diabetesresearchandclinicalpractice 239 (2026) 113436

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.journals.elsevier.com/diabetes-research-and-clinical-practice

Long-term metabolic consequences: persistence of visceral obesity and diabetes mellitus after remission from Cushing's syndrome

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ARTICLE INFO

Keywords:
Cushing'ssyndrome
Cushing'sdisease
Co-morbidities
Remission
Diabetesmellitus

ABSTRACT

Aims: Cushing's syndrome (CS) is associated with increased cardiovascular morbidity and mortality, both of which may persist after long-term remission. Our aim was to evaluate the prevalence of type 2 diabetes mellitus, fat distribution and other metabolic characteristics in patients with prior CS compared with matched population-based controls to assess metabolic risk factors.

Methods: Comorbidities were retrospectively analyzed in a cohort of 99 patients with CS from a single tertiary care center. Patients were longitudinally evaluated at baseline during active disease and at 7 years after biochemical remission. Data were compared to a control group matched for age and sex (n = 396) from the KORA study in a 1:4 fashion.

Results: Despite long-term improvements, patients with CS in sustained remission still exhibit adverse metabolic outcomes 7 years after remission, including higher relative fat mass (39% vs. 35%, $p = 0.0013$), a higher waist-to-hip ratio (0.89 vs. 0.82, $p < 0.0001$), elevated HbA1c (5.5% vs. 5.4%, $p = 0.0087$), and increased diabetes prevalence (19% vs. 4%, $p < 0.0001$) compared with controls. These persistent metabolic alterations were strongly associated with inflammatory markers, suggesting inflammation as a potential contributor to the sustained diabetes risk.

Abbreviations: BMI, Body mass index; ACTH, adrenocorticotropic hormone; CS, Cushing's syndrome; DST, dexamethasone suppression test; HDL, high-density lipoprotein-cholesterol; IQR, interquartile range; KORA, Cooperative Health Research in the Region of Augsburg study; LDL, low-density lipoprotein-cholesterol; LNSC, late-night salivary cortisol; RFM, relative fat mass; UFC, urinary free cortisol measurement; T2DM, type 2 diabetes mellitus.

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https://doi.org/10.1016/j.diabres.2026.113436
Received 22 October 2025; Received in revised form 20 March 2026; Accepted 12 July 2026
Available online 13 July 2026

Conclusion: Patients with prior CS remain burdened by adverse metabolic profiles that may contribute to their increased long-term cardiovascular risk.

1. Introduction

Endogenous Cushing's syndrome (CS) is a rare, but severe endocrine disease with a chronic state of hypercortisolism leading to a distinct metabolic phenotype, characterized by central obesity, impaired glucose metabolism and dyslipidemia [1]. Even after surgical cure and long-time remission, patients have a persistently higher mortality rate mainly due to cardiovascular disease, based on a recent *meta*-analysis including 20 cohorts with over 3500 patients [2]. In two studies from 2013 the traditional cardiovascular risk factors hypertension and diabetes mellitus were the main predictive factors for mortality besides older age at diagnosis and the duration of untreated hypercortisolism [3,4].

Previous work from our group has demonstrated that the prevalence of hypertension and impaired kidney function remain elevated in patients with CS, even years after the achievement of biochemical remission, thereby suggesting a potential contribution to unfavorable long-term clinical outcomes [5].

In CS, excess cortisol overstimulates glucocorticoid receptors, thereby increasing hepatic glucose output, reducing peripheral glucose uptake [6], and impairing beta cell function and thereby insulin secretion [7]. These mechanisms ultimately result in pathological glucose tolerance (21–64%) or overt type 2 diabetes mellitus (T2DM) (20–47%) during the active phase of hypercortisolism [8,9]. However, little is known about the long-term outcome of T2DM after surgical cure from CS with sustained long-term remission. An older study from 1999 with 15 patients in remission from Cushing's disease for 5 years found higher BMI, waist-to-hip ratio, fasting glucose and insulin levels than matched controls [10]. A recent systematic review reported that in three cohorts with CS normalization of glucose levels could be reached in 56–83% of patients with a remission time of 4–11 years [11], however, these rates were not compared to a control group. In addition, a recent study in 151 patients with Cushing's disease, of whom 53% had pathological glucose metabolism (T2DM 37%, both impaired fasting glucose and impaired glucose tolerance 16%) during active hypercortisolism, reported a reduction of this proportion to 24% of patients one year after curative surgery [12].

We hypothesized that increased mortality despite long-term remission from hypercortisolism may be due to the persistence of traditional cardiovascular risk factors. The aim of our study was, therefore, to investigate whether patients with CS continued to exhibit a higher prevalence of T2DM and related metabolic abnormalities even after long-term remission. To address this question, we compared patients with CS with a control group of the same ethnic and environmental background from a population-based longitudinal study.

2. Methods

2.1. Study design

We performed a retrospective analysis of patients with CS within the Munich center of the German Cushing's registry. All patients were diagnosed and treated for CS at the Department of Endocrinology, University Hospital LMU Munich, Germany, and gave written informed consent to being included in the German Cushing's registry (Ethical approval: Ethics Committee LMU Munich, No. 152-10). CS was diagnosed using the three recommended screening tests urinary free cortisol (UFC), late-night salivary cortisol (LNSC), and 1 mg overnight dexamethasone suppression test (DST). These tests were also applied annually to define remission after therapeutic interventions. Further subtyping was performed according to the updated guidelines of the Endocrine Society [13].

Inclusion criteria for our study were successful surgical treatment of CS and the availability of data with a follow-up of at least 7 years after achieving sustained remission. Patients with mild autonomous cortisol secretion and CS caused by malignant tumors were excluded.

We compared these patients to matched controls from the KORA (Cooperative Health Research in the Region of Augsburg) cohort study. Patients were matched 1:4 based on age at baseline and sex.

KORA is a prospective adult cohort study in the Region of Augsburg, Germany for population-based health research with randomly selected participants from population registries. Participants were recruited between 1999 and 2001 (KORA S4, N = 4261 participants aged 25 to 74 years) and followed up after 7 years in 2006–2008 (F4, N = 3080) and after 14 years in 2013–2014 (FF4, N = 2279), Ethical approval: Ethics Committee of the Bavarian Chamber of Physicians (S4: EC No. 99186, F4 and FF4: EC No. 06068). Further information for recruitment and eligibility criteria were described elsewhere [14].

Participants were excluded when they declared use of glucocorticoids in the questionnaire.

2.2. Data collection

We collected clinical and biochemical data from the patients with CS and from KORA participants at baseline (for CS patients before treatment, i.e. during active CS), after 7 and after 14 years. The clinical data included weight (kg), height (cm), waist and hip circumference (m), waist-to-hip ratio (WHR), body mass index (BMI; kg/m^2), relative fat mass (RFM; 64 − (20 × height/waist circumference) + (12 × sex (0 for male, 1 for female) [15]), blood pressure (average between the second and third office blood pressure measurements, mmHg), fasting serum glucose (mg/dl), fasting insulin (μU/ml), glycated hemoglobin (HbA1c, % and mmol/mol), fasting triglycerides, total cholesterol, high-density lipoprotein-cholesterol (HDL), low-density lipoprotein-cholesterol (LDL; mg/dl for all lipid parameters), current medication, and current comorbidities. We calculated the HOMA-IR (insulin (μU/ml) × glucose (mg/dl)/405) and the HOMA-B (360 x insulin (μU/ml)/(glucose (mg/dl) – 63)) as markers of insulin resistance and beta-cell function [16].

Patients were classified as having T2DM according to the use of antihyperglycemic drugs and/or a HbA1c ≥ 6.5% (>48 mmol/mol). Hypercholesterolemia was diagnosed in patients taking lipid lowering drugs or having an LDL ≥ 130 mg/dl (3.4 mmol/l). Patients were instructed to take their medication on the morning of their visit.

2.3. Biochemical assays

Blood samples were drawn in the fasting state in the early morning between 8 and 9 a.m. in a seated position. In patients with CS, serum cortisol was measured by chemiluminescence immuno-assay (Liaison, DiaSorin Cat# 313261, RRID:AB_2893155), UFC was measured by the same chemiluminescence immuno-assay after extraction with dichloromethane. LNSC was measured by chemiluminescence immunoassay (Immunodiagnostic Systems Cat# IS-4900, RRID:AB_3095089) and ACTH by chemiluminescence immuno-assay (Liaison, DiaSorin Cat# 313221, RRID:AB_3095090).

Serum total cholesterol, triglycerides, HDL, LDL, glucose, insulin and HbA1c levels were determined by standard enzymatic methods.

2.4. Statistical analysis

The statistical data are presented as median and interquartile range

(IQR). Normality was assessed using the Shapiro-Wilk test. Significant differences among variables were tested using the Student's *t*-test and mixed-effects models; for nonparametric data, the Mann-Whitney and Kruskal-Wallis tests were applied. The chi-square test was utilized to examine the distribution of categorical variables between the two groups. Associations among variables were assessed using Spearman correlation coefficients.

Odds ratios (ORs) along with 95% confidence intervals were computed from logistic regression analyses.

All statistical tests were conducted in a two-sided manner, with a significance threshold of $p < 0.05$. The analyses were executed using standard statistical software (Prism 10.3.0, GraphPad Software, Boston, MA, USA).

3. Results

3.1. Description of the cohorts

After excluding malignant, metastatic and subclinical forms of CS we screened 296 patients with CS from our center, of whom 127 had an available follow-up of at least 7 years. 28 patients were, however, not in sustained remission due to recurrent CS. In total, 99 patients with CS and sustained remission were analyzed at baseline and 7 years of follow up. The cohort of patients with CS comprised 62 patients with Cushing's disease, 9 patients with ectopic CS and 28 patients with adrenal CS. We compared the patients with CS to 396 matched controls from the KORA S4 study. Characteristics of the two cohorts at baseline are reported in Table 1. A total of 49 patients with CS completed the 14-year follow-up. Because of the smaller sample size at this stage, the analyses lacked sufficient statistical power to formally evaluate differences between the Cushing's and the KORA cohort. The characteristics and comorbidities of both cohorts at 14 years are presented in the Supplemental Material (Supplemental Table S1). Detailed information about treatment modalities and duration of hypercortisolism is provided as Supplemental Material (Supplemental Text S1).

Table 1
Clinical characteristics at baseline of the cohort of patients with Cushing's syndrome (CS) and controls (KORA) in percentage or as median and IQR.

Characteristics at baseline	CS	KORA	P value
N	99	396	n.a.
Age at baseline (years)	43 (36–53)	43 (36–53)	1.0
Sex (female)	79%	79%	1.0
Weight (kg)	79.4 (70–96)	69.3 (61–80)	<0.0001
BMI (kg/m^2)	28.7 (24.4–33.4)	25.4 (22.7–28)	<0.0001
WHR	0.98 (0.9–1.1)	0.8 (0.75–0.87)	<0.0001
RFM (%)	40 (31.2–47.2)	33.4 (28.7–38.1)	0.0006
HbA1c			<0.0001
(%)	5.9 (5.6–6.9)	5.5 (5.3–5.7)	
(mmol/mol)	41 (38–52)	37 (34–39)	
HOMA-IR-Index	2.6 (1.3–4.1)	2 (1.6–2.7)	0.41
HOMA-B-Index	70 (34–166)	106 (54–148)	0.28
Triglycerides (mg/dl)	139 (85–202)	106 (80–154)	0.0193
Cholesterol (mg/dl)	217 (179–245)	214 (192–247)	0.68
LDL cholesterol (mg/dl)	134 (106–154)	123 (99–154)	0.41
HDL cholesterol (mg/dl)	59 (47–63)	60 (49–75)	0.17
BP syst. (mmHg)	147 (130–160)	119 (109–131)	<0.0001
BP diast. (mmHg)	90 (80–100)	79 (71–85)	<0.0001
Prevalence of arterial hypertension	85.3%	26.3%	<0.0001
Antidiabetic drugs	26%	2%	<0.0001
Type 2 diabetes mellitus	35%	2%	<0.0001
Hypercholesterolemia	60%	40%	0.0232
Antihypertensive drugs	62%	11%	<0.0001
Lipid lowering drugs	28%	4%	<0.0001
CRP (mg/l)	2.2 (1–5.6)	1 (0.5–2.3)	<0.0001
25-Hydroxyvitamine D (ng/ml)	26.1 (16.2–34.2)	19.4 (13–25.4)	0.0065

Abbreviations: IQR: interquartile range, BMI: Body mass index, WHR: waist-to-hip ratio, RFM: relative fat mass, BP: Blood pressure, CRP: C-reactive protein, HOMA-IR: Homeostasis Model Assessment of insulin resistance, HOMA-B: Homeostasis Model Assessment of β-cell function

3.2. Longitudinal data of the CS cohort

We observed a significant improvement of all parameters of obesity and visceral fat mass from baseline to 7 years of follow-up: Bodyweight (79.4 vs. 73.0 kg, $p < 0.0001$), BMI (28.7 vs. 26.2 kg/m^2, $p < 0.0001$), RFM (40% vs. 39%, $p < 0.0001$). Moreover, HbA1c as a marker of chronic hyperglycemia improved as well (5.9% vs. 5.5% (41 vs. 37 mmol/mol), $p < 0.0001$).

Initially, 35% of the patients with CS were diagnosed with T2DM, which decreased to 20% after 7 years ($p = 0.1023$). Correspondingly, the use of antidiabetic drugs decreased (26% vs. 20%, $p = 0.4129$).

Insulin therapy was used at baseline in 9% and at the 7-year follow-up 4% of patients in the CS cohort. As only a small proportion of patients received insulin therapy, any potential influence on HOMA estimates is likely to be limited.

Serum triglycerides showed a nonsignificant decrease (158 vs. 134 mg/dl, $p = 0.0713$). LDL cholesterol levels remained stable throughout the entire observation period (132 vs. 122 mg/dl, $p = 0.0303$). However, the use of lipid lowering drugs decreased with 28% at diagnosis and 21% after 7 years ($p = 0.33$). Parameters of cortisol metabolism and hormone substitution at baseline and 7 years after biochemical remission for the CS cohort are reported in Supplemental Material (Supplemental Table S2).

3.3. Analyses of metabolic parameters of the CS cohort vs. The KORA cohort

At baseline, during overt hypercortisolism, patients with CS showed significantly higher markers of obesity and visceral fat (BMI; WHR, RFM), as well as higher prevalence of T2DM and higher intake of lipid-lowering medication compared to controls, which is shown in Figs. 1 and 2. In contrast to the improvement in metabolic parameters following remission from hypercortisolism in the CS cohort, the KORA cohort, exhibited a worsening in most of these metabolic parameters.

Nevertheless, 7 years after achieving remission, patients with CS still had higher waist-to-hip ratio (0.89 vs 0.83, $p < 0.0001$), relative fat mass (39% vs 35%, $p = 0.0013$), HbA1c (5.5% vs. 5.4% (37 vs. 36 mmol/mol), $p = 0.0087$) and more patients had T2DM (20% vs. 4%, $p < 0.0001$) and more frequently used antidiabetic (19% vs 3%, $p < 0.0001$) and lipid-lowering medications (21 vs 9%, $p = 0.0020$), shown as well in Figs. 1 and 2. The absolute changes (Δ) of BMI and HbA1c from baseline to the 7 years follow are shown in the Supplemental Material (Supplemental Fig. S1). Triglyceride levels remained significantly higher in the CS cohort compared with the KORA cohort (124 vs 93 mg/dl, $p = 0.0008$). Similarly, markers of systemic inflammation were elevated, with higher CRP concentrations in patients with CS (2.4 vs 1 mg/l, $p < 0.0001$). In addition, circulating 25-hydroxyvitamin D levels were higher in the CS cohort (29 vs 17 ng/ml, $p < 0.0001$), likely reflecting more frequent vitamin D supplementation in patients with Cushing's syndrome. Characteristics and co-morbidities of the two cohorts at 7 years of follow-up are reported on Table 2.

3.4. Parameters associated with type 2 diabetes mellitus and obesity in the CS cohort

We performed a subgroup analysis, evaluating all parameters separately for patients with and without a diagnosis of T2DM at the 7-year follow-up. Patients with T2DM had a significantly higher body weight and BMI both at baseline and after 7 years. In addition, these patients exhibited a higher RFM and elevated CRP levels at 7 years. No differences were observed in baseline cortisol parameters, i.e., the severity of

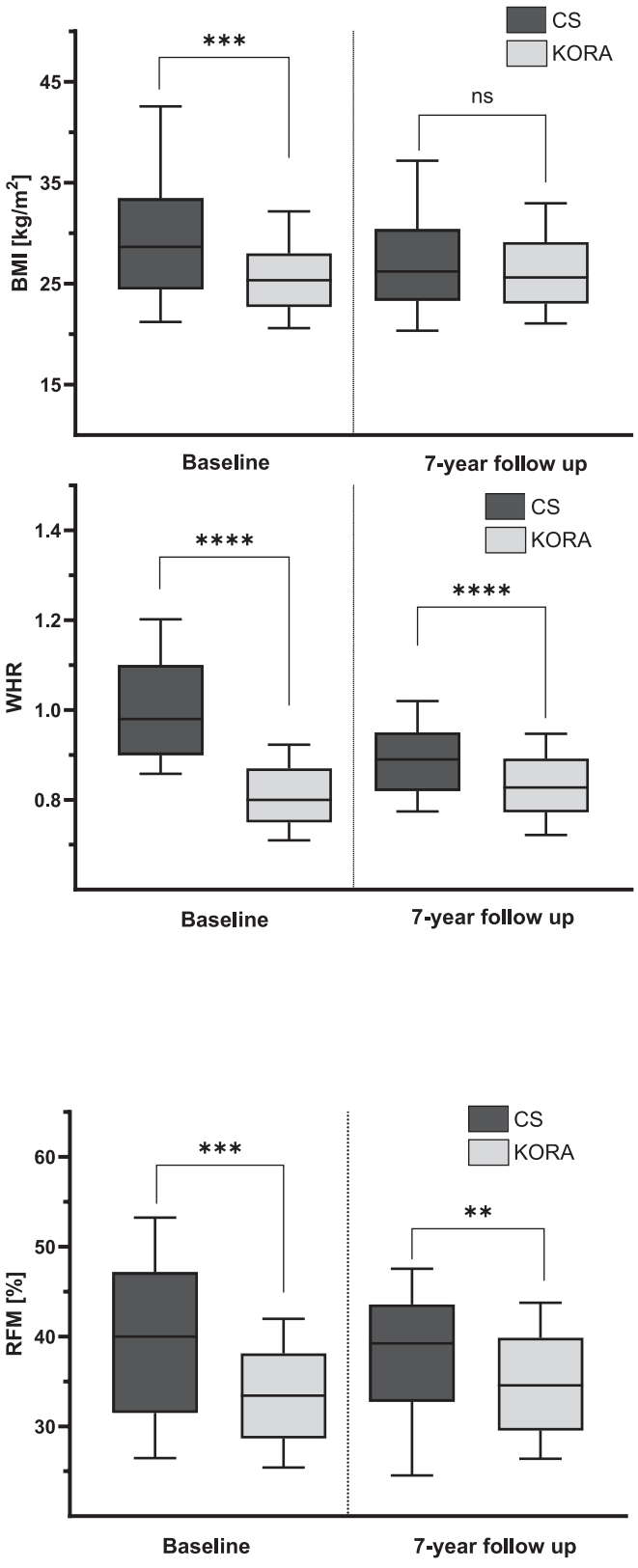

Fig. 1. BMI (A), WHR (B) and RFM (C) in the patients with CS and controls from the KORA study at baseline and 7 years after biochemical remission of CS. Box plots are displaying the 90/10 percentile at the whiskers, the 75/25 percentiles at the boxes, and the median in the center line.

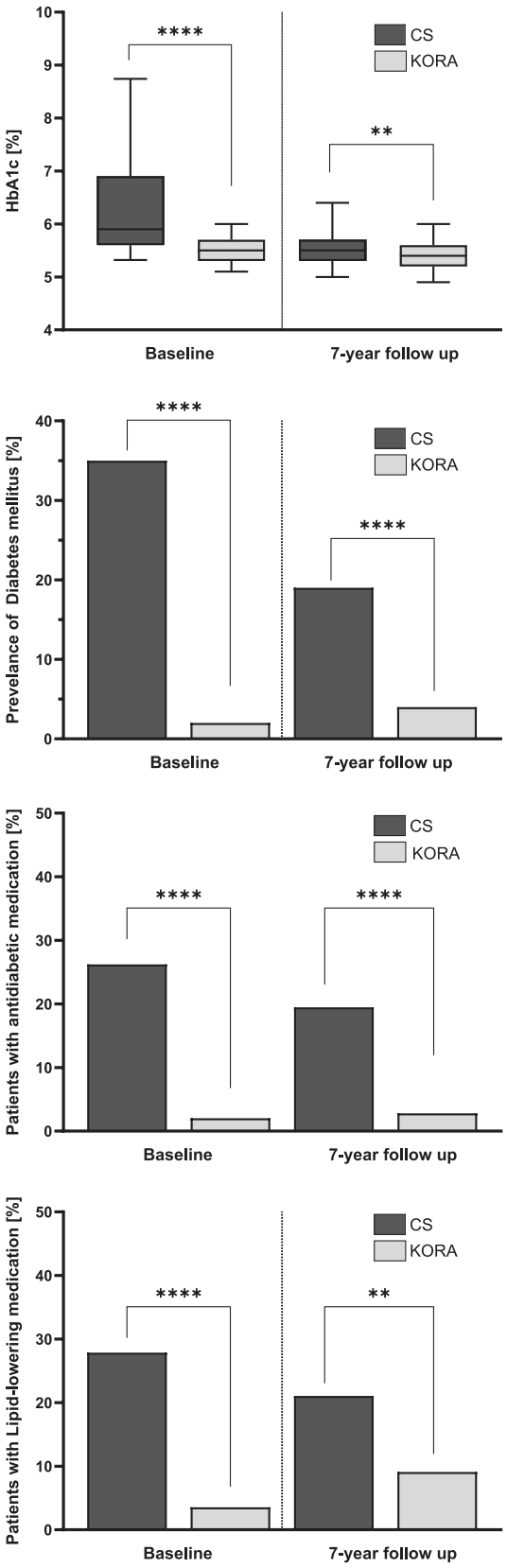

Fig. 2. HbA1c (A), prevalence of diabetes mellitus (B) and rate of antidiabetic medication (C) and lipid-lowering drug treatment (D) in the patients with CS and controls from the KORA study at baseline and 7 years after biochemical remission of CS.

Table 2
Clinical characteristics at 7 years of follow up of the CS and KORA cohorts in percentage or as median and IQR. Abbreviations: IQR: interquartile range, BMI: Body mass index, WHR: waist-to-hip ratio, RFM: relative fat mass.

	CS	KORA	P value
	Characteristics at 7 years of follow up		
N	99	396	
Weight (kg)	73 (63–85)	72 (62–83)	0.30
BMI (kg/m^2)	26.2 (23.3–30.4)	25.6 (23–29)	0.19
WHR	0.89 (0.82–0.95)	0.82 (0.77–0.89)	<0.0001
RFM (%)	39.2 (32.8–43.5)	34.5 (29.5–39.9)	0.0013
HbA1c (%) (mmol/mol)	5.5 (5.3–5.7) 37 (34–39)	5.4 (5.2–5.6) 36 (33–38)	0.0087
HOMA-IR-Index	1.6 (0.68–3.7)	1.8 (1.3–2.8)	0.08
HOMA-B-Index	96 (54–140)	105 (71–160)	0.12
Triglycerides (mg/dl)	124 (83–174)	93 (63–141)	0.0008
Cholesterol (mg/dl)	205 (182–236)	211 (184–236)	0.58
LDL cholesterol (mg/dl)	126 (93–149)	128 (104–150)	0.16
HDL cholesterol (mg/dl)	61 (50–74)	59 (49–69)	0.31
Type 2 diabetes mellitus	20%	4%	<0.0001
Antidiabetic drugs	19%	3%	<0.0001
Lipid lowering drugs	21%	9%	0.0020
CRP (mg/l)	2.4 (1–5)	1 (0.45–2.2)	<0.0001
25-Hydroxyvitamine D (ng/ml)	29 (21–35)	17 (11–24)	<0.0001

hypercortisolism, or the time from diagnosis time to remission. Detailed results are presented in Table 3.

To identify parameters associated with T2DM in the CS cohort, we applied Spearman's rank-order correlation. HbA1c, Insulin levels and markers of obesity at 7 years showed no significant relationship with morning serum cortisol concentrations, cortisol after dexamethasone suppression, LNSC, UFC indices before and 7 years after remission, or the duration of initially untreated cortisol excess.

On the other hand, measures of overall and visceral adiposity demonstrated strong associations with HbA1c (RFM correlated with HbA1c at 7 years: $r = 0.50$, $p < 0.001$ and BMI correlated with HbA1c at 7 years: $r = 0.44$, $p < 0.0001$). CRP, as an inflammatory marker, correlated with HbA1c ($r = 0.32$, $p = 0.0072$), BMI ($r = 0.48$, $p < 0.0001$), and RFM ($r = 0.38$, $p = 0.0037$). Insulin levels, but not HOMA-indices, were significantly associated with the HbA1c ($r = 0.27$, $p = 0.039$), with the BMI ($r = 0.63$, $p < 0.0001$) and with the RFM ($r = 0.64$, $p < 0.0001$), all at 7 years.

Logistic regression analysis revealed a significant association between the prevalence of T2DM at 7 years and BMI at 7 years (OR 1.165; 95% CI 1.063–1.295; $p = 0.0009$), RFM at 7 years (OR 1.12; 95% CI 1.017–1.236; $p = 0.0339$), HbA1c at 7 years (OR 123.4; 95% CI 15.56–2144; $p < 0,0001$), and Insulin levels at 7 years (OR 1.130; 95% CI 1.033–1.253; $p = 0.0115$). Neither HOMA-IR nor HOMA-B were significantly associated with the prevalence of T2DM.

No additional factors were identified as being associated with the diagnosis of T2DM at follow-up in our statistical analysis.

4. Discussion

Previous research has shown that patients with CS remain at increased risk of mortality even after successful remission, with obesity and diabetes mellitus as key drivers. However, robust longitudinal studies that directly compare patients in remission of endogenous CS with carefully matched aging controls are scarce. Closing this gap is essential to better define long-term risks and guide targeted interventions. In our longitudinal evaluation of patients with CS who achieved sustained remission following surgical cure, we observed improvements in body weight, BMI, WHR, RFM, and HbA1c at follow-up assessments 7 and 14 years after surgery. In parallel, they had a reduction in the prevalence of T2DM and a decreased need for antidiabetic and lipid-lowering medications. Nevertheless, metabolic health remained significantly impaired compared with matched disease-free controls. At 7 years, patients in remission still showed higher WHR, elevated RFM and HbA1c, and a greater prevalence of diabetes and metabolic medication use relative to the KORA cohort. Although the smaller sample size limited statistical power at 14 years, the observed trends were consistent, with persistently higher relative fat mass, diabetes prevalence, and triglyceride and CRP levels. Persistent elevation of triglycerides may reflect ongoing hepatic insulin resistance and adipose tissue dysfunction, consistent with the concept of a metabolically active fat reservoir persisting after remission of hypercortisolism.

Weight loss and reduced visceral obesity after remission from hypercortisolism were consistently reported in preceding studies [17–19]. For example, a recent retrospective analysis of 99 patients with

Table 3
Subgroup-Analysis of CS patients with and without diagnosis of type 2 diabetes mellitus at 7 years as median and IQR.

Diabetes mellitus at 7 years of follow-up in patients with CS	Type 2 diabetes mellitus	No type 2 diabetes mellitus	P value
N	16	63	n.a.
Age at baseline (years)	43 (36–53)	43 (36–53)	1.0
Sex (female)	79%	79%	1.0
Weight (kg)			
at baseline	95 (79.1–115.4)	78 (70–93)	0.03*
at 7 years of follow-up	87 (73–103)	73 (61–84)	0.02*
BMI (kg/m^2)			
at baseline	34.4 (27.9–44.8)	27.9 (24.5–32.3)	0.03*
at 7 years of follow-up	34.3 (29.8–37.3)	25.6 (22.9–29.4)	0.0006***
WHR			
at baseline	0.98 (0.95–1.15)	0.97 (0.88–1.1)	0.49
at 7 years of follow-up	0.93 (0.86–1)	0.88 (0.91–0.95)	0.27
RFM (%)			
at baseline	43.5 (32–52.3)	38.5 (30.9–45.7)	0.32
at 7 years of follow-up	45.4 (42.6–46.5)	38 (31.3–42.7)	0.0016**
HbA1c (%)			
at baseline			
(%)	7.6 (6.7–9.3)	5.9 (5.6–6.2)	<0.0001****
(mmol/mol)	60 (50–78)	41 (38–44)	
at 7 years of follow-up			
(%)	6.4 (6.2–7.2)	5.5 (5.1–5.7)	<0.0001****
(mmol/mol)	46 (44–55)	37 (32–39)	
HOMA-IR-Index			
at baseline	2.7 (1.7–4.3)	3 (1.3–5.7)	0.7
at 7 years of follow-up	2.4 (1.5–4)	1.4 (0.6–3.8)	0.14
Triglycerides (mg/dl)			
at baseline	160 (74–201)	119 (78–200)	0.62
at 7 years of follow-up	142 (95–200)	120 (81–161)	0.23
LDL cholesterol (mg/dl)			
at baseline	119 (91–148)	137 (104–163)	0.29
at 7 years of follow-up	88 (64–133)	129 (100–150)	0.015*
CRP (mg/l)			
at baseline	1.1 (1–5.3)	2.2 (1–5.7)	0.67
at 7 years of follow-up	3.5 (2.8–7)	2 (1–4.1)	0.049*
Basal cortisol at baseline (µg/dl)	24.1 (17.7–37.6)	21.4 (14.1–27)	0.2
24-hour UFC index at baseline	2.9 (2–4.5)	3.1 (1.2–5.1)	0.84
LNSC at baseline (ng/ml)	9.1 (4.8–15.7)	5.7 (4–13.3)	0.25
1 mg DST, Cortisol at baseline (µg/dl)	13.9 (7.6–24.4)	11.6 (5.3–18.3)	0.38
Time to remission (d)	915 (267–4499)	1582 (651–3439)	0.55

Abbreviations: IQR: interquartile range, BMI: Body mass index, WHR: waist-to-hip ratio, RFM: relative fat mass.

Cushing's disease reported on an improvement of glucose metabolism in approximately two-thirds of patients one year after curative surgery [12]. Another study showed in a prospective cohort of 32 patients with Cushing's disease, the waist-to-hip ratio decreased from 0.99 to 0.88 one year after remission [20]. Long-term follow-up has also shown partial recovery of metabolic and cardiovascular disease, where in 118 patients, diabetes and hypertension resolved in 56% and 36%, respectively after 7.9 years [21], while a multicenter study of 320 patients in remission for 10 years suggested that many metabolic risk factors improve over time [22].

However, most of these studies were observational and did not include matched control groups. This distinction is critical, as improvement does not necessarily equal normalization.

Indeed, control-group studies have demonstrated that patients in remission from hypercortisolism continue to carry an excess of metabolic disorders. Persistent central adiposity, pathological fat distribution, and adverse adipokine profiles have been reported by Barahona, Wagenmakers, Ragnarsson, Ceccato [19,23–25], and Sasson [26], while Terzolo and colleagues confirmed that cardiometabolic risk factors remain higher in remission than in healthy individuals [27]. However, these investigations were generally limited by small patient numbers, cross-sectional designs, or short follow-up durations.

Our study helps closing this gap. By directly comparing 99 patients with at least 7 years of follow-up against carefully matched controls, we demonstrate that metabolic health remains significantly impaired long after remission. WHR and RFM remained elevated, HbA1c levels higher, and both diabetes prevalence and metabolic medication use was greater than in the KORA cohort. These findings strengthen the evidence that remission from hypercortisolism, while essential, does not restore metabolic complications. The lack of correlation between measures of obesity and glucose metabolism long after remission with cortisol-related parameters at baseline further suggests that metabolic and inflammatory pathways initiated during hypercortisolism can persist despite biochemical cure in some patients.

The persistence of metabolic impairment after remission raises important questions about the underlying mechanisms. One explanation is that remission does not eliminate the increased number of adipocytes formed during hypercortisolism, leaving behind a reservoir of metabolically active fat cells [18]. These cells may sustain a proinflammatory state through altered adipokine production. Supporting this, Barahona et al. found that 37 patients with cured CS, even 11 years post-remission, exhibited lower adiponectin but higher sTNF-R1 and IL-6 levels, alongside persistent central fat distribution when compared with 85 controls [19]. Our analyses support this hypothesis. In the CS cohort, we observed strong associations between relative fat mass (RFM), HbA1c, BMI, and CRP, indicating that residual adiposity is linked to both impaired glucose metabolism and systemic inflammation. Patients with persistent T2DM at 7 years had significantly higher BMI and CRP levels, suggesting that baseline obesity, glycemic status, and comorbidity burden may predict long-term outcomes [21,26].

Notably, the degree of insulin resistance in patients with CS was relatively modest. Given that hypercortisolism impairs both insulin sensitivity and β-cell function, the HOMA-IR index, which depends on insulin levels, may underestimate insulin resistance in this setting and thus be less reliable than direct measurement methods.

Taken together, our findings highlight that cardiometabolic risk persists long after biochemical remission, exceeding that of both the general population and matched controls. Clinically, this underscores the need for long-term management focused on weight control and optimization of cardiovascular risk factors. We suggest that a history of CS should be considered an independent cardiovascular risk factor, warranting stricter therapeutic targets such as LDL < 70 mg/dL (1.8 mmol/l) and normotensive blood pressure, a view endorsed by other expert centers as well [28].

Recent advances in cardiometabolic pharmacotherapy may offer promising strategies to address the persistent metabolic disturbances observed after remission of Cushing's syndrome. Incretin-based agents and sodium–glucose cotransporter-2 (SGLT2) inhibitors, which are established treatments for both type 2 diabetes mellitus and obesity, reduce visceral adiposity and have consistently demonstrated robust cardiovascular and renal protective effects in large-scale outcome trials, and may therefore represent attractive options for long-term risk reduction in this population.

The strengths of our study include extended follow-up, systematic monitoring of metabolic parameters, and the use of carefully matched controls, which enhance the reliability and clinical relevance of our findings. Limitations include the retrospective, single-center design which limits causal inference and generalizability. Moreover, the absence of longitudinal imaging precludes detailed analysis of changes in fat distribution over time.

Future research should test targeted strategies to reduce visceral adiposity and inflammation—such as structured exercise, nutritional interventions, and pharmacological approaches (e.g., metformin, incretin-based agents, SGLT2-inhibitors) and explore longitudinal profiling of adipokines and inflammatory markers to better predict long-term outcomes.

5. Conclusion

Despite improvements in body weight, visceral fat, and glycemic control after biochemical remission, patients with CS continue to show an increased metabolic burden compared with controls. Residual risk is driven by obesity and inflammation, emphasizing long-term lifestyle/metabolic follow-up. We propose that a history of CS should be considered an independent cardiovascular risk factor.

6. Data availability

The participants of this study did not give written consent for their data to be shared publicly, so due to the sensitive nature of the research data cannot be shared.

KORA data and bio samples can be requested by scientists for research projects by means of a project agreement via the KORA.PASST use and access hub (https://helmholtz-muenchen.managed-otrs.com/external). The KORA Board is responsible for review and approval of the requests. The rights of study participants, adherence to Good Scientific Practice and the goals of the KORA study guide the decision. The European General Data Protection Regulation (GDPR) applies to all applicants.

CRediT authorship contribution statement

German Rubinstein: Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Vanessa Fedtke:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Cornelia Then:** Writing – review & editing, Methodology. **Elisabeth Nowak:** Writing – review & editing, Methodology, Data curation. **Frederick Vogel:** Writing – review & editing. **Leah Braun:** Writing – review & editing, Formal analysis, Data curation. **Stephanie Zopp:** Project administration. **Petra Zimmermann:** Writing – review & editing. **Annette Peters:** Writing – review & editing, Methodology, Investigation, Data curation. **Margit Heier:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Birgit Linkohr:** Writing – review & editing, Formal analysis, Data curation. **Michael Roden:** Writing – review & editing. **Martin Bidlingmaier:** Writing – review & editing. **Felix Beuschlein:** Writing – review & editing. **Martin Reincke:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Katrin Ritzel:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work is part of the German Cushing's Registry CUSTODES and has been supported by a grant from the Else Kröner-Fresenius Stiftung to MR. (2012_A103 and 2015_A228). MB, FB and MR are supported by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation, project number: 314061271-TRR 205). FV is supported by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation, project number: 413635475 (FV) and the Munich Clinician Scientist Program (MCSP) of the LMU München. LB and EN are supported by the Clinician Scientist Program RISE (Rare Important Syndromes in Endocrinology), supported by the Else-Kröner-Fresenius Stiftung and Eva Luise und Horst Köhler Stiftung. MRo is supported by grants from the German Research Foundation (DFG) (GRK 2576), the European Community (HORIZON-HLTH-2022-STAYHLTH-02-01: Panel A) to the INTERCEPT-T2D consortium, the Schmutzler-Stiftung and by grants of the Ministry of Culture and Science of the State of North Rhine-Westphalia and the German Federal Ministry of Health (BMG) to the German Diabetes Center (DDZ) and by grants of the Federal Ministry for Research (BMBF) to the German Center for Diabetes Research (DZD). We thank the COST Action CA20122 Harmonisation for supportive networking.

The KORA study was initiated and financed by the Helmholtz Zentrum München – German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research (BMBF) and by the State of Bavaria. Data collection in the KORA study is done in cooperation with the University Hospital of Augsburg.

We thank all participants for their long-term commitment to the KORA study, the staff for data collection and research data management and the members of the KORA Study Group (https://www.helmholtz-munich.de/en/epi/cohort/kora) who are responsible for the design and conduct of the study.

Appendix A. Additional material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2026.113436.

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