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

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

Prevalence of hidden hypercortisolism

In recent years, less severe and less apparent hypercortisolism has been frequently found in patients with incidentally discovered adrenal adenomas. This subtle form of hypercortisolism—often called hidden hypercortisolism—is characterized by the presence of excess cortisol in the absence of the typical signs and symptoms of Cushing syndrome.

Hidden hypercortisolism has been associated with an increased prevalence of chronic diseases, including:

- Type 2 diabetes (T2DM)
- Hypertension
- Osteoporosis

The prevalence of hidden hypercortisolism has been suggested as high as 10% in advanced or difficult-to-treat T2DM

Study objective

This meta-analysis investigates available literature to help identify the clinical characteristics of patients with T2DM and hidden hypercortisolism.

Current literature was used to identify the clinical characteristics of hidden hypercortisolism

Methods

PubMed, Scopus, Web of Science, and ScienceDirect were searched between August 1990 and April 2021. Among the 18 available studies, 6 studies had the necessary data for the meta-analysis.

For the diagnosis of hypercortisolism, the meta-analysis used the definition reported in the studies, shown below.

- 1 mg-dexamethasone suppression test (DST) > 1.8 µg/dL
- 1 mg-DST > 5 µg/dL
- 1 mg-DST > 1.8 µg/dL plus late-night salivary cortisol (LNSC) 0.35 µg/dL
- 1 mg-DST > 1.8 µg/dL plus LNSC > 0.5 µg/dL
- 2-mg 2-day (low dose) DST >1.8 µg/dL plus LNSC > 7.5 µg/dL
- 1 mg-DST > 1.8 µg/dL plus low dose DST > 1.8 mg/dL plus urinary free cortisol levels above the limit of the normal range (ie, ≥109 mg/24 hour)
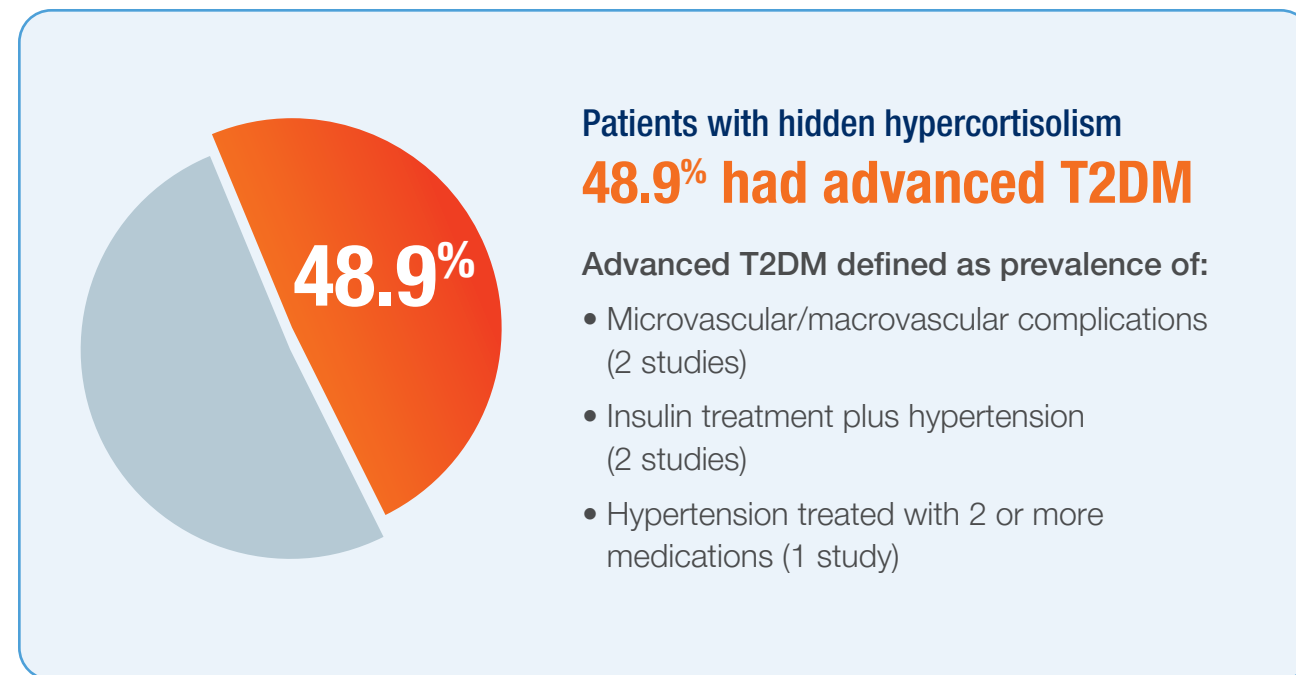
The biochemical definition of hidden hypercortisolism was not unanimous in the literature, which may lead to different outcomes. A high 1 mg-DST cutoff > 5 µg/dL would result in patients with 1 mg-DST between 1.8 and 5 µg/dL being possibly missed for a hypercortisolism diagnosis.

DST=dexamethasone suppression test; LNSC=late-night salivary cortisol; T2DM=type 2 diabetes.

Advanced T2DM increased risk of hidden hypercortisolism

Almost half of patients (48.9%) with hidden hypercortisolism had advanced T2DM

Patients with hidden hypercortisolism
48.9% had advanced T2DM

48.9%

Advanced T2DM defined as prevalence of:
- Microvascular/macrovascular complications (2 studies)
- Insulin treatment plus hypertension (2 studies)
- Hypertension treated with 2 or more medications (1 study)

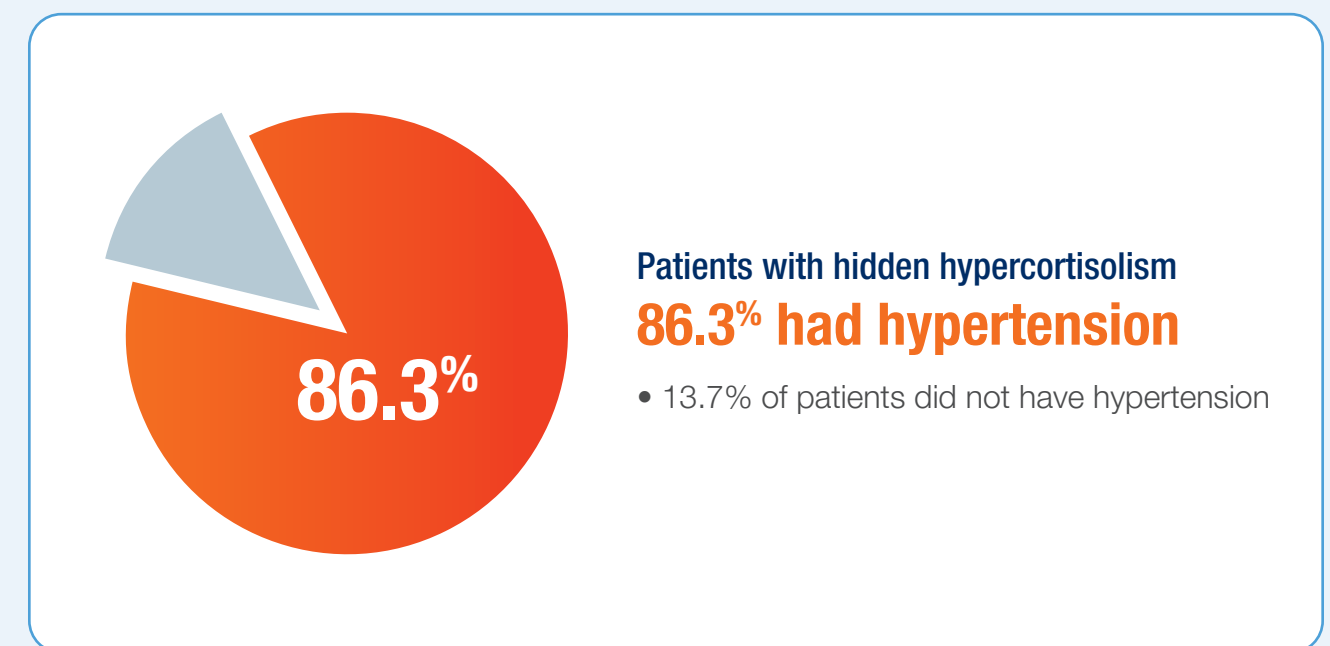## The prevalence of advanced T2DM was significantly associated with hidden hypercortisolism

- Patients with advanced T2DM were **~3.5x more likely** (n=2184) to be diagnosed with hypercortisolism*

*DSL method (OR, 3.4; 95% CI, 2.12-5.67; $P<0.0001$) and HKSJ method (OR, 3.60; 95% CI, 2.03-6.41; $P=0.004$)

"These data suggest that the more severe the T2DM condition (whatever the definition), the more likely is the possibility of hidden hypercortisolism"

Hypertension and T2DM increased risk of hidden hypercortisolism

8 out of 10 (86.3%) of patients with hidden hypercortisolism had hypertension

86.3%

Patients with hidden hypercortisolism
86.3% had hypertension

- 13.7% of patients did not have hypertension

The prevalence of T2DM and hypertension was associated with hidden hypercortisolism

- Patients with T2DM and hypertension were almost **2x more likely** (n=2283) to be diagnosed with hypercortisolism†
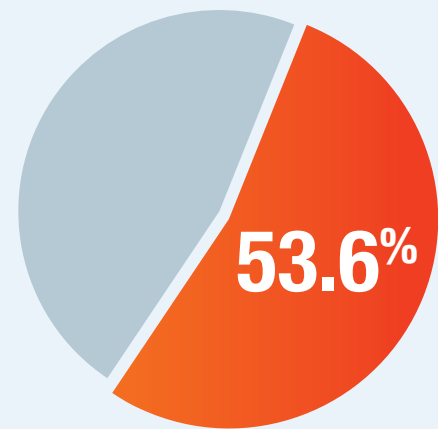
†DSL method (OR, 1.92; 95% CI, 1.05-3.50; $P=0.034$) and HKSJ method (OR, 2.13; 95% CI, 0.81-5.65; $P=0.100$).

CI=confidence interval; DSL=DerSimonian and Laird; HKSJ=Hartung-Knapp-Sidik-Jonkman; OR=odds ratio.

The use of insulin increased risk of hidden hypercortisolism

More than half (53.6%) of patients with hidden hypercortisolism required insulin treatment

53.6%

Patients with hidden hypercortisolism
53.6% required insulin treatment

• 46.4% of patients did not receive insulin treatment

The use of insulin treatment was associated with hidden hypercortisolism

• Patients with T2DM requiring insulin therapy were **about 2x more likely** (n=1400) to be diagnosed with hypercortisolism*

†DSL method (OR, 2.29; 95% CI,1.07-4.91; *P*=0.034) and HKSJ method (OR, 2.13; 95% CI, 0.81-5.65; *P*=0.100).

CI=confidence interval; DSL=DerSimonian and Laird; HKSJ=Hartung-Knapp-Sidik-Jonkman; OR=odds ratio.

"
…patients with T2DM with hypertension (in particular if treated with at least 2 drugs) and requiring insulin therapy…should be considered for hidden hypercortisolism screening.
"

The importance of screening for hidden hypercortisolism in T2DM

Untreated hidden hypercortisolism increases risk of mortality due to cardiovascular events, which are partially independent of the level of control of diabetes and hypertension

The result of this study indicates that the following patients should be screened for hidden hypercortisolism.

RECOMMENDED SCREENING FOR HIDDEN HYPERCORTISOLISM

Patients with T2DM and hypertension, particularly those treated with at least 2 drugs and insulin therapy

Patients with T2DM with microvascular and/or macrovascular complications

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Given the high diabetes prevalence in the general population, recognizing and treating patients with T2DM with hidden hypercortisolism could have important clinical consequences for many patients, particularly those with poor glycemic control and multiple T2DM-related comorbidities.
"

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BRING HYPERCORTISOLISM TO LIGHT

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Reference: Aresta C, Soranna D, Giovanelli L, et al. When to suspect hidden hypercortisolism in type 2 diabetes: a meta-analysis. *Endocr Pract*. 2021;27(12):1216-1224. doi:10.1016/j.eprac.2021.07.014

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