 (19)	77 (100)	47/30	6 (7.8)		27 (35)	7 (9)		6 (7.8)		2 (2.6)	0 (0)	0 (0)	2 (2.6)
9 (13)	100 (100)	60/40	0 (0)	3 (3)	0 (0)	0 (0)		0 (0)	0 (0)				0 (0)
10 (22)	304 (100)	181/123	7 (0.3)			1 (0.3)	1 (0.3)	1 (0.3)	0 (0)	0 (0)	14 (4.6)	0 (0)	1 (0.3)
11 (23)	201 (100)	119/91	7 (3.5)	47 (23)		7 (3.5)	0 (0)		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
12 (16)	90 (100)	53/37	9 (10)		57 (63.3)	9 (10)		0 (0)					8 (8.9)
13 (15)	148 (100)	35/113	4 (2.6)			9 (6.2)	4 (2.6)			2 (1.4)	2 (1.4)	0 (0)	4 (2.7)
14 (20)	813 (100)	428/385	6 (0.7)			40 (4.9)	6 (0.7)	1 (0.12)		0 (0)	3 (0.4)		6 (0.7)

LDDST, low-dose dexamethasone suppression test (48h); MCS, midnight salivary cortisol; MPC, midnight plasma cortisol; UFC, Urinary free cortisol.

Table 2 Screening algorithm.

Study	MSC	EC	MC	OD	LDDST	UFC	CRH	DST	DDAVP	ACTH	Imaging
(14)		2		1	2	2				2	3
(12)		2	2	1		2		2		2	3
(25)			2	1		2	2			2	3
(24)	1			2	3	2				4	5
(21)	1			1	2	3				3	4
(18)			3	1	2	3	3			3	4
(17)				1		2					
(19)			1	2						3	4
(13)	1			3		3				2	
(22)				2	2					2	1
(23)	1			2	3	3					
(16)		1	1	2					3	1	
(15)				1	2					2	3
(20)				1	2	3				3	4

1: First-line screening test; 2: second-line screening test; 3: third-line screening test; 4: fourth-line screening test; 5: fifth-line screening test.
ACTH, adrenocorticotrophin hormone; DDAVP, desmopressin test; DST, IV dexamethasone suppression test (4 mg); EC, early (morning) serum cortisol; LDDST, low-dose dexamethasone suppression test; MC, midnight serum cortisol; MSC, midnight salivary cortisol; OD, overnight dexamethasone suppression test (1 or 2 mg); UFC, urinary free cortisol corticotrophin releasing hormone test.

suppression test ($n=7$) and midnight salivary cortisol ($n=3$). Imaging was performed as third-step examination in 11 articles. In two articles, imaging was not performed as no patients with hypercortisolism or abnormal ACTH were found (13, 16). An overview of performed tests and their sequence is provided in Table 2. Seven studies diagnosed CS based on both positive biochemical tests and positive imaging (14, 15, 18, 19, 23, 24, 25), three studies used positive biochemical tests only, (16, 20, 22) and two studies required peroperative or histological evidence of an underlying tumor (12, 21).

Risk of bias

Three studies included a random selection of T2D patients, whereas 11 studies included patients with specific metabolic features such as poor glycemic control ($n=3$), hypertension ($n=1$), or BMI > 25 kg/m² ($n=9$). Exclusion of patients with concomitant use of corticosteroids was explicitly reported in all articles, as were patients with classic phenotypically features of CS.

Meta-analysis of prevalence of hypercortisolism in T2D

The prevalence of hypercortisolism ranged between 0 and 12.1% with a median of 3.6% (Fig. 2). The pooled prevalence from a random-effects model was 3.4% (95% CI: 1.5–5.9). The prevalence of hypercortisolism did not differ between studies with T2D as the only selection criteria and studies including T2D patients selected on the basis of additional features such as obesity and poor metabolic control ($P=0.41$ from meta-regression). Excluding the study from Hiroi and coworkers, which applied an inclusion criterion of abnormal imaging, did not influence the pooled estimate 4.2% (95% CI: 2.5–5.9). The prevalence of CS as defined and reported by the individual studies was 1.4% (95% CI: 0.4–2.9) (Fig. 3).

Imaging was performed in 102 patients with hypercortisolism, which revealed adrenal adenoma(s) or pituitary tumor in 53 (52%) and 15 (15%) patients respectively. Two patients (1.9%) were diagnosed with an ectopic tumor (Table 1).

Discussion

The aim of this study is to perform a systematic review and meta-analysis of the prevalence of hypercortisolism in T2D patients. Our study revealed a mean prevalence of hypercortisolism in 3.4% of T2D patients. This figure is based on our biochemical pre-definition of hypercortisolism, which we implemented to allow for a comparison between the studies. The prevalence of CS as defined by each study was lower (1.4%), which reflects the inclusion of additional criteria such as positive imaging or a histologically proven tumor. Subsequent imaging performed in the patients with hypercortisolism revealed either adrenal adenoma(s) or a pituitary adenoma in 52 and 15%, respectively, which points toward a potentially curable condition in these patients. In seven of the studies including 1873 patients (12, 14, 18, 19, 20, 22, 25),

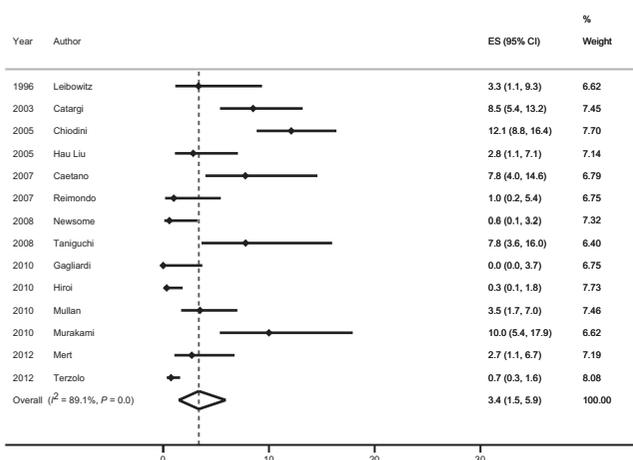## Hypercortisolism in type 2 diabetes

Figure 2

Prevalence of hypercortisolism in type 2 diabetes.

post-surgical outcome data were provided. Each of the 17 post-surgically evaluated patients (0.9%) showed significantly improved glycemic control, and weight loss and lowering of blood pressure were occurred in a subset.

Some studies only included patients with poor glycemic control, high BMI, or hypertension, and as an association between poor metabolic control and hypercortisolism has been suggested (26), such inclusion criteria might translate into a higher prevalence of hypercortisolism. However, the prevalence estimates did not differ in a meta-regression between studies with T2D as the only selection criteria and studies with additional

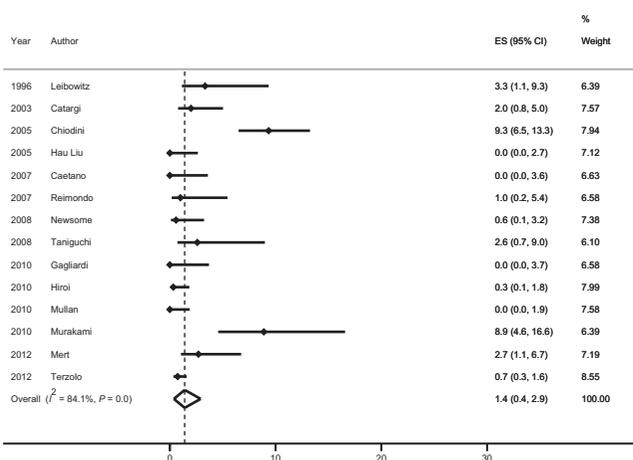## Cushing's Syndrome in type 2 diabetes

Figure 3

Prevalence of Cushing's syndrome in type 2 diabetes.

T2D-related selection criteria. It might however well be that more detailed phenotyping is able to detect DM patients at high risk for hypercortisolism.

Previous studies show an annual incidence of classic CS of 2.5/million, with pituitary adenomas accounting for ≈60% and benign adrenal adenomas ≈25% (3, 4, 7). This exemplifies the rarity of classic CS and also indicates that the etiology and pathogenesis of hypercortisolism in T2D differ from classic CS. Even though the natural history and clinical consequences of hypercortisolism detected during screening in T2D remain uncertain, it is noteworthy that adrenal adenomas are revealed in ≈50% of T2D with endogenous hypercortisolism. This is compatible with the high prevalence of so-called adrenal incidentalomas, where some degree of cortisol overproduction is encountered in 7.9% (27). Along this line, it is interesting that the incidence rate of diagnosed and operated patients with adrenal CS increased by more than 100% in 2000–2010 compared with 1980–1999 in a recent population-based study (7). Of additional interest, the mean age of the patients diagnosed between 2000 and 2010 had also increased (from 40 to 53 years) (7). The mechanisms underlying these observations are uncertain, but increased imaging is a plausible explanation.

Imaging was negative in 31% of T2D patients with documented hypercortisolism in this meta-analysis. To which degree hypercortisolism in T2D patients with negative imaging may reflect an underlying inflammatory component of T2D involving activation of the HPA axis (28) is uncertain. It is also possible that elevated cortisol levels occurred as a counter regulatory neuroendocrine response to hypoglycemia in T2D patients treated with insulin or sulfonylurea (29). Unfortunately, we were unable to retrieve data on antidiabetic treatment at the level of individual patients in this meta-analysis.

None of the studies in the present meta-analysis provided a concise distinction between subclinical and overt cases of CS among their patients with biochemical hypercortisolism, which is a limitation.

Screening for hypercortisolism in T2D patients is at present time only recommended if a patient shows signs and symptoms of CS (10). Screening interventions are designed to early identification of disease in a community setting to enable early intervention in order to reduce morbidity and mortality of the disease (30). Obviously, screening is associated with untoward effects including over diagnosis and side effects of the provided treatment.

According to the World Health Organization, the prevalence of diabetes in the adult European population

is approximately 10% (http://www.euro.who.int/en/health-topics/noncommunicable-diseases/diabetes/data-and-statistics). If 0.9% of these patients in fact have hypercortisolism, associated diabetes due to a resectable tumor, more than 0.5 million people in Europe alone could potentially be cured of diabetes. This number is clearly an exaggeration, but it may help to promote the understanding of the challenges and possibilities. It is important to note that no study so far has documented a clear effect of surgical removal of adenomas in patients with subclinical CS.

In conclusion, the present meta-analysis reveals a relatively high prevalence of endogenous hypercortisolism and CS in T2D patients and a substantial proportion of the cases also presented with adrenal or pituitary neoplasia, which could provide the basis for surgical intervention. These findings may have therapeutic implications and controlled trials should be considered.

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