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Original Article

Relationship between salivary cortisol and metabolic syndrome in Uygur patients with obese hypertension

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Abstract: This study investigated the relationship between blood pressure, blood glucose, blood lipids, body mass index (BMI), waist circumference (WC), and various indexes of salivary cortisol in obese patients with hypertension in the Uygur region of Western China. A survey of approximately 150 people was carried out, individuals were place in 4 groups: obese hypertension, obesity with no hypertension, non-obese hypertension, and healthy subjects. Their saliva was collected, and the cortisol value was measured 10 times a day. The cortisol secretion curves were expressed as the cortisol concentrations upon awakening, the cortisol awakening response (CAR), and the early and late cortisol decline. Systolic blood pressure (SBP) was positively correlated with cortisol concentrations at 30 min post-awakening and negatively correlated with cortisol concentrations at 18:00, 24:00, and bedtime. Diastolic blood pressure (DBP) had a negative correlation with the early cortisol decline. Fasting blood glucose (FBG) was negatively correlated with cortisol concentrations at 23:00, 24:00, bedtime, and the full area under curve (AUC). Triglyceride (TG) in the blood lipids was positively associated with cortisol at 16:00, while it was negatively associated with the late decline. High-density lipoprotein cholesterol (HDL-C) had a positive correlation with the early decline. BMI negatively correlated with cortisol concentrations at bedtime and positively with cortisol concentrations at 60 min post-awakening. The relationship between the WC and cortisol concentrations at bedtime was negative; the CAR was negatively related with awakening cortisol and its early decline, while it was positively related with cortisol concentrations at 30 and 60 min post-awakening and the AUC of its early decline; the correlation was the strongest with the cortisol concentrations at 30 min post-awakening ($r=0.657$, $P<0.01$). Among the cortisol gradients, early decline had a positive correlation with HDL-C and a negative correlation with the CAR, while its late decline had a negative correlation with TC. The salivary cortisol curves of the patients in the obesity with no hypertension group were higher compared with those of the other 3 groups. Our study provided the basic data of the salivary cortisol secretion patterns of obese Uygur patients with hypertension and controls.

Keywords: Salivary cortisol, Uygur, blood pressure, blood glucose, blood lipids

Introduction

Because of its special geographical environment, dietary structure (high salinity, high fat), and national characteristics, the hypertension incidence in the Xinjiang area ranks the highest in China. Further, hypertension has become a disease with an extremely high incidence in Xinjiang [1], known for its obvious ethnic differences [2]. The incidence of being overweight or obese is way above the national average, and Uygur is a high-risk group for being overweight and having abdominal obesity [2]. Since being overweight is related with BMI, and is an independent hypertension risk factor, obese hypertension is rapidly gaining popularity as a research focus [3-6].

Cortisol is an adrenocortical hormone synthesized from the adrenal cortex, and it has a strong effect on carbohydrate metabolism. It is also the terminal product of the hypothalamus-pituitary-adrenal (HPA) axis and can directly reflect its own action. There have been a number of publications demonstrating that the increase of cortisol is an important mechanism

leading to hypertension [7, 8]. However, some studies suggest that cortisol has nothing to do with hypertension but is related to blood glucose [9] or blood pressure and blood lipids [10]. Cortisol's normal metabolism follows certain physiological rhythms, and abnormal secretion can induce a variety of diseases. Since cortisol secretion is pulsatile, it varies in terms of both time and quantity. At present, it is hard to explore the relationship between the HPA axis and chronic stress and metabolic disorders (obesity, diabetes, cardiovascular disease) only by examining plasma cortisol [10]. Furthermore, since the detection of cortisol secretion is susceptible to various factors, each with large fluctuations, it is of practical importance to use multiple sampling techniques and comprehensive analyses using various indexes.

Salivary cortisol (SC) is derived from biologically active free-state cortisol in the blood, diffusing into the saliva by passing through the salivary glands' acinar cells. Because SC has prominent liposoluble properties and easy diffusion, it is free from the saliva flow rate, close to the free-state cortisol concentration in the blood, displays a circadian periodicity, and it can be conveniently detected; therefore, it is currently good metric for researchers to use to evaluate HPA axis changes [11, 12]. Although many intensive studies about related diseases and the means of detecting cortisol have been conducted by domestic and foreign scholars, no broad consensus has been reached. The relationship between cortisol and blood pressure, blood glucose, blood lipids, and obesity remains unsolved. Hence, our research seeks to find the correlation of blood glucose, blood lipids, blood pressure, BMI, WC, and the SC value its secretion curve using a multipoint measurement of cortisol and a subsequent multiparameter evaluation.

Material and methods

General data

The data sources were derived from patients in a traditional Chinese medicine hospital in the Xinjiang Uygur Autonomous Region and from people in a medical examination center. A total of 150 patients were selected in this study, which were divided into 4 different groups. Every five years was regarded as an age bracket. To ensure a homogenous age distribution, there were 12 people in each age bracket in the healthy group, while there were 6 people in each age bracket in the other 3 groups.

Inclusion criteria

All the subjects involved in the study gave consent with signed informed consent. The surveyed patients were aged from 40 to 64 years old. The diagnostic criteria for hypertension were the following: blood pressure values SBP≥140 mmHg and/or a DBP≥90 mmHg. The diagnostic criteria of obesity were a BMI = weight/height^2, with a measuring unit of kg/m^2. The normal BMI (kg/m^2) of Chinese adults was 18.5-24; while 24≤BMI<28 was considered overweight, a BMI≥28 represented obesity. When WC was used as a judging criterion, a WC≥90 cm for males or a WC≥85 cm for females was classified as obesity [13, 14]. Patients meeting the following conditions were excluded from this study: 1) patients with serious heart, brain, liver, and kidney diseases and hematopoietic system diseases; 2) patients with mental disorders accompanied by anxiety, depression, and those who could not express themselves; 3) patients involved in other clinical trials.

Determination methods

Determination of blood pressure

Clinical blood pressure measurements were performed in all involved patients. An appropriate cuff size was selected to avoid pseudohypertension, as the airbag wrapped at least 80% of the upper arm. For the majority of adults with an arm circumference of 25-35 cm, the standard cuff (the airbag was 22-26 cm long and 12 cm wide) was adopted. At present, the airbag specifications of the domestic commercial mercury sphygmomanometer were 22 cm in length and 12 cm in width. For an arm circumference of 35-44 cm, the cuff airbag should be 38×16 cm^2; for an arm circumference of 45-52 cm, the cuff airbag should be 42×20 cm^2. The clinical blood pressure was measured and recorded using the right arm blood pressure with the cuff at the same height as the heart in a sitting position after calm rest for 15 min. The measurement was repeated 3 times continuously, with the average value recorded as the patient's clinical blood pressure.

Determination of blood glucose and blood lipids

Three microliters of morning fasting blood were extracted from each subject's cubital vein and detected by an automatic biochemical analyzer using the clinically modified enzyme method.

Determination of height, weight, and WC

Determination of height: the measurement gauge was fixed perpendicular to the ground. The subjects removed their shoes and stood upright with heels together and close to the gauge. The shoulders and hips were also close to the gauge. Next, the survey crew put a square on the subject's head, with one right-angle side close to the gauge while the other side was close to the subject's scalp. The reading on the gauge was read with an accuracy of 0.5 cm.

Determination of weight: The weight of all subjects was measured by a standard weighting scale after correction. The subjects fasted, removed their shoes, wore only thin clothes with the body relaxed, and stood upright in the middle of the scale. The reading on the scale was read by a survey crew with an accuracy of 0.5 kg.

Determination of WC: The subjects stood upright with feet spread apart (30-40 cm). The measurements were performed with a soft leather ruler (without elasticity) at 1 cm above the navel. The leather ruler was put close to the skin surface without compression on the soft tissue. The WC length was measured at the end of normal expiration with an accuracy of 0.5 cm.

Determination of salivary cortisol

The samples were collected 10 times within 24 h (at awakening, 30 min post-awakening, 60 min post-awakening, 120 min post-awakening, 16:00, 17:00, 18:00, 23:00, 24:00, and at sleep). The awakening and sleep times were recorded with telephone or message reminders of the sample collection. To avoid the cortisol secretion being induced by blood contamination or food, tooth brushing or food consumption was avoided 15 min before sampling. Subjects were informed they were allowed to keep the swabs, and the saliva samples were kept in a freezer at -20°C. Before detection, the samples were unfrozen and centrifuged at 3000 rpm for 3 min. The analysis process was performed by a full-automatic chemiluminescence immunoassay analyzer with machine-matching reagents and a chemiluminescence sequence.

Statistical analysis

All the index data were inputted in Excel forms immediately after determination and analyzed using the SPSS 22.0 statistical software. A Shapiro-Wilk (S-W) test was adopted for the normality test, with an inspection level of α=0.05. Because the cortisol values showed a non-normal distribution, it was analyzed with a nonparametric test. The comparison between the mean values of multiple groups was carried out by a single-factor multiple-sample variance analysis. Correlations between the variables were analyzed by a correlation analysis, with $P<0.05$ indicating relevance. The comparison of the data distribution constituent ratio was analyzed by a χ^2 test. To obtain all the correlation curves of the circadian rhythm changes, the data were made into model curves by origin. The whole day cortisol data was a time-function model, taking advantage of the awakening time as the cutoff point. The slope of the curves in different time periods was acquired by linear fitting, and the AUC values were calculated by integral operation.

Results

Metabolic syndrome of obese patients with hypertension

There is variation in blood pressure, blood glucose, blood lipids, BMI, and WC in Uygur patients with hypertension or obesity. The results showed there were significant differences in BMI, WC, SBP, DBP, and TG between the 4 groups. The entire obese group had higher BMIs and WCs, which were unrelated to hypertension. The group with hypertension showed elevated SBPs and DBPs. Meanwhile, obesity and hypertension are closely related to serum TG levels. Since obesity induced the TG elevation, hypertension likely does not contribute to down-regulating TG levels ($P<0.05$, **Table 1**). We found that the awakening time and sleep time in the 4 groups were distributed evenly without any statistically significant difference ($P>0.05$, **Table 2**).

Table 1. The comparison of age, obesity, blood pressure, and blood glucose relevant data between different groups

Variables	Groups				F	P
	Healthy	Obese hypertension	Obesity with no hypertension	Non-obesity hypertension		
Age (years)	52.32±7.70	53.50±7.91	52.63±7.02	52.66±7.44	1.170	0.916
BMI (kg/m^2)	22.03±1.56	31.83±2.98	31.80±2.62	22.33±1.65	214.872	<0.0001
WC (cm)	82.28±5.02	109.07±10.06	114.43±9.77	83.37±5.87	184.006	<0.0001
SBP (mmHg)	117.32±8.15	143.97±15.48	125.33±9.64	149.50±13.73	70.290	<0.0001
DBP (mmHg)	72.80±6.96	87.60±10.31	76.83±8.36	87.00±11.72	26.732	<0.0001
FBG (mmol/L)	5.27±1.64	6.24±2.23	6.10±2.14	5.83±1.65	2.348	0.0751
TG (mmol/L)	1.68±1.26	1.83±0.90	2.84±2.48	2.10±0.89	4.290	0.006
TC (mmol/L)	4.54±0.96	4.72±1.18	4.72±1.12	4.28±1.14	1.091	0.355
HDL-C (mmol/L)	1.01±0.31	1.00±0.29	1.03±0.38	0.97±0.44	0.137	0.938
LDL-C (mmol/L)	2.48±0.70	2.78±0.88	2.51±0.79	2.24±0.75	2.494	0.062

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AUC, area under curve.

Table 2. The χ^2 test of awakening, sleep time and taking β receptors or not between different groups

Variables	Classification	Groups				χ^2	P
		Healthy	Obese hypertension	Obesity with no hypertension	Non-obesity hypertension		
Awakening time distribution	6:30-6:59	0 (0.00%)	0 (0.00%)	1 (0.00%)	0 (0.00%)	18.967	0.215
	7:00-7:29	8 (5.33%)	1 (0.67%)	6 (4.00%)	6 (4.00%)		
	7:30-7:59	15 (10.00%)	13 (8.67%)	11 (7.33%)	8 (5.33%)		
	8:00-8:29	26 (17.33%)	14 (9.33%)	10 (6.67%)	10 (6.67%)		
	8:30-8:59	7 (4.67%)	0 (0%)	1 (0.67%)	5 (3.33%)		
	9:00-9:29	4 (2.67%)	2 (1.33%)	1 (0.76%)	1 (0.67%)		
Sleep time distribution	23:30-23:59	1 (0.67%)	0 (0%)	1 (0.67%)	0 (0%)	11.207	0.511
	00:0-00:29	22 (14.67%)	10 (6.67%)	7 (4.67%)	7 (4.67%)		
	00:30-00:59	22 (14.76%)	14 (9.33%)	14 (9.33%)	20 (13.33%)		
	1:00-1:29	13 (8.67%)	6 (4.00%)	7 (4.67%)	3 (2.00%)		
	1:30-1:39	2 (2.00%)	0 (0%)	1 (0.67%)	0 (0%)		
Taking β receptors or not	Taken	-	25 (41.67%)	-	24 (40%)	0.111	0.739
	Not taken		5 (8.335%)		6 (10%)		

The salivary cortisol level of obese patients with hypertension

Next we studied the cortisol throughout the day, and collecting times, and evaluated changes in the CAR, cortisol at night, and the cortisol slope. According to the detection of the whole day SC secretion curve and indexes (**Figure 1**), further analysis found that the differences in the cortisol values at 60 min post-awakening, 18:00, 23:00, 24:00, and before sleep were statistically significant (P<0.05) in 4 groups, while there were no statistically significant differences in the CAR and AUC between the different groups (**Table 3**). The entire day cortisol peak was at 30 min post-awakening and dropped gradually. The whole day SC curve of the healthy group was relatively low and flat. There was no significant difference between the SC curves of the obese hypertension and non-obese hypertension groups. Moreover, the SC curve of the obesity with no hypertension group shifted up when compared to that of other groups (**Figure 2**).

The correlation between metabolic syndrome and the salivary cortisol level

BMI negatively correlated with cortisol concentrations at bedtime and positively with cortisol

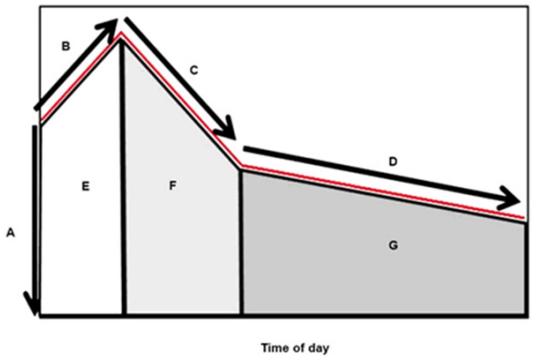

Figure 1. The whole day secretion curve of salivary cortisol and marked indexes (15). A. Awakening cortisol at time zero; B. Cortisol awakening response (CAR) denoting rise from awakening to 30 min post-awakening; C. Early decline from 30 min post-awakening to 2 h post-awakening; D. Late decline from 2 h post-awakening to bedtime; E. Area under curve (AUC) for CAR; F. AUC for early decline; G. AUC for late decline. The full AUC is the sum E+F+G.

concentrations at 60 min post-awakening. The relationship between WC and the cortisol concentrations at bedtime was negative; SBP positively correlated with the cortisol concentrations at 30 min post-awakening and negatively with the cortisol concentrations at 18:00, 24:00, and bedtime. DBP had a negative correlation with the early cortisol decline, but the correlations were not high. BMI, WC, and blood pressure were not related to cortisol's AUC and CAR (**Table 4**). Our results showed that: 1) SBP had a positive correlation with SC at 30 min post-awakening, while it was negatively correlated to cortisol at 18:00, 23:00, 24:00, and before sleep; 2) DBP displayed a negative relation with the early decline slope, but the relevance was not high; 3) There was no statistically significant difference of the relevance between the full AUC of the SC secretion curve and SBP or DBP.

Metabolic disorder was a risk factor for hypertension. However, the relationship between SC and metabolic syndrome is still unknown. Data showed that FBG negatively correlated with cortisol concentrations at 23:00, 24:00, and bedtime and with the full AUC. TG in the blood lipids positively associated with cortisol at 16:00, while it was negatively associated with the late decline. Throughout this study, we found that the CAR had a negative correlation with awakening cortisol and a positive correlation with the early decline AUC. In addition, the CAR was independent of the full AUC of the whole day cortisol secretion curve. Consistent with the results of Golden SH, a higher CAR had a significant correlation with a lower awakening cortisol and a higher AUC of the early descending curve but had nothing to do with its full AUC. Meanwhile, we found that the CAR related negatively to the early decline slope but positively to cortisol at 60 min post-awakening and particularly at 30 min post-awakening, with a significant positive correlation. HDL-C had a positive correlation with the early decline slope (**Table 5**).

Evaluation of the correlation between the CAR, AUC, and salivary cortisol levels

The CAR was negatively related with awakening cortisol and its early decline, while it was positively related with cortisol concentrations at 30 and 60 min post-awakening and the AUC of its early decline. The correlation was the strongest with the cortisol concentrations at 30 min post-awakening ($r=0.657$, $P<0.01$). Moreover, the CAR was unrelated to the full AUC of cortisol and cortisol at night (**Table 6**).

The full AUC related to all the SC curve parameters except the CAR and the early and late decline, with correlations arranged from highest to lowest, as follows: the late decline AUC, cortisol at 16:00, 18:00, 120 min post-awakening, 17:00, and so on (**Table 7**).

Discussion

Our study mapped the numerical range and SC secretion curves of Uygur patients with obesity, hypertension and controls. The correlations between cortisol and blood pressure, blood glucose, blood lipids, BMI, WC, and fluctuating SC variables were analyzed. We will concentrate on the results from the detection index of relevant metabolic syndromes and cortisol, different parameters of evaluating cortisol levels, and multifactor influences on the detections of the correlations between cortisol and blood pressure, blood glucose, blood lipids, and obesity.

It has been widely accepted that obesity and hypertension lead to metabolic disorder and induces abnormalities in blood pressure, blood glucose, blood lipids, BMI, WC, and SC. First, we evaluated metabolic syndrome changes in

Table 3. The comparison of salivary cortisol, and its slope, AUC of curves between different groups

SC	Healthy	Obese hypertension	Obesity with no hypertension	Non-obesity hypertension	χ^2	P
Awakening	0.295 (0.123 0.508)	0.275 (0.120 0.460)	0.340 (0.258 0.548)	0.210 (0.078 0.435)	5.480	0.139
30 min post-awakening	0.295 (0.130 0.618)	0.420 (0.298 0.683)	0.525 (0.315 0.688)	0.415 (0.200 0.570)	7.435	0.059
60 min post-awakening	0.265 (0.123 0.408)	0.310 (0.215 0.413)	0.405 (0.260 0.548)	0.290 (0.165 0.443)	9.322	0.025
120 min post-awakening	0.240 (0.120 0.348)	0.190 (0.108 0.330)	0.265 (0.158 0.343)	0.175 (0.088 0.303)	2.876	0.411
16:00	0.165 (0.090 0.293)	0.160 (0.120 0.253)	0.165 (0.128 0.273)	0.140 (0.095 0.195)	2.621	0.454
17:00	0.170 (0.073 0.238)	0.155 (0.098 0.248)	0.155 (0.095 0.250)	0.120 (0.068 0.190)	4.482	0.214
18:00	0.130 (0.090 0.180)	0.100 (0.050 0.163)	0.090 (0.050 0.183)	0.060 (0.030 0.120)	10.742	0.013
23:00	0.080 (0.040 0.148)	0.080 (0.040 0.140)	0.060 (0.030 0.118)	0.030 (0.020 0.075)	10.644	0.014
24:00	0.080 (0.040 0.140)	0.040 (0.010 0.095)	0.030 (0.020 0.070)	0.020 (0.010 0.075)	10.277	0.016
Before sleep	0.090 (0.020 0.208)	0.020 (0.010 0.070)	0.015 (0.010 0.120)	0.010 (0.010 0.1325)	11.895	0.008
CAR	0.090 (-0.220 0.380)	0.300 (-0.190 0.655)	0.270 (-0.165 0.565)	0.270 (-0.065 0.745)	3.641	0.303
Slope of early decline	-0.040 (-0.214 0.031)	-0.152 (-0.279 -.002)	-0.175 (-0.305 -0.075)	-0.099 (-0.207 -0.039)	3.715	0.294
Slope of late decline	-0.007 (-0.014 -0.002)	-0.121 (-0.017 -0.006)	-0.013 (-0.020 -0.009)	-0.007 (-0.020 -0.002)	3.547	0.315
AUC of CAR	0.198 (0.091 0.318)	0.563 (0.350 0.856)	0.245 (0.170 0.343)	0.198 (0.138 0.264)	3.649	0.302
AUC of early decline	0.420 (0.199 0.652)	0.463 (0.367 0.625)	0.573 (0.399 0.749)	0.433 (0.260 0.594)	3.458	0.326
AUC of late decline	2.538 (1.543 3.356)	1.941 (1.267 2.912)	2.060 (1.626 3.059)	1.731 (1.109 2.507)	6.346	0.096
full AUC	3.055 (2.151 4.438)	2.557 (1.802 3.717)	2.887 (2.375 3.962)	2.218 (1.843 3.614)	5.754	0.124

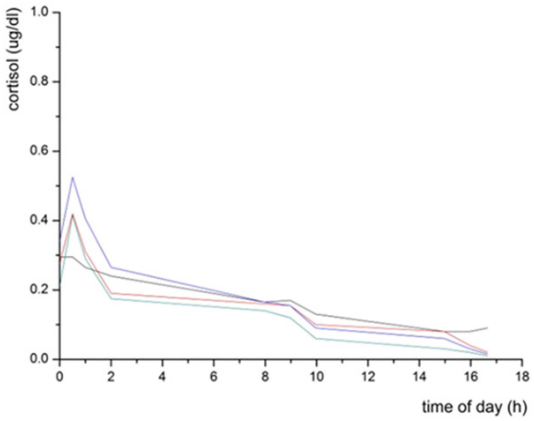

Figure 2. The whole day secretion curve of salivary cortisol of four different groups. Black: healthy group; green: non-obesity hypertension group; red: obese hypertension group; blue: obesity with no hypertension group.

patients with obesity and hypertension to determine the validity and correctness of the different groups. Second, our research further explored whether there is a specific relevance between cortisol and metabolic syndrome. It is known that elevated cortisol is one of the important mechanisms giving rise to hypertension [7, 15]. A diurnal cortisol variation is a significant predictor of blood pressure variability. There was a positive correlation between cortisol and DBP and mean arterial pressure, although others have also demonstrated that cortisol is not related to hypertension [16]. In our research, the data proved the positive correlation between cortisol and hypertension, in accordance with many studies. In fact, numerous confounding factors posed formidable obstacles to clearly pointing out definite relationships. Therefore, we also considered the impact of blood glucose on cortisol. It is widely believed that hyperglycemia and insulin resistance can induce the dysfunction of the HPA axis, resulting in cortisol hypersecretion [17]. According to our study, FBG was negatively correlated with cortisol at night and the AUC. Some studies shared the same detecting points with ours; their results were as follows: the blood cortisol concentration in elderly patients with T2DM positively correlated with FBG [18]. In clinical, there were also some T2DM patients who did not show elevated or lower cortisol levels. On one hand, the blood glucose fluctuation might disturb the normal hormone secretion rhythm of the HPA axis, leading to pituitary injury or dysfunction and cortisol secretion disorders. On the other hand, due to insufficient HPA axis function and cortisol hyposecretion, hyperglycemic hormones may not be quickly employed to elevate glucose levels in a hypoglycemia condition. As a result, negative feedback regulation mechanism are forced to launch, which gives rise to a hyperglycemia state after hypoglycemia by increasing the secretion of hyperglycemic hormones and increasing the blood glucose volatility. Further research is needed to discern which

Table 4. The correlation between BMI, WC, SBP, DBP and values, slopes, AUC of salivary cortisol

SC	BMI		WC		SBP		DBP	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Awakening	0.054	0.514	0.108	0.188	0.022	0.787	-0.045	0.584
30 min post-awakening	0.140	0.087	0.117	0.153	0.165	0.044	0.079	0.336
60 min post-awakening	0.175	0.032	0.156	0.056	0.094	0.252	0.082	0.316
120 min post-awakening	0.012	0.883	0.014	0.867	0.029	0.728	-0.050	0.543
16:00	0.081	0.324	0.048	0.561	-0.013	0.872	-0.007	0.930
17:00	0.133	0.104	0.068	0.406	-0.047	0.564	-0.010	0.907
18:00	0.009	0.911	-0.064	0.440	-0.204	0.013	-0.110	0.182
23:00	0.068	0.408	0.005	0.948	-0.138	0.093	-0.046	0.577
24:00	-0.124	0.135	-0.120	0.146	-0.207	0.012	-0.112	0.175
Before sleep	-0.172	0.036	-0.211	0.009	-0.164	0.046	-0.154	0.060
CAR	0.063	0.443	0.007	0.933	0.152	0.064	0.103	0.209
Slope of early decline	-0.093	0.638	-0.008	0.923	-0.105	0.203	-0.169	0.039
Slope of late decline	-0.033	0.686	-0.084	0.310	0.069	0.399	-0.003	0.970
AUC of CAR	0.065	0.432	0.136	0.098	0.076	0.352	0.052	0.525
AUC of early decline	0.088	0.283	0.060	0.468	0.019	0.815	0.052	0.526
AUC of late decline	0.030	0.717	-0.015	0.852	-0.089	0.278	-0.115	0.162
full AUC	0.051	0.538	0.011	0.893	-0.062	0.449	-0.087	0.289

Table 5. The analysis of correlation between blood glucose, blood lipids and cortisol, slopes and AUC of cortisol curves

SC	FBG		TC		TG		HDL-C		LDL-C	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Awakening	-0.030	0.716	-0.081	0.329	-0.083	0.318	-0.003	0.967	-0.019	0.822
30 min post-awakening	-0.049	0.549	0.068	0.411	0.044	0.593	-0.023	0.781	0.043	0.605
60 min post-awakening	-0.021	0.795	0.136	0.099	-0.023	0.779	-0.125	0.130	-0.064	0.440
120 min post-awakening	-0.046	0.577	0.029	0.725	-0.025	0.761	0.016	0.848	0.076	0.356
16:00	-0.065	0.430	0.217	0.008	0.065	0.436	-0.027	0.745	-0.026	0.753
17:00	-0.115	0.164	0.047	0.570	0.030	0.722	-0.071	0.388	-0.009	0.918
18:00	-0.134	0.103	0.021	0.802	0.064	0.440	0.004	0.958	-0.017	0.835
23:00	-0.293	0.001	-0.078	0.345	0.001	0.992	-0.014	0.870	-0.040	0.630
24:00	-0.263	0.001	0.023	0.780	-0.007	0.938	0.003	0.968	-0.035	0.671
Before sleep	-0.287	0.001	-0.053	0.521	-0.018	0.832	0.041	0.619	-0.027	0.749
CAR	-0.036	0.661	0.111	0.178	0.097	0.239	0.009	0.915	0.042	0.614
Slope of early decline	-0.016	0.844	-0.122	0.141	0.045	0.587	0.221	0.007	0.134	0.105
Slope of late decline	-0.144	0.157	-0.190	0.021	-0.049	0.558	0.143	0.084	0.064	0.437
AUC of CAR	-0.033	0.691	-0.044	0.595	-0.104	0.209	-0.071	0.390	-0.043	0.605
AUC of early decline	-0.155	0.059	0.055	0.505	0.068	0.412	-0.047	0.567	0.085	0.306
AUC of late decline	-0.150	0.068	0.071	0.392	0.049	0.551	-0.014	0.870	0.042	0.610
full AUC	-0.184	0.024	0.073	0.379	0.014	0.862	-0.039	0.634	0.024	0.773

time point is best for determining the correlation between cortisol and blood glucose under the functioning of multisystem and multi-hormone secretion. Irrespective of the result, considering cortisol as an evaluation index for blood glucose control was at least meaningful for the optimization of individual treatment. Further, atypical cortisol rhythms were associated with lipid metabolism. Lipid metabolism disorder is a risk factor for hypertension. Moreover, patients with obese hypertension also have accompanying dyslipidemia. It is believed

Table 6. The correlation between CAR and cortisol values at different times, slope, AUC of cortisol curves

SC	r	P
Awakening	0.351	<0.01
30 min post-awakening	0.657	<0.01
60 min post-awakening	0.256	<0.01
120 min post-awakening	0.111	0.176
16:00	0.031	0.702
17:00	0.112	0.174
18:00	0.055	0.504
23:00	0.075	0.364
24:00	-0.052	0.533
Before sleep	-0.117	0.154
Slope of early decline	-0.268	0.01
Slope of late decline	0.039	0.637
AUC of CAR	-0.114	0.165
AUC of early decline	0.238	0.003
AUC of late decline	0.065	0.430
full AUC	0.096	0.243

Table 7. The correlation between full AUC and cortisol values at different times, slope, AUC of cortisol curves

SC	r	P
Awakening	0.281	<0.01
30 min post-awakening	0.327	<0.01
60 min post-awakening	0.383	<0.01
120 min post-awakening	0.673	<0.01
16:00	0.708	<0.01
17:00	0.616	<0.01
18:00	0.694	<0.01
23:00	0.557	<0.01
24:00	0.522	<0.01
Before sleep	0.432	<0.01
CAR	0.096	0.243
Slope of early decline	0.124	0.130
Slope of late decline	0.045	0.583
AUC of CAR	0.265	<0.01
AUC of early decline	0.414	<0.01
AUC of late decline	0.968	<0.01

that the effect of cortisol on lipid metabolism is to mobilize fat, promote TG decomposition to inhibit fat synthesis, and prevent the conversion of glucose into fat by entering the adipocytes. Because cortisol also plays roles in inhibiting glucose utilization and enhancing hepatic gluconeogenesis and subsequently increasing blood glucose levels, stimulating increased insulin secretion promoted fat synthesis and induced dyslipidemia. One of the clinical manifestations of patients with elevated cortisol is hyperlipidemia. However, the relationship between some blood lipid indexes and cortisol is still unclear. We found that cortisol at 16:00 was positively correlated to TG while negatively correlated to the slope of the late decline curve. HDL-C had a positive relation with the slope of the early decline curve, which is consistent with the previous study. Abdominal obesity was positively related to TG, while it had a negative correlation with HDL-C and had nothing to do with TC and LDL-C [27]. Blood lipid and cortisol levels function together to maintain the balance of body metabolism under normal conditions, but abnormity appeared since they were also affected by numerous disease and non-disease factors. Hence, it is difficult to study the relationship between them. Further and more comprehensive clinical and scientific research must be conducted in the future.

The 2010 Chinese Guidelines for the Management of Hypertension illustrated that BMI-related extra body weight was an independent risk factor for hypertension [14]. With the increase in BMI, body fat would increase, thereby affecting the secretion of cortisol [8]. Patients with abdominal obesity might have abnormal HPA axis function. According to our research, BMI was negatively related to cortisol before sleep, while it was positively related to cortisol at 60 min post-awakening. A previous obesity-themed study showed that, in overweight and obese subjects with at least two signs of Cushing's syndrome, SC tended to increase with an increasing BMI [19]. But another large population study of obese and nonobese patients divided by BMI=25 kg/m^2 found that higher BMI levels were associated with lower cortisol levels [20]. There is controversy regarding the relationship between the cortisol and BMI of T2DM patients [21]. Moreover, with the BMI increase and corresponding increase in male WC and female SBP and SC, presented as an increasing trend [22-24]. The difference between our results and the previous studies' might stem from the small sample size, a single ethnic group, or the wrong use of a single cortisol index as an indicator to replace or clearly reflect the cortisol rhythm.

Because of the great diurnal changes in cortisol secretion, it is difficult to reflect cortisol secretion using a single cortisol detection, which requires a comprehensive analysis of various indicators, including the CAR, cortisol at night, cortisol slope, whole day cortisol, and multiple collecting times [8, 19, 24, 25]. The CAR is an increase of cortisol within 30-45 min post-awakening, thought to be a distinct facet of the circadian cortisol rhythm associated with various health conditions and risk factors [19], and it is an effective index to evaluate the HPA axis in behavioral research. An abnormal CAR (high or blunt) is associated with certain neuropsychological or metabolic disorders. Nevertheless, it is still unclear whether the CAR angle (steep or shallow) is related to the full-day cortisol load, especially whether the CAR can be used as a detection index of cortisol secretion. If the CAR cannot reflect the HPA axis function and the full-day cortisol secretion, it is important to discern whether other cortisol circadian rhythm indicators (awakening cortisol, bedtime cortisol, diurnal cortisol slope) can reflect the full-day cortisol secretion. There were studies suggesting that cortisol at 23:00 or bedtime should be adopted because it was associated with the full AUC of the whole day cortisol secretion and was a reliable measuring time point that could at least partly reflect cortisol secretion throughout the day. Although awakening cortisol was also associated with the full AUC of the whole day cortisol secretion, the study showed that an individuals' awakening cortisol stability was lower than that before bedtime. The levels of cortisol in the night and the CAR were the indexes of evaluating the adrenal cortex function [12]. In our study, cortisol at night was unrelated to the CAR but was related to the full AUC. Combined with domestic and foreign research, it was considered that nocturnal cortisol could be used as a potential representative of the whole day cortisol secretion, and the combination of the CAR and curve slope can be used for simultaneous assessment of the whole day cortisol secretion. However, a recent report suggested that cortisol at 23:00 could replace cortisol at 24:00 [26]. From the results of a nonclinical population, it was suggested that the flat slopes in SC, particularly in the raised evening cortisol levels, were a robust predictor of cardiovascular mortality in middle-aged adults [14]. One study stated that whether the present cortisol acquisition time was a higher longitudinal cortisol secretion time could not be determined, as it was a cross-sectional study. Some researchers used cortisol at different collection times of 15, 30, 45, and 60 min post-awakening to define the CAR [27, 28]. Since which indexes has the maximum correlation with the whole day cortisol secretion is still controversial, in our research, we used one or a few data points in the SC secretion curve to find which indexes have the maximum meaningful correlation with the SC curve. Studies showed that the full AUC of the cortisol secretion curve was significantly related to awakening cortisol, cortisol before sleep, and the AUC of other curves. Bedtime cortisol showed the strongest correlation with the whole day cortisol secretion, which could be used as a detection index of the whole day cortisol release amount [17]. Herein, we used cortisol at 30 min post-awakening to calculate the CAR. In conclusion, the AUC was related to all the SC curve parameters except the CAR and the slopes of the early and late decline. The following sequence was ordered from highest correlation to lowest: the AUC for late decline, cortisol at 16:00, 18:00, 120 min post-awakening, 17:00, and so on. The correlation between the AUC and multiple cortisol parameters, which can be used as an index reflecting the whole day cortisol secretion, requires further study. Studies have shown that the cortisol slopes of two consecutive days were relatively stable, without significant gender differences [29, 30]. However, flat slope or elevated cortisol levels at night might be related to stress, long-term chronic stress stimulation, and injury of the HPA axis or feedback sensitivity. The low variability and flat slope of the whole day cortisol might reflect excessive stimulation of the HPA axis in the early stage and cortisol storage in the visceral adipose tissue stimulated by a high concentration of plasma cortisol. Low cortisol values with a small fluctuation range throughout the day were found in healthy subjects. While Kumari et al, held that most people with a high or low BMI and WC might display a relatively flat SC slope [25], it should be considered that healthy subjects might be more sensitive to hormone secretion feedback and negative feedback coordination, which can be controlled in a dynamic equilibrium within a certain range. In the description of the relationship between disease detection and other cortisol parameters, we only found that the early de-

cline slope was positively correlated with HDL-C and negatively correlated with the CAR. The negative correlation between the late slope and TC was also confirmed.

Cortisol rhythm was affected by different factors, such as age, sex [31], working day and weekend, lighting time, season, sunrise time, and race, all of which affect the level of cortisol secretion [32]. The time of sunrise, season, and cortisol collection were the most important factors influencing median cortisol. Meanwhile, the descriptive characteristics of cortisol in relation to age and gender were discovered by cross-sectional study. Other findings included generally higher cortisol levels in women than in men of all ages. Older age was significantly associated with higher levels in both genders. Moreover, the strong correlation between abdominal obesity, a low awakening cortisol, and a low variability of whole day cortisol was only found in women [31]. Thus, it can be seen that confounding factors still play an important role in the present study. If we study the relationship between cortisol and blood pressure, blood glucose, blood lipids, and obesity, more confounding factors should be controlled and result in more accurate conclusions using multifactor analysis.

Although many studies have shown that there is a correlation between cortisol levels and blood pressure, blood glucose, blood lipids, and obesity, there are still many disputes since the results are inconsistent. Though a large number of studies have shown that cortisol plays a role in people with cardiovascular or metabolic disorders, establishing an exact correlation between them is difficult. The inconsistent results may be due to the different research designs, genders, ages, cortisol parameters and timing, and the presence and severity of comorbidities [19]. Therefore, as we further explore the relationship between cortisol, the biochemical index and BMI, and WC in the future, it is important to explore the clues of disease diagnosis and treatment, as well as find new ways to provide better treatment options, alleviate the suffering of patients, and achieve better therapeutic effects.

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