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Stronger association between morning serum cortisol level and diurnal time in range in type 2 diabetes?

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Abstract

Background The hypothalamic-pituitary-adrenal axis is thought to play a vital role in glucose homeostasis and diabetes. This study investigated the association between morning serum cortisol and time in range (TIR), including daytime TIR, in type 2 diabetes (T2DM).

Methods 310 patients with T2DM had serum cortisol measured at 8 a.m. All participants underwent continuous glucose monitoring (CGM) for three consecutive days, then TIR and glycemic variability (GV) parameters were evaluated. Using 100 g standard steamed bread meal test, blood glucose, C peptide and insulin at different points were collected to assess insulin sensitivity and islet function.

Results Patients with higher serum cortisol exhibited lower TIR and TITR ($P<0.001$). Spearman correlation analysis showed that the negative correlation between cortisol and daytime TIR (r=-0.231, $P<0.001$) was stronger than that of overnight TIR (r=-0.134, $P=0.028$). Similarly, there existed a negative correlation between cortisol and pancreatic function indicators such as HOMA-β, insulinogenic index (IGI), area under the curve of C-peptide within half an hour (AUCCp0.5 h) and three hours (AUCCp3h) (r=-0.248, -0.176, -0.140, -0.185, respectively, $P<0.05$). In contrast, cortisol was positively associated with TAR ($r=0.217$, $P<0.001$) and GV parameters including MBG, MAGE, LAGE, HBGI, MODD, ADDR (P of MAGE and MODD > 0.05). Multiple stepwise regression revealed that cortisol was an independent contributor of TIR, TITR and diurnal TIR, with diurnal TIR of stronger relevance.

Conclusions Morning serum cortisol is negatively correlated with TIR, especially diurnal TIR and positively associated with GV parameters. Inappropriate cortisol secretion may have an adverse influence on glucose homeostasis in T2DM.

Keywords Cortisol, The HPA axis, Continuous glucose monitoring, Time in range, Diurnal time in range, Type 2 diabetes mellitus

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Background

Cortisol is a type of steroid hormone secreted by zona fasciculata cells of the adrenal cortex. The secretion of cortisol is mostly controlled by the hypothalamic-pituitary-adrenal (HPA) axis, which has a circadian rhythm, generally reaching a peak in the morning [1]. Whereas in fact, the HPA axis is considered a neuroendocrine system that has been extensively studied in terms of acute challenges or stressors. Under stress conditions, activation of the HPA axis leads to increased cortisol secretion, which is the most important response to stress [2]. A widely accepted mechanism by which cortisol enhances the body's resistance to stimulation is that it can promote protein breakdown and gluconeogenesis. Studies have proved that cortisol influences glucose metabolism by promoting liver gluconeogenesis, inhibiting glucose uptake in adipocytes and skeletal muscle, restraining insulin secretion, and causing insulin resistance and inflammation. In other words, cortisol is recognized to participate in glucose metabolism and maintain glucose homeostasis through various pathways.

With guidelines for diabetes treatment highlighting personalized treatment in diabetes management, continuous glucose monitoring (CGM), an optimal method to describe a patient's recent glycemic status, is becoming more broadly used in clinical practice. HbA1c has long been recognized as the gold standard in clinical practice to assess long-standing glycemic control during the last 2 to 3 months [3, 4], while limitations like inaccuracy measurement and poor reflection of glycemic variability can hardly be neglected [5, 6]. Meanwhile, CGM supplies us with a more precise glycemic profile by detecting blood glucose for several consecutive days. Time in range (TIR) is regarded as the proportion of time that blood sugar values vary in the purpose range of 3.9–10 mmol /L throughout a day [3] and the newly proposed time in tight range (TITR) strictly limits the range to 3.9–7.8 mmol /L. The key parameters of CGM also include TAR, TBR, SD, CV, MBG, MAGE, MODD and ADDR [7], which capture valuable supplementary information about glycemic fluctuation and daily pattern of blood glucose.

Considering multiple clinical evidence, the ADA recommended TIR to be one of the target indicators for the evaluation of blood glucose control [8]. In addition, a variety of studies has confirmed that TIR can act as a surrogate indicator for the occurrence of long-running diabetic complications. Lu explored the independent correlation between TIR and carotid intima-media thickness in T2DM [9]. A subsequent study involving 6225 patients revealed that lower TIR led to growing risk of all-cause death and cardiovascular disease death [10]. Another study [11] closely associated TIR with the risk of DR and microalbuminuria and pointed out that it should be an acceptable endpoint in clinical trials.

Compared with traditional measures, glycemic variability parameters accurately reflect hypoglycemia, hyperglycemia, daily and day-to-day glycemic fluctuations, each of which has been associated with oxidative stress [12, 13]. Oxidative stress is an important pathological mechanism of multiple diseases, including diabetes and its complications. Accumulating evidence supports the role of glycemic variability in the development of diabetic complications, especially cardiovascular complications [14]. Therefore, attention should be paid to glycemic variability in contemporary diabetes management.

Since cortisol is believed to be involved in glucose metabolism, there has been a considerable number of studies on the the association between cortisol and diabetes, which used to concentrate on traditional glycemic indexes like HbA1c, fasting and postprandial blood glucose. However, there still exist blank spaces in this field that can be filled. As CGM parameters outline a comprehensive and detailed blood glucose profile, while traditional parameters only reflect glycemic status unilaterally, not to mention that TIR can be subdivided vertically into daytime TIR and nighttime TIR so as to explore whether glucose metabolic rhythm echoes to cortisol circadian rhythm. This retrospective observational study was designed to investigate the correlation between morning serum cortisol and CGM parameters, especially TIR and diurnal TIR, in patients with T2DM.

Methods

Study subjects

Based on the 1999 diagnostic criteria of T2DM by the WHO [15], a total of 310 hospitalized patients (Fig. 1) between January 2015 and May 2022 were enrolled at the Department of Endocrinology, Jinling Hospital affiliated to Nanjing University. Patients over 18 with a stable glucose-lowering regimen over the past quarter were included. Exclusion criteria were the followings: diabetic ketoacidosis, hyperosmolar hyperglycemic syndrome and recurrent severe hypoglycemia within 3 months or during hospitalization; serious systemic diseases, such as cancer and severe infections; diagnosis of cardiovascular and cerebrovascular diseases; hepatic or renal insufficiency; medication that may promote or inhibit the secretion of ACTH and cortisol; history of pituitary or adrenal surgery; suffering from anxiety, depression, bipolar or other mental disorders that affect hormone levels, or suffering from severe insomnia. The ethics committee from locality approved this protocol in conformity to the principles of Declaration of Helsinki.

CGM parameters

Blood glucose was monitored by implanting a probe into subcutaneous tissue for 72 h, which detected and collected blood glucose data every other three minutes,

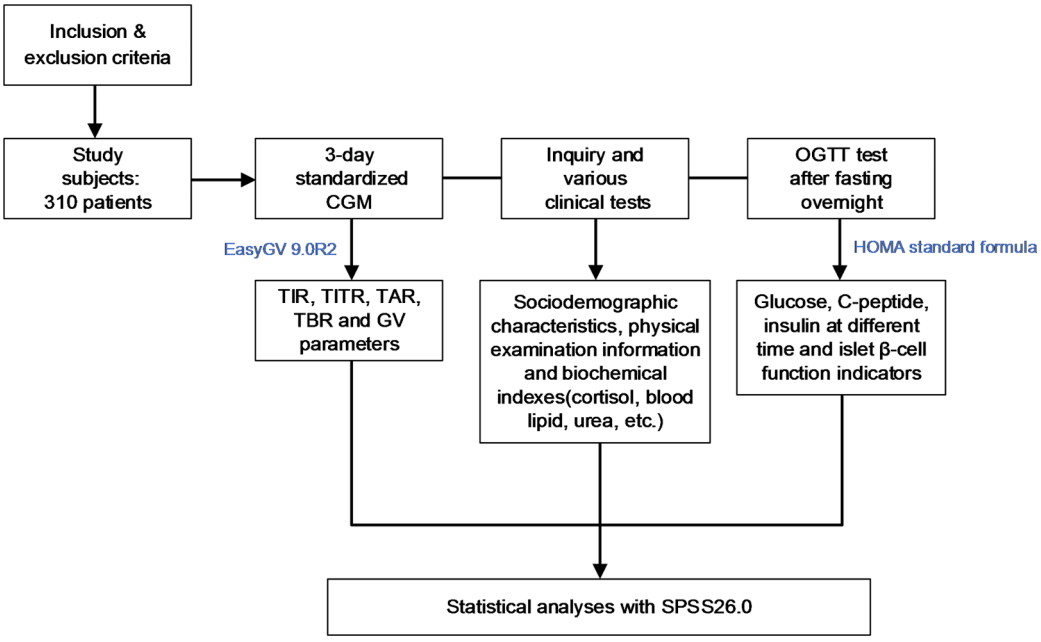

Fig. 1 Flow chat of study protocol

invisible to the patient. The CGM sensors from Meiqi Company were applied, which had been widely used in China and the accuracy and stability had been confirmed by clinical trials, with mean absolute relative difference (MARD) similar to other mainstream CGM systems [16]. All participants were previously notified of the novel technology and its safety by a certified professional, and were instructed to stick to a standardized diet and to avoid strenuous activities. During the 3-day CGM, patients were adhered to their original glucose-lowering regimen, which refer to oral medications that have no effect on C-peptide and insulin.

Using Oxford's EasyGV version 9.0R2, we calculated TIR and other glucose metrics derived from CGM. TIR referred to the percentage of time that blood sugar remained in the target range of 3.9–10 mmol/L during the day, and for TITR the goal was 3.9–7.8 mmol/L. TBR represented the proportion that blood glucose was <3.9 mmol/L in 24 h, oppositely TAR was for the part that exceeded 10.0 mmol/L. Glycemic variability (GV) metrics such as coefficient of standard deviation (SD), variation of glucose (CV), largest amplitude of glucose excursion (LAGE), low glycemic index (LBGI), high glycemic index (HBGI), mean amplitude of glucose excursion (MAGE), mean daily difference (MODD) and mean daily risk range (ADDR) were calculated.

Anthropometric and biochemical measurements

Sociodemographic characteristics and physical examination information including sex, age, duration of diabetes, height and weight, were collected by trained physicians. Body mass index (BMI) was calculated as international formula: weight (kg) divided by height (m) squared. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by an electronic sphygmomanometer.

After fasting overnight, intravenous samples were drawn from participants before CGM. Biochemical indexes such as blood lipid, urea and creatinine were measured by automatic biochemical analyzer (7600 series automatic analyzer, Hitachi, Japan). Fasting blood glucose was determined by glucose oxidase method and HbA1c by high performance liquid chromatography (HLC-723G8 automated glycated hemoglobin analyzer, TOSOH, Japan). Concentrations of cortisol, ACTH, insulin and C-peptide were obtained by fluorescence immunoassay (IMMULITE 2000 XPi, Siemens, Germany).

Assessment of insulin resistance and islet function

All participants underwent a 100 g standard steamed bread meal test after fasting for at least 8 h and discontinuation of medication that affect blood glucose and insulin, which could substitute oral glucose tolerance test (OGTT) and simultaneous insulin-C-peptide-glucagon releasing test. Serum glucose, C peptide and insulin at different time points were then recorded. According to the homeostasis model assessment (HOMA) standard formula, HOMA-IR = [fasting plasma glucose (mmol/L) * fasting insulin (mIU/L)]/22.5, HOMA-β = 20*fasting insulin (mIU/L) / [fasting plasma glucose (mmol/L) −3.5]. Insulinogenic index (IGI) was evaluated as △insulin (0.5 h–0 h) /△glucose (0.5 h–0 h) to estimate early insulin secretion. The area under the C-peptide curve (AUCCp) in half an hour and in three hours were calculated by

trapezoidal method. All antidiabetic treatments were suspended during this process.

Statistical analyses

SPSS26.0 software was performed for statistical analyses. According to the tertiles of cortisol levels, patients were classified as G1 (2.8–120 umol/L), G2 (121-166.7 umol/L) and G3 (168–822 umol/L), with data presented as mean ± SD or median [25%, 75%]. Concerning continuous and normally distributed variables, we applied one-way ANOVA to assess trends across groups, whereas Kruskal-Wallis H test was used for anomalies. Chi-square test was adopted for categorical variables. The Spearman coefficient determines the relationship between cortisol and other variables. Multiple linear regression analysis was used to explore the the independent correlation between cortisol and CGM parameters. We consider that $P<0.05$ was statistically significant.

Results

Comparison of baseline characteristics

A population of 310 patients with diabetes was divided into 3 groups by tertiles of serum cortisol at 8, the concentrations of which were 82.55(65.76, 107.75) umol/L, 142.12(133, 152) umol/L, 239.35(177, 242) umol/L, severally. No significant difference was found between groups in clinical characteristics such as gender, age, duration of diabetes, height and weight, BMI and blood pressure ($P>0.05$). Results were the same for biochemical indicators including TC, TG, HDL-C, LDL-C, urea and creatinine ($P>0.05$), as shown in Table 1. In other words, baseline indexes in groups were balanced, making glucose metabolism parameters comparable.

Comparison of CGM parameters between groups

Patients from groups with higher cortisol displayed lower TIR, TITR and daytime TIR ($P=0.000$, 0.001, 0.002, respectively), while TAR, HbA1C ($P=0.002$, 0.001, respectively) and GV parameters such as MBG, LAGE, ADDR and HBGI ($P<0.05$) tended to be higher (Table 1). In addition, comparison between groups indicated that elevated cortisol level had an inclination for oral medication ($P<0.001$).

Correlation of cortisol and glucose metabolism parameters

Spearman correlation analysis made clear that there existed a negative correlation between cortisol and TIR, TITR (r=-0.241, -0.218, $P<0.001$) as well as LBGI (r=-0.129, $P=0.033$). The negative correlation between cortisol and daytime TIR (r=-0.231, $P<0.001$) was stronger than that of overnight TIR (r=-0.134, $P=0.028$). Similarly, cortisol was negatively associated with pancreatic β-cell function indicators including HOMA-β, insulinogenic index (IGI), area under the curve of C-peptide within half an hour (AUCCp0.5 h) and area under the curve of C-peptide within three hours (AUCCp3h) (r=-0.248, -0.176, -0.140, -0.185, separately, $P<0.05$) (Table 2).

On the contrary, cortisol was positively correlated with TAR ($r=0.217$, $P<0.001$), TBR ($r=0.01$, $P=0.865$), HbA1c ($r=0.210$, $P<0.001$) and GV parameters including MBG, MAGE, LAGE, HBGI, MODD, ADDR (P of MAGE and MODD>0.05). To make the study more complete, we also investigated the correlation of ACTH, but the results showed slight association compared with cortisol, as Table 2 demonstrated.

Multiple stepwise regression analysis of the factors that influence TIR, TITR and diurnal TIR

Multiple stepwise regression analysis was employed to investigate the influencing factors of TIR. It turned out that cortisol at 8a.m. was an independent influencing factor of TIR (ß = -0.042, $P=0.019$), TITR (ß = -0.036, $P=0.033$) and daytime TIR (ß = -0.047, $P=0.015$), daytime TIR having a stronger correlation (Table 3).

Discusssion

Cortisol, one of the most important human glucocorticoids, is a powerful modulator of physiological systems, including the central nervous system. When initially discovered in the 1950s, it was applied to rheumatic patients with remarkable results [17]. Subsequent experiments expanded the scope and validated powerful effects in anti-inflammation, anti-allergy and anti-shock.

The HPA axis mainly includes the parvocellular corticotropin-releasing hormone (CRH), argininevasopressin (AVP) neurons of the hypothalamic paraventricular nuclei (PVN), anterior pituitary corticotrophs and adrenal cortisol-producing cells. Altogether they administer the secretion of cortisol through a complex positive and negative feedback system. Normal cortisol management follows a circadian pattern. The amplitude of CRH and AVP pulses surges sharply at dawn, leading to a burst of corticotropin (ACTH) secretion in the systemic circulation [1]. Consequently, cortisol is usually high upon awakening, then rises within 30–40 min and slowly falls throughout the day. It reaches its nadir around midnight, the amount of which is about a quarter of that in the early morning. During the rest of the day, it was secreted in pulses at a frequency of approximately twenty to thirty minutes at a time [18]. The balance of the HPA axis is vital for maintaining physical and mental health, for both overactivity and underactivity of the HPA axis may contribute to diseases.

Cortisol acts as a systemic effector of the HPA axis, whose secretion is closely connected with environmental and empirical events. Stress is a threatened state of homeostasis or dissonance caused by internal or external adverse forces or stressors [2, 19]. Stressful circumstances

Table 1 Characteristics among groups by tertiles of cortisol

Variables	G1	G2	G3	*P*
Number	104	103	103	
Male/Female	70/34	69/34	66/37	
Cortisol (umol/L)	82.55(65.76, 107.75)	142.12(133, 152)	239.35(177, 242)	
ACTH	28.78(15.10,36.90)*#	40.84(23.10,48.60)*	48.00(28.83,62.60)#	< 0.001
TIR(%)	71.80(59.69,89.18)*#	63.75(49.06,83.75)*	56.05(32.30,82.29)#	< 0.001
TITR(%)	40.38(23.12,57.81)*#	32.26(12.08,50.37)*	27.32(6.67,41.48)#	0.001
TAR(%)	27.86(10.68,40.23)*#	35.68(13.85,50.63)*	41.27(17.29,64.38)#	0.002
TBR(%)	0.34(0,0)	0.56(0,0)	2.67(0,0)	0.863
Daytime TIR(%)	75.44(63.50,87.50)*#	62.02(39.63,85.00)*	33.87(11.69,57.57)#	0.002
Daytime TAR(%)	24.41(12.40,36.50)*#	37.84(14.72,60.37)*	65.79(42.43,88.31)#	0.003
Daytime TBR(%)	0.14(0.00,0.00)	0.13(0.00,0.00)	3.95(0.00,0.00)	0.201
Nighttime TIR(%)	80.86(66.04,100.00)*	73.93(48.96,100.00)	69.33(42.09,99.44)*	0.401
Nighttime TAR(%)	17.94(0.00,33.33)*	25.74(0.00,51.04)	30.26(0.28,51.92)*	0.035
Nighttime TBR(%)	1.20(0.00,0.00)	0.34(0.00,0.00)	0.42(0.00,0.00)	0.100
Age(years)	52.41 ± 15.09	54.73 ± 15.52	51.71 ± 14.30	0.254
Duration(years)	7.90(2,12)	8.76(2,14)	8.14(1,14)	0.604
Height(m)	167.67 ± 7.76	167.62 ± 7.80	167.38 ± 7.17	0.895
Weight(Kg)	74.64 ± 13.93	71.65 ± 12.53	71.91 ± 15.52	0.230
BMI(Kg/m2)	26.47 ± 4.12	25.43 ± 3.68	25.60 ± 5.03	0.114
SBP(mmHg)	137.69 ± 20.98	134.12 ± 16.93	132.51 ± 16.16	0.547
DBP(mmHg)	81.81 ± 11.05	82.15 ± 11.04	81.22 ± 11.06	0.982
TG(mmol/L)	2.55(1.08,2.52)	2.26(1.19,2.90)	3.74(1.15,2.44)	0.664
TC(mmol/L)	4.58(3.79,5.12)	4.54(3.78,5.36)	5.57(4.00,5.65)	0.150
HDL(g/L)	1.06 ± 0.25	1.08 ± 0.28	1.10 ± 0.27	0.488
LDL(g/L)	2.73 ± 1.04	2.64 ± 0.83	2.83 ± 1.06	0.605
Urea(mmol/L)	6.41(4.80,7.30)	11.09(4.70,7.03)	6.16(4.80,6.80)	0.708
Creatinine(umol/L)	74.24(49.05,76.25)	64.55(48,72)	67.86(45.00,69.90)	0.374
HbA1C(%)	8.51 ± 1.95(69.51 ± 21.31mmol/mol)*	8.60 ± 1.84(70.49 ± 20.11mmol/mol)^	9.71 ± 2.34(82.62 ± 25.57mmol/mol)*^	0.001
FPG(mmol/L)	8.16 ± 1.76*	8.69 ± 2.11	9.21 ± 2.32*	0.004
MBG(mmol/L)	8.88 ± 1.60*	9.40 ± 1.88	9.70 ± 2.62*	0.017
LAGE(mmol/L)	11.25(8.33,13.13)*	11.93(9.31,14.37)	13.35(9.56,14.5)*	0.043
MODD(mmol/L)	2.25 ± 1.19	2.36 ± 1.08	2.57 ± 1.32	0.223
MAGE(mmol/L)	4.48 ± 1.93	4.61 ± 1.71	4.75 ± 1.75	0.393
ADDR(mmol/L)	22.31(13.27,28.44)*	25.09(17.98,31.32)	28.28(18.93,32.23)*	0.048
SD	2.10 ± 0.76	2.27 ± 0.74	2.31 ± 0.94	0.227
CV	0.24(0.19,0.28)	0.24(0.20,0.28)	0.27(0.17,0.28)	0.353
LBGI	3.04(0.06,1.31)	0.74(0.10,0.89)	0.69(0,0.93)	0.073
HBGI	7.42(3.53,9.82)*#	9.23(4.96,12.04)*	10.59(0,13.24)#	0.005
No Antidiabetic Treatment	4,3.85%	1,0.09%	1,0.09%	
Insulin	60,57.69%	71,68.93%	73,70.87%	
Oral Medication	59,56.73%*#	86,83.50%*	86,83.50%#	< 0.001
Insulin & Oral Medication	27,5.96%*#	55,53.40%*	57,55.34%#	< 0.001

Table 1 (continued)

Variables	G1	G2	G3	*P*
Antihypertensive Drugs	51,49.04%	49,47.57%	47,45.63%	
Lipid Medications	38,36.54%	32,31.07%	37,35.92%	

Data are presented as means ± SD, median (25% and 75% interquartiles), and count (percentages) according to characteristics of the distribution. Between-group, comparisons were conducted by One-way ANOVA, Kruskal- Wallis H test, and the chi-squared test. BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, TG: triglycerides, TC: total cholesterol, HDL: high-density lipoprotein, LDL: low-density lipoprotein, HbA1c: hemoglobin A1C, TIR: time in range, TITR: time in tight range, TBR: time below range, TAR: time above range, FPG: fasting plasma glucose, MBG: mean blood glucose, LAGE: largest amplitude of glucose excursions, MODD: mean of daily differences, MAGE: mean amplitude of glucose excursions, ADDR: average daily danger range, CV: coefficient variation, SD: standard deviation, LBGI: low blood glucose index, HBGI: high blood glucose index

* Significant difference between group 1 and group 2($P<0.05$)

\# Significant difference between group 1 and group 3($P<0.05$)

^ Significant difference between group 2 and group 3($P<0.05$)

and other stimuli that may not constitute stress (like exercise, anxiolytics or sexual experience) can elicit cortisol secretion. Stress response is an upward generative, dynamically regulated but evolutionarily conserved response, during which the activation of the HPA axis is mild but brings about amplified and prolonged secretory responses [20].

It is well known as early as the last century that chronic stress influences glucose homeostasis and links to T2DM because of the diabetogenic effects of glucocorticoid and stress hormones [21, 22]. A 1980 study [23] found that stress had a much greater adverse effect on blood glucose regulation in diabetic patients compared with normal subjects. An American article [24] in 1996 suggested that the 24-hour cortisol rhythm is responsible, at least in part, for the circadian variation in glucose tolerance. In recent years, we discovered that elevated plasma cortisol in the morning is associated with greater insulin resistance, reduced β-cell function [25] and a higher risk of diabetes [26]. This result was revalidated in African Americans in 2019 [27], where morning cortisol was associated with a variety of glucose metabolism indicators (increased FPG and HbA1c, decreased β-cell function) and the prevalence of T2DM in AA. Moreover, cortisol is bound up with diabetic complications and long-term prognosis. Roy and Chiodini verified that cortisol concentration is correlated with the degree of diabetic complications, respectively [28, 29].

To explore the relationship between cortisol and GV parameters, we employed CGM in our study to monitor blood glucose fluctuations. As an emerging indicator, TIR not only provides comprehensive, continuous and reliable short-term glucose variability information, but can be used to predict diabetic complications and evaluate clinical terminal outcomes as well [11]. Besides, TIR is highly correlated with HbA1C, both of which have been currently recommended as major indicators to assess individual glycemic control [30].

Since plenty of studies have elucidated the unfavourable effects of cortisol on glucose metabolism, our present study added several chief new components. To begin with, we adopted a novel and popular clinical technique, CGM. The traditional hormone cortisol and the brand-new blood glucose assessment index TIR were combined together for the first time. There existed a stronger negative correlation between cortisol and TIR than the current gold standard HbA1C. Compared with previous studies that used to choose FPG and blood glucose at different time points as indexes, GV parameters stemmed from CGM were more comprehensive and detailed. It turned out that higher cortisol was concerned with reduced LBGI and increased TAR, TBR, HbA1c and GV parameters such as TAR, MBG, HBGI and LAGE. Obviously, these results suggested that cortisol was an adverse factor for glucose stability, which added new cogent evidence to this heated issue. In addition, our finding echoed the rhythm of hormone secretion. Based on glycemic profile for three consecutive days, we converted TIR into daytime TIR and nighttime TIR so as to conduct more targeted research. The correlation between cortisol and daytime TIR was obviously stronger than that of overnight TIR. Plus, cortisol was verified an independent contributor of TIR and diurnal TIR, with diurnal TIR of stronger relevance. This implied that the effect of cortisol on blood glucose was closely allied to its circadian rhythm. Dawn phenomenon is defined as a state of hyperglycemia in the early morning (typically 3 to 9 am) without hypoglycemia at night in diabetic patients, which is mainly caused by the unbalanced secretion of various glucose-raising hormones, such as growth hormone, adrenocortical hormone, catecholamines and glucagon [31]. Cortisol reaches its peak at 8 in the morning and drops down gradually throughout the day, roughly in accordance with the occurrence time of the "dawn phenomenon". The basal insulin secretion of normal people goes up with the increase of glucose-producing hormones, while the insulin secretion of diabetic patients is insufficient, which cannot effectively counteract the glucose-producing effect caused by glucose-producing hormones. Our finding suggested that cortisol had an improved impact on glycemic control during the day than during the night, thanks to the circadian rhythm

Table 2 Spearman correlation among cortisol/ACTH and glucose metabolism parameters

Variables	Cortisol		ACTH	
TIR	*r* = -0.241*	*P* < 0.001	*r* = -0.144*	*P* = 0.013
TITR	*r* = -0.218*	*P* < 0.001	*r* = -0.125*	*P* = 0.038
TAR	*r* = 0.217*	*P* < 0.001	*r* = 0.150*	*P* = 0.009
TBR	*r* = 0.01	*P* = 0.865	*r* = -0.087	*P* = 0.132
Daytime TIR	*r* = -0.231*	*P* < 0.001	*r* = -0.113	*P* = 0.068
Daytime TAR	*r* = 0.228*	*P* < 0.001	*r* = 0.115	*P* = 0.064
Daytime TBR	*r* = 0.107	*P* = 0.061	*r* = -0.017	*P* = 0.768
Nighttime TIR	*r* = -0.134*	*P* = 0.028	*r* = -0.025	*P* = 0.692
Nighttime TAR	*r* = 0.165*	*P* = 0.007	*r* = 0.047	*P* = 0.453
Nighttime TBR	*r* = -0.109	*P* = 0.074	*r* = -0.106	*P* = 0.087
HbA1C	*r* = 0.210*	*P* < 0.001	*r* = 0.071	*P* = 0.226
INS0.5 h	*r* = -0.143*	*P* = 0.03	*r* = -0.071	*P* = 0.293
INS1h	*r* = -0.171*	*P* = 0.009	*r* = -0.112	*P* = 0.094
INS2h	*r* = -0.181*	*P* = 0.002	*r* = -0.144*	*P* = 0.015
INS3h	*r* = -0.181*	*P* = 0.006	*r* = -0.111	*P* = 0.099
Cp0	*r* = -0.144*	*P* = 0.013	*r* = -0.048	*P* = 0.412
Cp0.5 h	*r* = -0.14*	*P* = 0.033	*r* = -0.086	*P* = 0.198
Cp1h	*r* = -0.183*	*P* = 0.005	*r* = -0.123	*P* = 0.065
Cp2h	*r* = -0.183*	*P* = 0.002	*r* = -0.122*	*P* = 0.040
Cp3h	*r* = -0.142*	*P* = 0.031	*r* = -0.095	*P* = 0.156
Glu0	*r* = 0.165*	*P* = 0.004	*r* = 0.070	*P* = 0.022
Glu0.5 h	*r* = 0.277*	*P* < 0.001	*r* = 0.148*	*P* = 0.025
Glu1h	*r* = 0.213*	*P* < 0.001	*r* = 0.109	*P* = 0.097
Glu2h	*r* = 0.228*	*P* < 0.001	*r* = 0.114	*P* = 0.063
Glu3h	*r* = 0.262*	*P* < 0.001	*r* = 0.125	*P* = 0.057
FPG	*r* = 0.244*	*P* < 0.001	*r* = 0.184*	*P* = 0.002
MBG	*r* = 0.186*	*P* = 0.001	*r* = 0.146*	*P* = 0.012
MAGE	*r* = 0.081	*P* = 0.193	*r* = 0.077	*P* = 0.219
LAGE	*r* = 0.167*	*P* = 0.005	*r* = 0.085	*P* = 0.162
MODD	*r* = 0.115	*P* = 0.081	*r* = 0.030	*P* = 0.660
ADDR	*r* = 0.185*	*P* = 0.005	*r* = 0.122	*P* = 0.070
SD	*r* = 0.096	*P* = 0.094	*r* = 0.050	*P* = 0.389
CV	*r* = -0.044	*P* = 0.441	*r* = -0.025	*P* = 0.664
LBGI	*r* = -0.129*	*P* = 0.033	*r* = -0.073	*P* = 0.238
HBGI	*r* = 0.22*	*P* < 0.001	*r* = 0.140*	*P* = 0.022
HOMA-β	*r* = -0.248*	P < 0.001	*r* = -0.087	*P* = 0.146
IGI	*r* = -0.176*	*P* = 0.006	*r* = -0.117	*P* = 0.071
AUCcp0.5 h	*r* = -0.140*	*P* = 0.033	*r* = -0.041	*P* = 0.539
AUCcp3h	*r* = -0.185*	*P* = 0.005	*r* = -0.093	*P* = 0.171
HOMA-IR	*r* = -0.103	*P* = 0.079	*r* = -0.024	*P* = 0.686
ACTH	*r* = 0.406*	P < 0.001		

Abbreviation: HbA1c: hemoglobin A1C, INS: insulin, Cp: C-peptide, Glu: postprandial glucose, TIR: time in range, TITR: time in tight range, TBR: time below range, TAR: time above range, FPG: fasting plasma glucose, MBG: mean blood glucose, LAGE: largest amplitude of glucose excursions, MODD: mean of daily differences, MAGE: mean amplitude of glucose excursions, ADDR: average daily danger range, CV: coefficient variation, SD: standard deviation, LBGI: low blood glucose index, HBGI: high blood glucose index, HOMA-β: homeostasis model assessment of β-cell function, HOMA-IR: homeostasis model assessment of insulin resistance, IGI: Insulinogenic index, AUCCp: area under the curve of C-peptide

Table 3 Multiple stepwise regression analysis of influencing factors of TIR, TITR and diurnal TIR

	β	*P*	95%CI
(Constant)	130.658	< 0.001	94.745 to 166.571
Cortisol	-0.042	0.019	-0.076 to -0.007
Duration	-0.577	0.027	-1.089 to –0.066
HbA1c	-3.633	< 0.001	-5.139 to -2.127
Creatinine	-0.127	0.022	-0.864 to -0.085
Dependent Variable: TIR (R^2 = 0.244)			
(Constant)	76.748	< 0.001	62.463 to 91.034
HbA1c	-3.710	< 0.001	-5.129 to -2.290
Creatinine	-0.074	0.016	-0.134 to -0.014
Cortisol	-0.036	0.033	-0.069 to -0.003
Dependent Variable: TITR (R^2 = 0.137)			
(Constant)	119.070	< 0.001	103.217 to 134.934
HbA1c	-4.240	< 0.001	-5.801 to -2.679
Creatinine	-0.109	0.002	-0.176 to -0.041
Cortisol	-0.047	0.015	-0.085 to -0.009
TG	-1.057	0.021	-1.965 to -0.159
Duration	-0.495	0.035	-0.956 to -0.035
Dependent Variable: Diurnal TIR (R^2 = 0.218)			

Abbreviation: Cp: C-peptide, Glu: postprandial glucose, TIR: time in range, TITR: time in tight range, SBP: systolic blood pressure

of cortisol secretion and intenser activities in the daytime. Last but not least, a more comprehensive array of indexes was picked to assess islet β-cell function. Cortisol was negatively associated with C-peptide at different time points after meal, AUCCp0.5 h, AUCCp3h, IGI and HOMA-β. These results provided direct clinical evidence to explain the mechanism by which cortisol influences blood glucose, for it results in reduced β-cell function and insulin secretion. No significant relation was shown between cortisol and HOMA-IR, consistent with previous research findings [27].

Actually, a variety of pathways has been preliminarily studied through which cortisol elevates blood glucose. Glucocorticoids enhance the expression of gluconeogenic enzymes, reduce key mediators of insulin action in peripheral tissues and stimulate skeletal muscle protein and adipose tissue hydrolysis in order to promote gluconeogenesis, leading to hyperglycemia and insulin resistance in the body. Besides, glucocorticoids also regulate gene expression through ribocortin receptors, impairing glucose uptake and metabolism in islet β-cells [32]. Meanwhile, the aggregation of visceral fat, immunosuppression and secretion of various cytokines, as well as the recalibulation of mitochondrial function and the accumulation damage to mitochondrial DNA caused by high cortisol, are all connected to the pathogenesis of hyperglycemia [33].

To delve deeper, alterations in the HPA axis activity spectrum are associated with a series of pathological biomedical conditions, including mental disorders (depression, panic anxiety and anorexia nervosa) [2, 34]

and other physiological diseases (T2DM, hypertension, obesity, atherosclerosis and Alzheimer's disease) [35, 36]. It is not difficult to speculate that there exists a complex interaction between the HPA axis and diabetes status. Apart from the adverse effects of excessive cortisol on blood glucose mentioned above, the glycemic state of diabetic patients has a counterproductive effect on the HPA axis at the same time. Diabetes status is a stress metabolic condition of cells that induces lingering activation of the HPA axis. Enduring distress and depression caused by chronic illness is concerned with the turbulence of the HPA axis as well, for at least 10–15% of patients with diabetes suffer from depression [34]. The centrality hypothesis proposes that hyperglycemia is associated with hippocampal atrophy and a hypothetical decrease in hypothalamic inhibition of the hippocampus. Moreover, patients with diabetes may have impaired pituitary feedback [37]. In the meantime, available literature supports the assumption that modifications in cortisol occur before the onset of insulin resistance and T2DM [27].

In terms of clinical application, cortisol intervention may be a new treatment idea for diabetes. Patients with extravagant cortisol, known as Cushing's syndrome, have a phenotype similar to metabolic syndrome, making glucocorticoids an attractive therapeutic target. On top of expanding engagement of the sympathetic nervous system and the HPA axis, another common pathological mechanism in diabetes is advanced expression of 11-βHSD 1 in adipose tissue (Fig. 2), which converts inactive cortisone to cortisol, raising local levels of glucocorticoids. Studies conducted in rodents show improved metabolic profiles using 11β-HSD 1 inhibition. In humans, 11β-HSD 1 inhibition (currently mainly the selective compound carbenoxolone) has beneficial metabolic effects, most notably in models of insulin resistance and T2DM [38].

Over and above, diabetes is known to damage the nervous system and increase the risk of dementia and depression, for T2DM appears to share common pathophysiological mechanisms with cognitive disorders like Alzheimer's disease, which is affiliated with insulin resistance. Coincidentally, hypercortisolemia is similarly associated with cognitive dysfunction. The human body requires basal levels of glucocorticoids to maintain neurons, but very high morning cortisol in older adults with T2DM has deleterious effects on cognitive function [26]. It has been perceived that cognitive disorders and depression in diabetic patients may be linked with hyperactivity of the HPA axis, both of which can be ameliorated by normalizing the HPA axis. GLP-1 receptor agonists compensate for the reduction of GLP-1 levels and secretion in diabetic patients, giving an excellent answer in improving cognition and protecting nerves. However, its role in the physiological regulation of the HPA axis is far from fully understood, as Fig. 2 demonstrated. GLP-1 receptor agonists activate circuits engaged in the

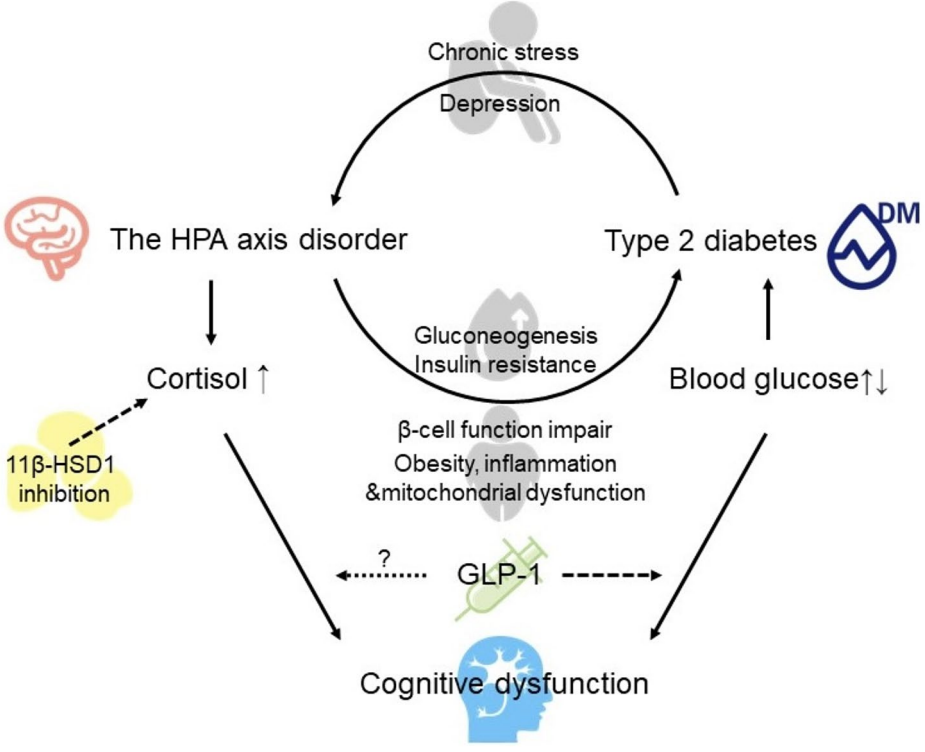

Fig. 2 Partial pathways of interaction between the HPA axis and type 2 diabetes and possible drug targets

acute neuroendocrine response to stress, promoting the HPA axis activation and CRH secretion, but appear to be attenuated in humans over a relatively short period of time (like one week), without relevant functional consequences in the long term [39]. The utilize of GLP-1 receptor agonists in patients diagnosed with diabetic encephalopathy along with elevated cortisol is a potential clinical issue to be explored.

To add a little more, there is an interesting result worth discussing that cortisol is thought to have an effect on blood pressure and lipid levels at the same time, while no differences were shown among groups in this study. The number of patients with antihypertensive or lipid medications across groups agrees. Although cortisol dose have some effects on blood pressure, actually it is aldosterone that plays a decisive role. The main function of the renin-angiotensin-aldosterone system (RAAS) is to regulate human blood pressure and maintain water and electrolyte balance, the over activation of which is one of the major causes of hypertension. It is widely accepted that mineralocorticoids play a much more important role than glucocorticoids in regulating blood pressure. Study has revealed that cortisol influences weakly the level of blood pressure independently from plasma aldosterone and that plasma cortisol at 8 is not associated with blood pressure [40]. Analogously, lipolytic rate-limiting enzymes play a major role in the catabolism of lipids. Lipolytic rate-limiting enzymes include hormone-sensitive lipase (HSL) and lipoprotein lipase (LPL), which are affected mostly by medullary hormones such as adrenal and norepinephrine, and glucose-metabolism-related hormones such as insulin and glucagon. Cortisol levels of participants in this study were basically within the normal physiological range, which failed to cause a statistically significant difference in blood serum lipid profiles in different individuals.

Our study has certain limitations, though. First of all, patients in our study received a 3-day CGM testing rather than those of 10–14 days recommended at international level [3, 41]. Besides, the detection of plasma free cortisol was relatively single, with only one time point (8 in the morning). A flattened circadian cortisol rhythm provides forceful evidence for a specific HPA system dysfunction, which requires detection of cortisol at multiple time points like 16 and 24. And hospitalization stress such as unfamiliar environment, insomnia, and anxiety might affect cortisol results. Moreover, cell or animal experiments were requested in order to explore possible mechanisms. Last of all, a retrospective observational study with a rather minor sample size might be considered unconvincing. In the future, a larger multi-center prospective study is demanded to validate the findings.

To recapitulate, serum cortisol at 8 o' clock is negatively correlated with TIR, especially diurnal TIR due to its circadian rhythm and positively correlated with GV parameters. Immoderate cortisol may have an adverse influence on glucose homeostasis in T2DM, which may become a potential new target for future interference of diabetes and its complications.

Abbreviations

T2DM	Type 2 diabetes
CGM	Continuous glucose monitoring
BMI	Body mass index
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
TC	Total cholesterol
TG	Triglyceride
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
HbA1c	Hemoglobin A1c
TIR	Time in range
TITR	Time in tight range
TBR	Time below range
TAR	Time above range
FPG	Fasting plasma glucose
MBG	Mean blood glucose
LAGE	Largest amplitude of glucose excursions
MODD	Mean of daily differences
MAGE	Mean amplitude of glucose excursions
ADDR	Average daily danger range
CV	Coefficient variation
SD	Standard deviation
LBGI	Low blood glucose index
HBGI	High blood glucose index
INS	Insulin
Cp	C-peptide
Glu	Postprandial glucose
HOMA-β	Homeostasis model assessment of β-cell function
HOMA-IR	Homeostasis model assessment of insulin resistancel
IGI	Insulinogenic index
AUCCp	Area under the curve of C-peptide

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Author contributions
YL, JL, WJ, WW, and XY conceived and designed the research. WW, XY, YL, QG and YX collected the data. YL, JL, WJ and XJ analyzed and interpreted the data. YL wrote the manuscript. BL, PG and JS critically revised the manuscript and contributed to the discussion. YL, JL, and WJ contributed equally to this work. All authors have read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was approved by the ethics committee of Jinling Hospital affiliated with Nanjing University. Approval date: April 11, 2019; Reference number: 2019NZKY-008-08.

Consent for publication
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Competing interests
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