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Original Article

When to Suspect Hidden Hypercortisolism in Type 2 Diabetes: A Meta-Analysis

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ABSTRACT

Objective: To investigate whether the available literature helps to identify the characteristics of patients with type 2 diabetes (T2D) more frequently associated with hidden hypercortisolism (HidHyCo).
Methods: A meta-analysis was performed using studies that assessed both the prevalence of HidHyCo in patients with T2D and the characteristics of these patients with and without HidHyCo. The DerSimonian and Laird (DSL) and Hartung-Knapp-Sidik-Jonkman (HKSJ) methods were utilized.
Results: Among the 18 available studies, 6 provided the necessary data. The association between HidHyCo and advanced T2D (based on the patients' description given in each study in the presence of microvascular/macrovascular complications or insulin treatment plus hypertension or hypertension treated with 2 or more drugs), hypertension, insulin treatment, and dyslipidemia was reported in 5 (2184 patients), 6 (2283 patients), 3 (1440 patients), and 3 (987 patients) studies, respectively. HidHyCo was associated with advanced T2D as assessed by both the DSL (odds ratio [OR], 3.4; 95% confidence interval [95% CI], 2.12-5.67) and HKSJ (OR, 3.60; 95% CI, 2.03-6.41) methods and with the prevalence of hypertension or insulin treatment as assessed by the DSL method (OR, 1.92; 95% CI, 1.05-3.50 and OR, 2.29; 95% CI, 1.07-4.91, respectively) but not as assessed by the HKSJ method.
Conclusion: Patients with advanced T2D have a higher prevalence of HidHyCo. These data inform about the selection of patients with T2D for HidHyCo screening.

Introduction

Clinically overt hypercortisolism (Cushing syndrome) is known to cause hypertension, diabetes mellitus, and osteoporosis.[1] More recently, less severe and clinically less apparent hypercortisolism (previously known as "subclinical hypercortisolism" or "mild

Abbreviations: CI, confidence interval; DSL, DerSimonian and Laird; HidHyCo, hidden hypercortisolism; HKSJ, Hartung-Knapp-Sidik-Jonkman; 1mg-DST, 1-mg overnight dexamethasone suppression test; OR, odds ratio; T2D, type 2 diabetes.

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autonomous cortisol secretion," frequently found in patients with incidentally discovered adrenal adenomas) has been associated with an increased prevalence of chronic diseases potentially mediated by cortisol excess. These include type 2 diabetes (T2D), hypertension, and osteoporosis.[2] This subtle hypercortisolism, characterized by the presence of biochemical cortisol excess in the absence of the typical signs and symptoms of Cushing syndrome (ie, striae rubrae, buffalo hump, hypertrichosis, plethora, and easy bruising), is associated with an increased mortality due to an increased risk of cardiovascular events and infections.[3] Because less severe hypercortisolism is clearly not "subclinical," hidden hypercortisolism (HidHyCo) is a better term, appearing in current literature, describing this condition. Underlying HidHyCo in patients with T2D, hypertension, or osteoporosis may remain occult until its presence is suspected because of the progression and/or severity of the associated chronic diseases.[4]

The prevalence of HidHyCo in the general population is estimated to be 0.2% to 2%, but it has been suggested to be even higher (up to 10%) in some specific populations as, for example, in patients with fragility fracture or T2D.[1,2,5-7] The HidHyCo diagnosis is significant because patients affected with this form of hypercortisolism generally experience a reduction of fracture risk and an improvement in glycemic control in patients with T2D after the normalization of cortisol levels.[8,9]

Notwithstanding this, the high prevalence of T2D, hypertension, and osteoporosis in the general population and the relatively low specificity of the currently available tests for the HidHyCo detection make mass screening for HidHyCo among all patients with osteoporosis and T2D neither feasible nor recommended.[10-14] Although some guidance can be found in the literature regarding which patients with osteoporosis should be screened for HidHyCo, similar guidance for HidHyCo screening among patients with T2D is lacking. Indeed, even if several studies have assessed the prevalence of HidHyCo in patients with T2D, data regarding T2D patient characteristics more frequently associated with HidHyCo have not been consistently reported.[15-33]

The present study aimed to investigate if the current literature can be used to identify clinical characteristics of patients with T2D that are associated with an increased prevalence of HidHyCo. We have performed a meta-analysis of studies designed to assess HidHyCo prevalence in T2D patient populations in an attempt to define distinguishing clinical characteristics of patients with T2D with HidHyCo compared with those without HidHyCo.

Materials and Methods

Search Strategy and Eligibility Criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines have been followed for carrying out the meta-analysis. PubMed, Scopus, Web of Science, and ScienceDirect were searched between August 1990 and April 2021 using the phrases "diabetes and hypercortisolism" or "diabetes and Cushing syndrome" or "diabetes and cortisol excess" or "diabetes and subclinical Cushing syndrome" or "diabetes and mild hypercortisolism" as key words (Fig. 1). The Mendeley Desktop application (version 1.18, Mendeley Ltd) was used to remove the duplicates and apply the inclusion criteria. No language limits were applied.

We included all original studies (excluding case reports, review articles, editorial, and meta-analyses) specifically designed to evaluate the prevalence of HidHyCo in patients with T2D and reporting the clinical characteristics of patients with T2D with HidHyCo compared with patients with T2D without HidHyCo.

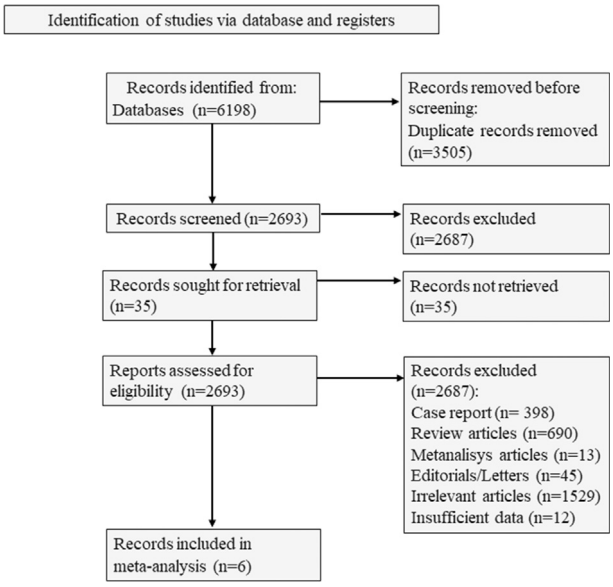

Fig. 1. Study selection process. PubMed, Scopus, Web of Science, and ScienceDirect were searched between August 1990 and April 2021, using the phrases "diabetes and hypercortisolism" or "diabetes and Cushing syndrome" or "diabetes and cortisol excess" or "diabetes and subclinical Cushing syndrome" or "diabetes and mild hypercortisolism" as key words.

Selection Studies and Data Extraction

The studies reporting less than 5 patients affected by HidHyCo and/or those studies not reporting the clinical characteristics of patients with HidHyCo and/or of patients without HidHyCo have been excluded as they did not provide enough useful data.[16-27]

For the diagnosis of HidHyCo, we used the definition reported in the included studies: 1 mg overnight dexamethasone suppression test (1mg-DST) > 1.8 μg/dL in 1 study, 1mg-DST > 5 μg/dL in 1 study, 1mg-DST > 1.8 μg/dL plus late night salivary cortisol 0.35 μg/dL in 1 study, 1mg-DST > 1.8 μg/dL plus late night salivary cortisol > 0.5 μg/dL in 1 study, 2-mg 2-day (low dose) dexamethasone suppression test >1.8 μg/dL plus late night serum cortisol > 7.5 μg/dL in 1 study, and 1mg-DST > 1.8 μg/dL plus low dose dexamethasone suppression test > 1.8 μg/dL plus urinary free cortisol levels above the limit of the normal range (ie, ≥109 μg/24 hour) in 1 study.[28-33]

Two authors (C.A. and I.C.) independently screened titles and abstracts and reviewed the full text of potentially relevant studies. Questionable studies were discussed among these 2 authors prior to the determination of inclusion eligibility.

The following data were extracted from the included studies when available: authors, study location, period of the year, data collection and study design, sample size, mean age, percentage of male patients, ethnicity, type of outcome (ie, clinical characteristics of patients with HidHyCo compared with those without HidHyCo), prevalence of outcome, association estimate (odds ratios [ORs] and 95% confidence intervals [CIs]), and use of adjustment approach for the association estimate. In the presence of studies with zero-cell counts, we added a fixed value equal to 0.5 to all cells of the study to estimate the raw OR.[34,35]

The same investigators independently assessed the quality of the included studies using the Newcastle-Ottawa Scale.[36] Discrepancies were discussed among the authors and resolved by consensus. The present meta-analysis has been registered on International Prospective Register of Systematic Reviews (PROSPERO) (ID CRD42021245183).

Statistical Analysis

Random-effects meta-analysis is commonly performed by first deriving an estimate of the between-study variation, the heterogeneity, and subsequently using this as the basis for combining results, that is, for estimating the effect, the figure of primary interest.[37] The DerSimonian and Laird (DSL) method is a conventional and widely used approach for random-effects meta-analysis. However, in some circumstances, particularly when the number of studies is small and there is moderate or substantial between-study heterogeneity, this method results in increased type I error rates (ie, false-positive assignment of statistical significance).[38] To address this issue, Hartung, Knapp, Sidik, and Jonkman proposed a modified method (Hartung-Knapp-Sidik-Jonkman [HKSJ] method) for calculating the summary association estimates and their 95% CI. The HKSJ method usually leads to more conservative results with wider CIs. We applied the HKSJ method for evaluation of each comorbidity/condition related to HidHyCo. As recommended by several authors, we also conducted a sensitivity analysis using results from the more conventional meta-analytical approach (DSL).[39] Forest plots were constructed for each comorbidity/condition. We implemented an influence analysis to investigate the impact of each study-specific association estimate on the pooled OR. Results were considered statistically significant when the 2-tailed *P* value was lower than .05. All analyses were performed with R version 4.0.3 (R Foundation for Statistical Computing).

Results

Study Selection Process

The study selection process is summarized in Figure 1. We identified 6198 studies from the different searched databases and excluded 3505 studies for duplication. The remaining 2693 studies were first screened by reading the title and abstract. All studies reporting the clinical characteristics (ie, prevalence of T2D chronic complications and need of insulin treatment) and/or other comorbidities (ie, hypertension, dyslipidemia, obesity, and cardiovascular events) of patients with T2D with HidHyCo compared with those without HidHyCo were evaluated for inclusion. A total of 2687 studies were excluded as they were case reports (n = 398), review articles (n = 69), meta-analysis articles (n = 13), and editorial or letters (n = 45) or because they were not relevant for the aims of the present meta-analysis (n = 1529). Among the remaining 18 studies, 12 were excluded due to insufficient data, as reported in Table 1.[16-27] The interrate reliability between the 2 authors in selection process was strong ($\kappa = 0.88$).[40]

Study Characteristics

The characteristics of the 6 studies that were used in the meta-analysis are summarized in Table 2.[28-33] Among the 6 included studies, data collection was prospective in 4 studies, whereas it was not reported in 2 studies. The outcomes derivable from these studies were the prevalence of hypertension, need of insulin treatment, status of advanced diabetes, and prevalence of dyslipidemia. All 6 included studies reported the association between the prevalence of HidHyCo and hypertension, 3 reported the association between the prevalence of HidHyCo and the need of insulin treatment, 3 reported the association between the prevalence of HidHyCo and the prevalence of dyslipidemia, and 5 reported the association between the prevalence of HidHyCo and the prevalence of advanced T2D. The definition of advanced T2D has been assigned on the basis of the patients description given in each study: prevalence of microvascular and/or macrovascular complications in 2 studies, prevalence of insulin treatment plus hypertension in 2 studies, and prevalence of hypertension treated with 2 or more drugs in 1 study.[28,30-33]

No study reported the prevalence of obesity among patients with T2D without HidHyCo; thus, we could not include obesity among the outcomes. However, 5 of the 6 studies showed that the mean body mass index of patients with T2D with HidHyCo was not different compared with that of patients with T2D without HidHyCo (Supplementary Table 1).[28-31] The geographic areas of the included studies were Europe (n = 3), Middle East Asia (n = 1), and South America (n = 2). The quality of included studies varied (Newcastle-Ottawa Scale between 6 and 8). The measured outcomes, sample sizes, and number of cases meeting outcomes in patients with HidHyCo and in controls, evaluated in the 6 included studies, are listed in Table 3.

Table 1
Summary of the Main Characteristics of the Excluded Studies

Author	Country	Sample (N)	Reasons for exclusion
Catargi et al, 2003[20]	France	200	No data on comorbidities in patients with T2D with and without HidHyCo
Reimondo et al, 2007[21]	Italy	100	Only 1 patient with confirmed HidHyCo; no data on comorbidities in patients with T2D without HidHyCo
Budyal et al, 2015[18]	India	993	No confirmed HidHyCo cases
Contreras et al, 2000[17]	Argentina	48	Only 1 patient with confirmed HidHyCo; no data on comorbidities in patients with T2D without HidHyCo
Gagliardi et al, 2010[26]	Australia	106	No confirmed HidHyCo cases
Mert et al, 2012[27]	Turkey	148	No data on comorbidities in patients with T2D with and without HidHyCo
Leibowitz et al, 1996[16]	Israel	63	No data on comorbidities in patients with T2D with and without HidHyCo
Mullan et al, 2010[25]	United Kingdom	201	No confirmed HidHyCo cases
Murakami et al, 2010[24]	Japan	90	No data on comorbidities in patients with T2D with and without HidHyCo
Newsome et al, 2007[22]	Australia	171	No confirmed HidHyCo cases
Taniguchi et al, 2008[23]	Japan	77	Only 2 patients with confirmed HidHyCo; no data on comorbidities in patients with T2D without HidHyCo
Liu H et al, 2005[19]	United States	154	No confirmed HidHyCo cases

Abbreviations: T2D = type 2 diabetes; HidHyCo = hidden hypercortisolism.

Table 2
Summary of Characteristics and Quality Evaluation by the Newcastle-Ottawa Scale Scores of the Studies Included in the Meta-Analysis

Author	Country	Period	Study design	Sample size (N)	Age (years)	Males (%)	Ethnicity	NOS score (0-9)
Outcome: hypertension								
Chiodini et al[28]	Italy	January 2003 to December 2004	Prospective	289	60.0	49	Caucasian	8
Terzolo et al[30]	Italy	June 2006 to April 2008	Prospective	813	58.9	53	Caucasian	7
Caetano et al[29]	Brazil	NA	NA	99	56.4	32	Black	6
Costa et al[31]	Brazil	May 2013 to August 2014	Prospective	298	58.4	36	Black	7
Cansu et al[32]	Turkey	NA	NA	400	56.0	48	NA	6
Steffensen et al[33]	Denmark	NA	Prospective	384	60.0	60	Caucasian	7
Outcome: insulin treatment								
Chiodini et al[28]	Italy	January 2003 to December 2004	Prospective	289	60.0	49	Caucasian	8
Terzolo et al[30]	Italy	June 2006 to April 2008	Prospective	813	58.9	53	Caucasian	7
Costa et al[31]	Brazil	May 2013 to August 2015	Prospective	298	58.4	36	Black	7
Outcome: dyslipidemia								
Chiodini et al[28]	Italy	January 2003 to December 2004	Prospective	289	60.0	49	Caucasian	8
Costa et al[31]	Brazil	May 2013 to August 2016	Prospective	298	58.4	36	Black	7
Cansu et al[32]	Turkey	-	NA	400	56.0	48	NA	6
Outcome: advanced T2D								
Chiodini et al[28]	Italy	January 2003 to December 2004	Prospective	289	60.0	52	Caucasian	8
Terzolo et al[30]	Italy	June 2006 to April 2008	Prospective	813	58.9	61	Caucasian	7
Costa et al[31]	Brazil	May 2013 to August 2016	Prospective	298	58.4	71	Black	7
Cansu et al[32]	Turkey	NA	NA	400	56	62	NA	6
Steffensen et al[33]	Denmark	NA	Prospective	384	58.7	61	Caucasian	7

Abbreviations: NA = not available; NOS = Newcastle-Ottawa Scale; T2D = type 2 diabetes.
The outcomes are the variables possibly associated with the presence of hidden hypercortisolism (HidHyCo) in studies specifically designed to assess the HidHyCo prevalence in patients with type 2 diabetes (T2D). Advanced T2D: presence of microvascular and/or macrovascular complications or presence of insulin treatment plus hypertension or presence of hypertension treated with 2 or more drugs.[28,30-33]

As expected, the overall HidHyCo prevalence in patients with T2D reduced as the specificity of the criteria used for HidHyCo screening increased. Indeed, as shown in Supplementary Table 2, the studies by Terzolo et al[30] and Costa et al[31] that used more specific—and therefore less sensitive—criteria had the lowest HidHyCo prevalence (0.7% and 1.3%, respectively); the studies by Steffensen et al[33] and Caetano et al[29] that used criteria with an intermediate specificity found prevalence rates of HidHyCo of 5.2% and 8.1%, respectively; and the studies by Chiodini et al[28] and Costa et al[31] that used less specific criteria found prevalence rates of HidHyCo of 10.4% and 11.1%, respectively.

At variance, the T2D duration was not reported to be different in patients with T2D with HidHyCo compared with patients with T2D without HidHyCo in any of the included study (Supplementary Table 2).

Association Between the HidHyCo Prevalence and the Reported Outcomes

The forest plot illustrating the association between the prevalence of hypertension and HidHyCo in patients with T2D is shown in Figure 2, and the results are summarized in Table 4.[28,30-32] All 6 included studies (total of 2283 patients) reported the prevalence of hypertension in patients with T2D; this prevalence was higher in patients with HidHyCo (86.3%) than in patients without HidHyCo (69.8%). The prevalence of hypertension was significantly associated with HidHyCo using the DSL method (OR, 1.92; 95% CI, 1.05-3.50; $P = .034$) but not when the HKSJ method was used (OR, 2.13; 95% CI, 0.81-5.65; $P = .100$).

The forest plot illustrating the association between the prevalence of insulin treatment and HidHyCo in patients with T2D is shown in Figure 2, and the results are summarized in Table 4.[28,30-32] Three studies (total of 1400 patients) reported the prevalence of insulin treatment in patients with T2D; this prevalence was higher in patients with HidHyCo (53.6%) than in patients without HidHyCo (25.8%). The prevalence of insulin treatment was significantly associated with HidHyCo using the DSL method (OR, 2.29; 95% CI, 1.07-4.91; $P = .034$) but not when the HKSJ method was used (OR, 2.50; 95% CI, 0.30-21.01; $P = .205$).

The forest plot illustrating the association between the prevalence of dyslipidemia and HidHyCo in patients with T2D is shown in Figure 2, and the results are summarized in Table 4.[28,30-32] Three

Table 3
Number of Included Studies and Sample Size Considered for Each Specific Outcome

Outcome	Included studies, n	Total subjects, n	HidHyCo cases, n	HidHyCo cases meeting the outcome, n (%)[a]	Controls meeting the outcome, n (%)[b]
Hypertension	6	2283	102	88 (86.3)	1550 (69.8)
Insulin treatment	3	1400	69	37 (53.6)	343 (25.8)
Dyslipidemia	3	987	68	46 (67.6)	581 (63.2)
Advanced T2D[c]	5	2184	94	46 (48.9)	655 (31.5)

Abbreviations: HidHyCo = hidden hypercortisolism; T2D = type 2 diabetes.
The outcomes are the variables possibly associated with the presence of HidHyCo in studies specifically designed to assess the HidHyCo prevalence in patients with T2D. Cases: patients with T2D with HidHyCo. Cases meeting the outcome: patients with HidHyCo with hypertension or insulin treatment or severe T2D or dyslipidemia. Controls: patients with T2D without HidHyCo. Controls meeting the outcome: patients with T2D without HidHyCo and with hypertension or insulin treatment or severe T2D or dyslipidemia.
[a] The percentage is referred to the total number of HidHyCo cases.
[b] The percentage is referred to the total number of controls.
[c] Advanced T2D: presence of microvascular and/or macrovascular complications or presence of insulin treatment plus hypertension or presence of hypertension treated with 2 or more drugs.[28,30-32]

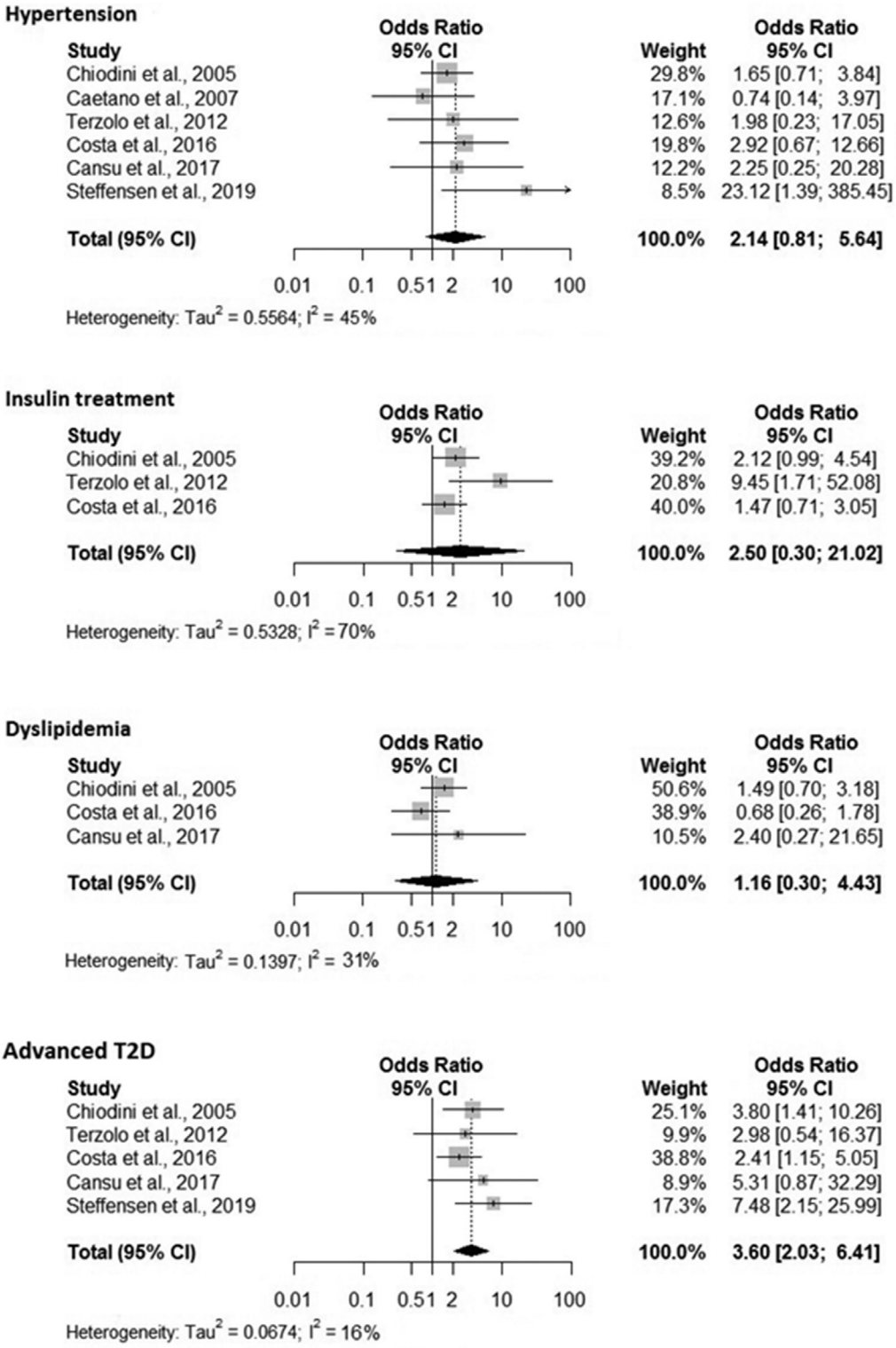

Fig. 2. Forest plots illustrating the association between the prevalence of advanced T2D or the need of insulin treatment or the presence of hypertension or of dyslipidemia and hidden hypercortisolism in patients with T2D. Advanced T2D: presence of microvascular and/or macrovascular complications or presence of insulin treatment plus hypertension or presence of hypertension treated with 2 or more drugs.[28,30-32] The Hartung, Knapp, Sidik, and Jonkman method for calculating the summary association estimates and their 95% CIs has been used. *T2D* = type 2 diabetes.

studies (total of 987 patients) reported the prevalence of dyslipidemia in patients with T2D; this prevalence was higher in patients with HidHyCo (67.6%) than in patients without HidHyCo (63.2%). The prevalence of dyslipidemia was not significantly associated with HidHyCo using either the DSL (OR, 1.16; 95% CI, 0.65-2.07; $P = .510$) or HKSJ (OR, 1.16; 95% CI, 0.30-4.43; $P = .686$) method.

The forest plot illustrating the association between the prevalence of advanced T2D and HidHyCo in patients with T2D is shown

Table 4
Odds Ratios and 95% Confidence Intervals for the Associations Between HidHyCo and the Presence of Hypertension, Insulin Treatment, Advanced Type 2 Diabetes, and Dyslipidemia in Studies Assessing the HidHyCo Prevalence in Patients With Type 2 Diabetes

Method: Hartung-Knapp-Sidik-Jonkman					
Potential predictors of HidHyCo	OR	95% CI	*P* value	I^2	Studies (n)
AH	2.13	0.81-5.65	.100	45%	6
Insulin treatment	2.50	0.30-21.01	.205	70%	3
Advanced T2D[a]	3.60	2.03-6.41	.004	16%	5
DL	1.16	0.30-4.43	.686	31%	3
Method: DerSimonian and Laird					
AH	1.92	1.05-3.50	.034	0%	6
Insulin treatment	2.29	1.07-4.91	.034	48%	3
Advanced T2D[a]	3.47	2.12-5.67	<.0001	0%	5
DL	1.16	0.65-2.07	.510	1%	3

Abbreviations: AH = hypertension; DL = dyslipidemia; HidHyCo = hidden hypercortisolism; I^2 = grade of heterogeneity; OR = odds ratio; T2D = type 2 diabetes.
[a] Advanced T2D: presence of microvascular and/or macrovascular complications or presence of insulin treatment plus hypertension or presence of hypertension treated with 2 or more drugs.[28,30-32]

in Figure 2, and the results are summarized in Table 4.[28,30-32] Five studies (total of 2184 patients) reported the prevalence of advanced T2D in patients with T2D; this prevalence was higher in patients with HidHyCo (48.9%) than in patients without HidHyCo (31.5%).The prevalence of advanced T2D was significantly associated with HidHyCo using both the DSL (OR, 3.4; 95% CI, 2.12-5.67; $P < .0001$) and HKSJ (OR, 3.60; 95% CI, 2.03-6.41; $P = .004$) methods. These results did not substantially change even considering the association between the presence of HidHyCo and that of advanced T2D as defined by the presence of hypertension treated with 2 or more drugs and/or insulin treatment or as the presence of T2D complications, even though for this latter association, the statistical significance was not reached due to the large studies' heterogeneity (Supplementary Fig. 1).[28,30-33] Finally, the influence analysis did not show a relevant impact of the single study-specific association estimate on pooled ORs between the presence of HidHyCo and either advanced T2D or hypertension (Fig. 3).

Discussion

The present study attempted to use data available in current literature to identify the clinical characteristics of patients with T2D that are associated with an increased prevalence of HidHyCo. We performed a meta-analysis of studies designed to assess HidHyCo prevalence in T2D patient populations in an attempt to define distinguishing clinical characteristics of patients with T2D with

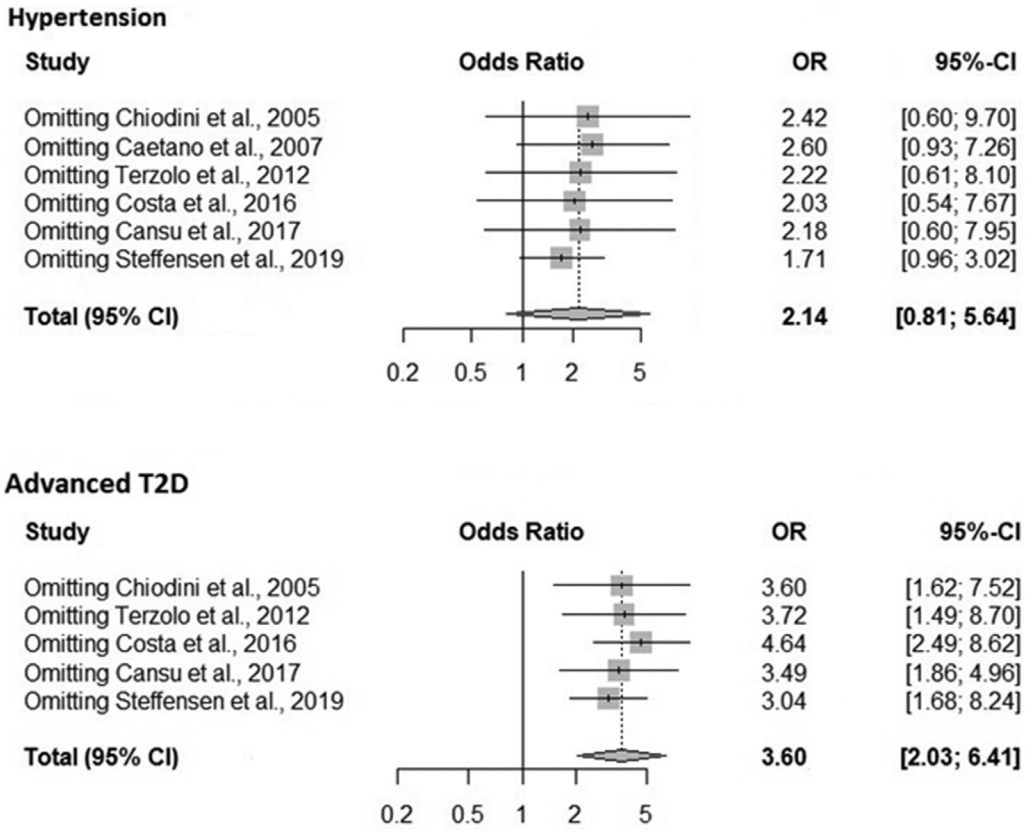

Fig. 3. Influence analysis on the impact of study-specific association estimate on pooled ORs. *OR* = odds ratio.

HidHyCo compared with those without HidHyCo. The prevalence of advanced T2D was significantly associated with increased odds of HidHyCo in patients with T2D using 2 different analytical methods. The prevalence of hypertension and that of requirement for insulin treatment were significantly associated with increased odds of HidHyCo in patients with T2D using 1 of the 2 analytical methods employed (DSL). In contrast, the prevalence of dyslipidemia, variously defined, was not significantly associated with increased odds of HidHyCo using either method.

In the present meta-analysis, all studies reporting the clinical characteristics (ie, prevalence of T2D chronic complications and need of insulin treatment) and/or other comorbidities (ie, hypertension, dyslipidemia, obesity, and cardiovascular events) of patients with T2D with HidHyCo compared with those without HidHyCo were potentially eligible for inclusion. However, the available studies provided data on the association between the prevalence of HidHyCo and only hypertension, advanced T2D, need of insulin treatment, and dyslipidemia. Quite surprisingly, no study reported the prevalence of obesity among patients with T2D without HidHyCo; thus, we could not include obesity among the outcomes. However, 5 of the 6 studies showed that the mean body mass index of patients with T2D with HidHyCo was not different compared with that of patients with T2D without HidHyCo (Supplementary Table 1).[28-31,33] Thus, to date, we have no data to consider obesity as an additional risk factor for patients with T2D to have HidHyCo. This is in contrast with the recent finding that obesity was found to be among the comorbidities independently predictive of hypercortisolism in a cohort of patients referred for a clinical suspicion of cortisol excess.[41] Therefore, we are aware that the available data may not even be enough to accurately categorize the presence or absence of HidHyCo and that other important clinical characteristics of patients with T2D need to be considered, such as morbid obesity, obstructive sleep apnea, and responsiveness of blood pressure and glycemic control to the medical therapy.[1] Unfortunately, the current literature limited the ability of this meta-analysis to include other comorbidities besides the ones evaluated in the present study.

Indeed, although several studies have tried to assess the prevalence of HidHyCo in patients with T2D, we found only 6 studies that reported distinguishing clinical characteristics of patients with T2D with HidHyCo compared with those without HidHyCo.[16-33] Indeed, most studies did not find a meaningful number of patients with HidHyCo and/or did not describe the relevant clinical characteristics in patients with HidHyCo compared with controls without HidHyCo.[16-27] By pooling data from the 6 available relevant studies and by using 2 different meta-analytical techniques, the results of the present study indicate that patients with T2D with hypertension (in particular if treated with at least 2 drugs) and requiring insulin therapy and, possibly, patients with T2D with microvascular and/or macrovascular complications should be considered for HidHyCo screening. The prevalence of hypertension and that of requirement for insulin treatment were statistically significantly associated with the prevalence of HidHyCo in our study using the DSL method but not using the HKSJ method. This lack of statistical significance using the HKSJ method needs to be re-evaluated in a larger number of studies and may be the result of limited sample size. In addition, assessing the presence or absence of other very important comorbidities in patients with T2D with and without HidHyCo, such as morbid obesity, obstructive sleep apnea, and osteoporosis, would have been valuable clinical indicators to have considered, as well as the level of glycemic control and of blood pressure control.

At the present time, the diagnosis of HidHyCo has garnered increased interest and been found to be of great importance because this form of hypercortisolism is a potentially treatable condition, being commonly due to the presence of a cortisol-secreting adrenal adenoma, and adrenalectomy seems to be of benefit in patients with unilateral adrenal adenoma and hypertension, diabetes, and fracture risk.[8,9,42] Moreover, novel drugs are expanding treatment options for patients who may not be amenable to surgical management (poor surgical candidates or contraindications to surgery) or patients with bilateral adrenal adenomas or hyperplasia.[43] Untreated HidHyCo can expose patients to an increased mortality risk due to cardiovascular events, which are partially independent of the level of control of their diabetes and hypertension.[44-46] Importantly, at variance with clinically overt Cushing syndrome, which is considered a rare disease, the HidHyCo has no negligible prevalence, being estimated to be present in 0.8% to 2% of the adult population.[1,2] In particular in T2D, the prevalence of hypercortisolism has been estimated to be as low as 2% to 3% and as high as 60%, depending on the severity of T2D, insulin requirement, and comorbidity burden, in patients with severe insulin resistance.[4,47] In addition, a recent meta-analysis suggests that among patients with T2D, the prevalence of a confirmed HidHyCo is estimated to be approximately 3.6%.[7] However, the biochemical definition of HidHyCo is not unanimous in the literature, which may lead to different outcomes. Indeed, as shown in Supplementary Table 2, the studies using more specific—and therefore less sensitive—criteria had the lowest HidHyCo prevalence.[30,32] Unfortunately, the limited number of the available studies does not allow an evaluation of the possible influence of the biochemical HidHyCo definition on the phenotypical characteristics. At this regard, we are aware, for example, that a 1mg-DST cutoff of >5 μg/dL, which is associated with a low HidHyCo prevalence, may yield a different phenotype compared with much lower 1mg-DST cutoffs.[30] However, the influence analysis did not show a relevant impact of the study-specific association estimate on pooled ORs (Fig. 3). It is worth noting that using such a high cut point would result in all the patients with 1mg-DST between 1.8 and 5 μg/dL being missed and, thus, not suspected to have the presence of HidHyCo. We, therefore, hypothesize that using a highly specific screening test for HidHyCo mainly reduces the number of the HidHyCo diagnoses.

Therefore, given the high diabetes prevalence in the general population, recognizing and treating patients with T2D with HidHyCo could have important clinical consequences for many patients, particularly those with poor glycemic control and multiple T2D-related comorbidities. Unfortunately, the screening for hypercortisolism in the population at risk (ie, patients with unexplainable osteoporosis and/or fragility fracture, refractory hypertension, or rapid weight gain or patients with T2D requiring high insulin doses) is often difficult and may lead to many false-positive results, in particular when patients with low pretest probability of having the disease are screened.[5,6,48] This is of utmost importance in patients with T2D, in whom an activated hypothalamic-pituitary-adrenal axis has been described, which may render the diagnosis of autonomous cortisol secretion even more difficult.[48,49] To date, the best screening test for diagnosing HidHyCo is still a matter of debate, and therefore, no widely accepted indications are available for which patients with T2D should be screened for HidHyCo and with what test.[4,13,48] While awaiting larger studies to fill the current lack of indications on this matter, the present meta-analysis may provide some useful guidance for clinicians regarding when to consider the possibility of HidHyCo in patients with T2D and, thus, when it may be more appropriate to screen such patients.

This study has significant limitations. First, statistical power is limited by the small number of relevant studies available for analysis and characterized by moderate or high between-study heterogeneity. Second, the condition of advanced T2D was not consistently defined among the different studies analyzed. Indeed,

the definition of advanced T2D was variably assigned on the basis of the presence of microvascular and/or macrovascular complications or the presence of insulin treatment plus hypertension or the presence of hypertension treated with 2 or more drugs.[28,31-33] Moreover, in no study, the number of patients simultaneously affected with both hypertension and T2D among HidHyCo and non-HidHyCo subjects has been reported. Thus, no information is available on the independent effect of concomitant T2D and hypertension on the risk of HidHyCo. However, it is important to note that the results did not substantially change even considering the association between HidHyCo and the presence of T2D complications separately from the association between HidHyCo and the presence of hypertension treated with 2 or more drugs and/or insulin treatment.[28,30-33] Therefore, these data suggest that the more severe the T2D condition (whatever the definition), the more likely is the possibility of HidHyCo. We appreciate, however, that the result of this meta-analysis is difficult to translate into an expedient change in clinical practice. Third, the possibility that a different T2D duration could be associated with the HidHyCo remains to be investigated. Fourth, in addition to the presence of hypertension, need for insulin treatment, dyslipidemia, and severe T2D, many other outcomes undoubtedly influence the prevalence of HidHyCo among T2D patient populations. These may include morbid obesity, obstructive sleep apnea, osteoporosis, severity of diabetes, severity of hypertension, inadequate response to conventional treatments, rapidly worsening disease, and occurrence of cardiovascular events or diabetes-related complications even in the absence of long-standing disease. Unfortunately, the available literature did not consistently record and provide such information; thus, these variables and patient characteristics could not be included in our meta-analysis. Finally, we were unable to adjust all our association estimates for possible confounding factors such as age, gender, ethnicity, and presence of obesity.

Nonetheless, despite these limitations, the present data appear to deserve interest because they identify the importance of considering the possibility of HidHyCo in patients with insulin-treated T2D with severe hypertension and diabetes-related complications. Larger and better-designed studies are needed to further delineate the most important features of patients with T2D at risk of HidHyCo to better target the screening strategy.

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Disclosure

C.A. is an investigator in studies on relacorilant (Corcept Therapeutics) in patients with hypercortisolism. L.S.B. serves as a consultant for Genentech/Roche. D.B. has received speaking and consulting fees from Corcept Therapeutics, Novo Nordisk, and Merck. D.E. has been a consultant for Corcept, Novo Nordisk, Eli Lilly, Abbott, Janssen, Boehringer Ingelheim, Epitracker, GlySens, and Intuity Medical and speaker bureau for Abbott, Novo Nordisk, Eli Lilly, and Boehringer Ingelheim and has received research support from Novo Nordisk, Eli Lilly, AztraZeneca, Mylan, and Teva. R.P. has received consulting fees from Corcept Therapeutics, HRA Pharma, Strongbridge, and Recordati Rare Diseases and is principal investigator in studies on relacorilant (Corcept Therapeutics), osilodrostat (Recordati Rare Diseases), levoketoconazole (Strongbridge), and metyrapone (HRA Pharma). K.M.P. reports being a member of the speaker bureau of AstraZeneca, Corcept Therapeutics, Merck, and Novo Nordisk and a consultant for AstraZeneca, Bayer, Corcept Therapeutics, Novo Nordisk, Merck, and Sanofi and has received research support from Bayer, Novo Nordisk, and Merck. I.C. is an investigator in studies on relacorilant (Corcept Therapeutics) in patients with hypercortisolism and received consulting fees from Corcept Therapeutics and HRA Pharma. D.S., V.F., C.P., L.Gi., L.Ge., L.P., A.S., J.O.L.J., and A.Z. have no multiplicity of interest to disclose.

References

1. Pivonello R, Isidori AM, De Martino MC, Newell-Price J, Biller BMK, Colao A. Complications of Cushing's syndrome: state of the art. *Lancet Diabetes Endocrinol*. 2016;4(7):611–629.
2. Chiodini I. Clinical review: diagnosis and treatment of subclinical hypercortisolism. *J Clin Endocrinol Metab*. 2011;96(5):1223–1236.
3. Morelli V, Arosio M, Chiodini I. Cardiovascular mortality in patients with subclinical Cushing. *Ann Endocrinol (Paris)*. 2018;79(3):149–152.
4. Giovanelli L, Aresta C, Favero V, et al. Hidden hypercortisolism: a too frequently neglected clinical condition. *J Endocrinol Invest*. 2021;44(8):1581–1596.
5. Chiodini I, Mascia ML, Muscarella S, et al. Subclinical hypercortisolism among outpatients referred for osteoporosis. *Ann Intern Med*. 2007;147(8):541–548.
6. Chiodini I, Vainicher CE, Morelli V, et al. Mechanisms in endocrinology: endogenous subclinical hypercortisolism and bone: a clinical review. *Eur J Endocrinol*. 2016;175(6):R265–R282.
7. Steffensen C, Pereira AM, Dekkers OM, Jørgensen JO. Diagnosis of endocrine disease: prevalence of hypercortisolism in type 2 diabetes patients: a systematic review and meta-analysis. *Eur J Endocrinol*. 2016;175(6):R247–R253.
8. Salcuni AS, Morelli V, Vainicher CE, et al. Adrenalectomy reduces the risk of vertebral fractures in patients with monolateral adrenal incidentalomas and subclinical hypercortisolism. *Eur J Endocrinol*. 2016;174(3):261–269.
9. Bancos I, Alahdab F, Crowley RK, et al. Therapy of endocrine disease: improvement of cardiovascular risk factors after adrenalectomy in patients with adrenal tumors and subclinical Cushing's syndrome: a systematic review and meta-analysis. *Eur J Endocrinol*. 2016;175(6):R283–R295.
10. Palmieri S, Morelli V, Polledri E, et al. The role of salivary cortisol measured by liquid chromatography-tandem mass spectrometry in the diagnosis of subclinical hypercortisolism. *Eur J Endocrinol*. 2013;168(3):289–296.
11. Zavatta G, Di Dalmazi G. Recent advances on subclinical hypercortisolism. *Endocrinol Metab Clin North Am*. 2018;47(2):375–383.
12. Tabarin A. Do the diagnostic criteria for subclinical hypercortisolism exist? *Ann Endocrinol (Paris)*. 2018;79(3):146–148.
13. Chiodini I, Albani A, Ambrogio AG, et al. Six controversial issues on subclinical Cushing's syndrome. *Endocrine*. 2017;56(2):262–266.
14. Braun LT, Riester A, Oßwald-Kopp A, et al. Toward a diagnostic score in Cushing's syndrome. *Front Endocrinol (Lausanne)*. 2019;10:766.
15. Eller-Vainicher C, Falchetti A, Gennari L, et al. Diagnosis of endocrine disease: evaluation of bone fragility in endocrine disorders. *Eur J Endocrinol*. 2019. EJE-18-0991.R1.
16. Leibowitz G, Tsur A, Chayen SD, et al. Pre-clinical Cushing's syndrome: an unexpected frequent cause of poor glycaemic control in obese diabetic patients. *Clin Endocrinol (Oxf)*. 1996;44(6):717–722.
17. Contreras LN, Cardoso E, Lozano MP, Pozzo J, Pagano P, Claus-Hermbeg H. Deteccion de sindrome de cushing preclinico en pacientes con sobrepeso y diabetes mellitus tipo 2. *Medicina*. 2000;60:326–330.
18. Budyal S, Jadhav SS, Kasaliwal R, et al. Is it worthwhile to screen patients with type 2 diabetes mellitus for subclinical Cushing's syndrome? *Endocr Connect*. 2015;4(4):242–248.
19. Liu H, Bravata DM, Cabaccan J, Raff H, Ryzen E. Elevated late-night salivary cortisol levels in elderly male type 2 diabetic veterans. *Clin Endocrinol (Oxf)*. 2005;63(6):642–649.
20. Catargi B, Rigalleau V, Poussin A, et al. Occult Cushing's syndrome in type-2 diabetes. *J Clin Endocrinol Metab*. 2003;88(12):5808–5813.
21. Reimondo G, Pia A, Allasino B, et al. Screening of Cushing's syndrome in adult patients with newly diagnosed diabetes mellitus. *Clin Endocrinol (Oxf)*. 2007;67(2):225–229.
22. Newsome S, Chen K, Hoang J, Wilson JD, Potter JM, Hickman PE. Cushing's syndrome in a clinic population with diabetes. *Intern Med J*. 2008;38(3):178–182.
23. Taniguchi T, Hamasaki A, Okamoto M. Subclinical hypercortisolism in hospitalized patients with type 2 diabetes mellitus. *Endocr J*. 2008;55(2):429–432.
24. Murakami H, Nigawara T, Sakihara S, et al. The frequency of type 2 diabetic patients who meet the endocrinological screening criteria of subclinical Cushing's disease. *Endocr J*. 2010;57(3):267–272.
25. Mullan K, Black N, Thiraviaraj A, et al. Is there value in routine screening for Cushing's syndrome in patients with diabetes? *J Clin Endocrinol Metab*. 2010;95(5):2262–2265.
26. Gagliardi L, Chapman IM, O'Loughlin P, Torpy DJ. Screening for subclinical Cushing's syndrome in type 2 diabetes mellitus: low false-positive rates with nocturnal salivary cortisol. *Horm Metab Res*. 2010;42(4):280–284.
27. Mert M, Temizel M, Erol S, et al. Screening for Cushing's syndrome in obese type 2 diabetic patients and the predictive factors on the degree of serum cortisol suppression. *Int J Diabetes Dev Ctries*. 2012;32(4):199–202.

28. Chiodini I, Torlontano M, Scillitani A, et al. Association of subclinical hypercortisolism with type 2 diabetes mellitus: a case-control study in hospitalized patients. *Eur J Endocrinol*. 2005;153(6):837–844.
29. Caetano MS, Silva Rdo C, Kater CE. Increased diagnostic probability of subclinical Cushing's syndrome in a population sample of overweight adult patients with type 2 diabetes mellitus. *Arq Bras Endocrinol Metabol*. 2007;51(7):1118–1127.
30. Terzolo M, Reimondo G, Chiodini I, et al. Screening of Cushing's syndrome in outpatients with type 2 diabetes: results of a prospective multicentric study in Italy. *J Clin Endocrinol Metab*. 2012;97(10):3467–3475.
31. Costa DS, Conceição FL, Leite NC, Ferreira MT, Salles GF, Cardoso CR. Prevalence of subclinical hypercortisolism in type 2 diabetic patients from the Rio de Janeiro Type 2 Diabetes Cohort Study. *J Diabetes Complications*. 2016;30(6):1032–1038.
32. Cansu GB, Atılgan S, Balcı MK, Sarı R, Özdem S, Altunbaş HA. Which type 2 diabetes mellitus patients should be screened for subclinical Cushing's syndrome? *Hormones (Athens)*. 2017;16(1):22–32.
33. Steffensen C, Dekkers OM, Lyhne J, et al. Hypercortisolism in newly diagnosed type 2 diabetes: a prospective study of 384 newly diagnosed patients. *Horm Metab Res*. 2019;51(1):62–68.
34. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
35. Higgins JPT, Green S. *Chapter 16: Special topics in statistics. Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane Collaborative; 2011. Accessed September 29, 2021. https://handbook-5-1.cochrane.org/chapter_16/16_9_2_studies_with_zero_cell_counts.htm).
36. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Accessed February 1, 2009. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
37. Röver C, Knapp G, Friede T. Hartung-Knapp-Sidik-Jonkman approach and its modification for random-effects meta-analysis with few studies. *BMC Med Res Methodol*. 2015;15:99.
38. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med Res Methodol*. 2014;14:25.
39. Jackson D, Law M, Rücker G, Schwarzer G. The Hartung-Knapp modification for random-effects meta-analysis: a useful refinement but are there any residual concerns? *Stat Med*. 2017;36(25):3923–3934.
40. Fleiss JL. Measuring nominal scale agreement among many raters. *Psychol Bull*. 1971;76(5):378.
41. León-Justel A, Madrazo-Atutxa A, Alvarez-Rios AI, et al. A probabilistic model for Cushing's syndrome screening in at-risk populations: a prospective multicenter study. *J Clin Endocrinol Metab*. 2016;101(10):3747–3754.
42. Miller BS, Auchus RJ. Evaluation and treatment of patients with hypercortisolism: a review. *JAMA Surg*. 2020;155(12):1152–1159.
43. Bouys L, Chiodini I, Arlt W, Reincke M, Bertherat J. Update on primary bilateral macronodular adrenal hyperplasia (PBMAH). *Endocrine*. 2021;71(3):595–603.
44. Di Dalmazi G, Vicennati V, Garelli S, et al. Cardiovascular events and mortality in patients with adrenal incidentalomas that are either non-secreting or associated with intermediate phenotype or subclinical Cushing's syndrome: a 15-year retrospective study. *Lancet Diabetes Endocrinol*. 2014;2(5):396–405.
45. Debono M, Bradburn M, Bull M, Harrison B, Ross RJ, Newell-Price J. Cortisol as a marker for increased mortality in patients with incidental adrenocortical adenomas. *J Clin Endocrinol Metab*. 2014;99(12):4462–4470.
46. Patrova J, Kjellman M, Wahrenberg H, Falhammar H. Increased mortality in patients with adrenal incidentalomas and autonomous cortisol secretion: a 13-year retrospective study from one center. *Endocrine*. 2017;58(2):267–275.
47. Mathews J, Smith J. Screening of diabetic patients using U500 insulin uncovers a high percentage of undiagnosed hypercortisolism consistent with Cushing's syndrome. *Endocr Pract*. 2017;23(suppl 3):14–15.
48. Petersenn S. Biochemical diagnosis of Cushing's disease: screening and confirmatory testing. *Best Pract Res Clin Endocrinol Metab*. 2021;35(1):101519.
49. Chiodini I, Di Lembo S, Morelli V, et al. Hypothalamic-pituitary-adrenal activity in type 2 diabetes mellitus: role of autonomic imbalance. *Metabolism*. 2006;55(8):1135–1140.