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OPINION REVIEW

- 939 Access to novel anti-diabetic agents in resource limited settings: A brief commentary
Naidoo P, Naidoo K, Karamchand S, Leisegang RF

REVIEW

- 942 Detection, management, and prevention of diabetes-related foot disease in the Australian context
McNeil S, Waller K, Poy Lorenzo YS, Mateevici OC, Telianidis S, Qi S, Churilov I, MacIsaac RJ, Galligan A
- 958 Novel insights regarding the role of noncoding RNAs in diabetes
Macvanin MT, Gluvic Z, Bajic V, Isenovic ER
- 977 Implications of receptor for advanced glycation end products for progression from obesity to diabetes and from diabetes to cancer
Garza-Campos A, Prieto-Correa JR, Domínguez-Rosales JA, Hernández-Nazará ZH
- 995 Advanced glycation end product signaling and metabolic complications: Dietary approach
Khan MI, Ashfaq F, Alsayegh AA, Hamouda A, Khatoon F, Altamimi TN, Alhodieb FS, Beg MMA
- 1013 Tight junction disruption and the pathogenesis of the chronic complications of diabetes mellitus: A narrative review
Robles-Osorio ML, Sabath E

MINIREVIEWS

- 1027 Klotho: A new therapeutic target in diabetic retinopathy?
Puddu A, Maggi DC
- 1037 Type 2 diabetes and thyroid cancer: Synergized risk with rising air pollution
Kruger EM, Shehata SA, Toraih EA, Abdelghany AA, Fawzy MS
- 1049 Liver or kidney: Who has the oar in the gluconeogenesis boat and when?
Sahoo B, Srivastava M, Katiyar A, Ecelbarger C, Tiwari S

ORIGINAL ARTICLE

Basic Study

- 1057 Network-pharmacology-based research on protective effects and underlying mechanism of Shuxin decoction against myocardial ischemia/reperfusion injury with diabetes
Yang L, Jian Y, Zhang ZY, Qi BW, Li YB, Long P, Yang Y, Wang X, Huang S, Huang J, Zhou LF, Ma J, Jiang CQ, Hu YH, Xiao WJ

- 1077 Analysis of N6-methyladenosine-modified mRNAs in diabetic cataract

Cai L, Han XY, Li D, Ma DM, Shi YM, Lu Y, Yang J

Retrospective Cohort Study

- 1091 Long-term quality-of-care score for predicting the occurrence of acute myocardial infarction in patients with type 2 diabetes mellitus

Li PI, Guo HR

Retrospective Study

- 1103 Correlation between glycated hemoglobin A1c, urinary microalbumin, urinary creatinine, $\beta 2$ microglobulin, retinol binding protein and diabetic retinopathy

Song JJ, Han XF, Chen JF, Liu KM

Observational Study

- 1112 Glucose metabolism profile recorded by flash glucose monitoring system in patients with hypopituitarism during prednisone replacement

Han MM, Zhang JX, Liu ZA, Xu LX, Bai T, Xiang CY, Zhang J, Lv DQ, Liu YF, Wei YH, Wu BF, Zhang Y, Liu YF

- 1126 Association between cardiorespiratory fitness level and insulin resistance in adolescents with various obesity categories

La Grasta Sabolic L, Pozgaj Sepec M, Valent Moric B, Cigrovski Berkovic M

CASE REPORT

- 1137 Maturity-onset diabetes of the young type 9 or latent autoimmune diabetes in adults: A case report and review of literature

Zhou GH, Tao M, Wang Q, Chen XY, Liu J, Zhang LL

ABOUT COVER

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The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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Observational Study

Glucose metabolism profile recorded by flash glucose monitoring system in patients with hypopituitarism during prednisone replacement

Min-Min Han, Jia-Xin Zhang, Zi-Ang Liu, Lin-Xin Xu, Tao Bai, Chen-Yu Xiang, Jin Zhang, Dong-Qing Lv, Yan-Fang Liu, Yan-Hong Wei, Bao-Feng Wu, Yi Zhang, Yun-Feng Liu

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Abstract

BACKGROUND

Commonly used glucocorticoids replacement regimens in patients with hypopituitarism have difficulty mimicking physiological cortisol rhythms and are usually accompanied by risks of over-treatment, with adverse effects on glucose metabolism. Disorders associated with glucose metabolism are established risk factors of cardiovascular events, one of the life-threatening ramifications.

AIM

To investigate the glycometabolism profile in patients with hypopituitarism receiving prednisone (Pred) replacement, and to clarify the impacts of different Pred doses on glycometabolism and consequent adverse cardiovascular outcomes.

METHODS

Twenty patients with hypopituitarism receiving Pred replacement [patient group (PG)] and 20 normal controls (NCs) were recruited. A flash glucose monitoring system was used to record continuous glucose levels during the day, which

provided information on glucose-target-rate, glucose variability (GV), period glucose level, and hypoglycemia occurrence at certain periods. Islet β -cell function was also assessed. Based on the administered Pred dose per day, the PG was then regrouped into Pred > 5 mg/d and Pred \leq 5 mg/d subgroups. Comparative analysis was carried out between the PG and NCs.

RESULTS

Significantly altered glucose metabolism profiles were identified in the PG. This includes significant reductions in glucose-target-rate and nocturnal glucose level, along with elevations in GV, hypoglycemia occurrence and postprandial glucose level, when compared with those in NCs. Subgroup analysis indicated more significant glucose metabolism impairment in the Pred > 5 mg/d group, including significantly decreased glucose-target-rate and nocturnal glucose level, along with increased GV, hypoglycemia occurrence, and postprandial glucose level. With regard to islet β -cell function, PG showed significant difference in homeostasis model assessment (HOMA)- β compared with that of NCs; a notable difference in HOMA- β was identified in Pred > 5 mg/d group when compared with those of NCs; as for Pred \leq 5 mg/d group, significant differences were found in HOMA- β , and fasting glucose/insulin ratio when compared with NCs.

CONCLUSION

Our results demonstrated that Pred replacement disrupted glycometabolic homeostasis in patients with hypopituitarism. A Pred dose of > 5 mg/d seemed to cause more adverse effects on glycometabolism than a dose of \leq 5 mg/d. Comprehensive and accurate evaluation is necessary to consider a suitable Pred replacement regimen, wherein, flash glucose monitoring system is a kind of promising and reliable assessment device. The present data allows us to thoroughly examine our modern treatment standards, especially in difficult cases such as hormonal replacement mimicking delicate natural cycles, in conditions such as diabetes mellitus that are rapidly growing in worldwide prevalence.

Key Words: Hypopituitarism; Prednisone; Flash glucose monitoring system; Glucose-target-rate; Glucose variability; Period glucose level

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Core Tip: Glucocorticoids (GCs) replacement regimens for patients with hypopituitarism are hard to mimic physiological cortisol rhythms and carry risks of over-treatment, which can have adverse effects on glucose metabolism. We assessed the glucose metabolism profile of patients with hypopituitarism receiving prednisone (Pred) replacement, using a flash glucose monitoring system, to clarify impacts of different GCs preparations and prescriptions on glycometabolism, along with the resultant risks of consequent cardiovascular events. The study showed that Pred replacement disturbed glycometabolic homeostasis in patients with hypopituitarism. A dose of > 5 mg/d Pred caused more adverse effects on glycometabolism than \leq 5 mg/d, contributing to the higher risks of cardiovascular events.

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INTRODUCTION

As the growing amount of information consolidated in the field of glucocorticoids' (GCs) hyperglycemia effect[1,2], whether GCs replacement therapy disturbs glycometabolism homeostasis in patients with hypopituitarism has garnered considerable interest. Timely and adequate GCs replacement has been commonly recognized as a lifesaving prescription for those patients with hypopituitarism, which aims to restore hormone deficiency and improve well-being. Hydrocortisone (HC) is the default choice for GCs replacement because of its similarity to endogenously-generated cortisol. Prednisone (Pred), cortisone, and dexamethasone represent other viable alternatives[3].

Choosing an optimum GCs replacement regimen for patients with hypopituitarism continues to be a challenging problem as the physiological cortisol rhythm is difficult to replicate. The most commonly used GCs replacement regimen is usually accompanied by a risk of insufficient trough levels or subtly excessive post-dose peaks[4,5]. An inability to mimic physiological cortisol rhythms or over-treatment may make those patients receiving GCs replacement susceptible to metabolic disturbances and subsequent cardiovascular events[6,7]. To date, the majority of evidence collected suggests that the occurrence of cardiovascular events is reportedly higher in patients with hypopituitarism who undergo GCs replacement than that in healthy controls[8,9]. New evidence has also emerged revealing that GCs replacement increases

the prevalence of glycometabolism disorders[10], which are established risk factors for cardiovascular disease.

As the prevalence of adverse events increases in patients with hypopituitarism receiving GCs replacement, greater emphasis has been placed on choosing a suitable replacement regimen with as little influence on glycometabolism as possible. Therefore, this study was designed to assess the glucose metabolism profile recorded by a flash glucose monitoring system (FGMS) in patients with hypopituitarism, illuminating the impact of GCs preparation and prescription doses on glucose metabolism. In doing so, we hope to add novel insights into the existing body of evidence and provide references to guide the treatment choices for those patients with hypopituitarism, in order to reduce the incidence of cardiovascular events.

MATERIALS AND METHODS

This study was conducted at the Department of Endocrinology, First Hospital of Shanxi Medical University from December, 2018 to August, 2022. The study protocol was approved by Ethic Committee in First Hospital of Shanxi Medical University. Written informed consent was obtained from all the subjects after explanation of study design and purpose.

Subjects

Patients diagnosed with hypopituitarism and receiving Pred replacement were recruited in this study as patient group (PG). The hypopituitarism was diagnosed by the following criteria[3]: Medical history (including postpartum hemorrhage, hypophysectomy, and pituitary crisis); clinical manifestations (including hyponatremia, hypotension, and hypoglycemia); pituitary magnetic resonance imaging (including empty sella, pituitary hypoplasia, and pituitary stalk interruption); hormone assay (lower levels of hormones relevant to pituitary-adrenal/thyroid/gonad function); corticotropin stimulation test (stimulated cortisol < 500 nmol/L). Those who were under interventions known to influence cortisol metabolism and glucose metabolism were excluded. Age- and sex-matched normal controls (NCs) without known hypopituitary dysfunction or glycometabolic disorders were enrolled. At baseline, all the recruited patients underwent hypopituitary-adrenal/thyroid function assessment, along with electrolyte and glucose metabolism evaluation, including plasma sodium, glycosylated hemoglobin, fasting blood glucose, and fasting insulin. The NCs received laboratory tests similar to those of PG.

Subgroup analysis

Relevant studies have corroborated that > 20 mg/d of HC correlated with unfavorable metabolic profile and cardiovascular events[11-13], however, whether an equivalent dose of Pred (> 5 mg/d) contributes to similar consequences is a relatively unexplored field. Due to the limited availability of HC in China, most patients with hypopituitarism received a Pred replacement regimen. In this study, we enrolled patients with hypopituitarism treated with Pred as PG, and divided PG into Pred > 5 mg/d and Pred ≤ 5 mg/d groups, based on the recommended Pred dose per day.

FGMS

FGMS (FreeStyle Libre, Abbott Diabetes Care, Witney, United Kingdom) was used to record glucose profiles of those in PG and NCs. Due to unexpected dropping of the sensor or other unpredictable interferences, we failed to obtain a complete two-week monitoring data in each person. The data from the first-day of monitoring were removed due to poor accuracy. In the end, a total 222 d of monitoring data were collected from patients in PG (134 d for the Pred > 5 mg/d group, and 88 d for the Pred ≤ 5 mg/d group), while NCs provided 184 d of glucose data. The FGMS required a real-time scanned value within 8-h in order to ensure complete glucose data during the surveillance. Some glucose values at certain time points were therefore missing, owing either to the subjects' poor adherence or other reasons, such as sleep time exceeding 8 h. These missing values were filled in with the mean of values before and after the missing values.

Islet function assessment

β-cell function and insulin resistance (IR) were assessed by calculating the homeostasis model assessment (HOMA)-β along with HOMA-IR, fasting glucose/insulin ratio (G/I), and quantitative insulin sensitivity check index (QUICKI).

Statistical analysis

The statistical methods used in this study were reviewed by Chunni Zhao from Shanxi Medical University. The data of laboratory tests and FGMS in PG, subgroups, and NCs were allocated in a Microsoft Excel datasheet. Data analysis and graph plotting were performed using SPSS 21.0 and Sigmaplot 12.5. All data are shown as mean ± standard error (SE) unless otherwise stated. Some data are represented as median (first quartile, third quartile) due to their wide distribution. A compared two-group Student's t-test (for normally distributed data) or Mann-Whitney U test (for skewed data) was conducted between PG, each subgroup, and NCs, respectively. Statistical significance was set as $P < 0.05$.

FGMS data were analyzed according to methods used in previous publications[14,15]. Specifically, glucose-target-rate, glucose variability (GV), and period glucose level were analyzed. A sensor glucose value within 3.9-7.8 mmol/L was set as the normal range. Accordingly, parameters representing glucose-target-rate were analyzed, including percentile time 1 (PT1, the percentage of sensor glucose values less than 3.9 mmol/L during the day), PT2 (the percentage of sensor glucose values within the range of 3.9-7.8 mmol/L during the day), PT3 (the percentage of sensor glucose values above 7.8 mmol/L during the day), time in range (TIR, the time of sensor glucose values within 3.9-7.8 mmol/L during the day),

and time out of range (the time of sensor glucose values less than 3.9 mmol/L or above 7.8 mmol/L during the day). GV was analyzed from the following perspectives: General GV including 24-h mean glucose and coefficient of variance (CV); within-day GV consisting of SD and mean amplitude of glycemic excursion; mean of daily difference (MODD) and area of interquartile range (IQR) reflecting day-to-day GV.

The endogenous cortisol secretion rhythm begins with a rise at around 3 am towards a peak after awaking, and then falls throughout the day until culminates in a nadir around the midnight[16]. Accordingly, nocturnal and fasting periods were merged and readjusted to periods of 0-3 am and 3-8 am. Glucose levels and area under the curve of glucose level at 0-3 am, 3-8 am, and postprandial periods were analyzed. In addition, hypoglycemia occurrence (glucose value less than 3.9 mmol/L) was analyzed during the 0-3 am and 3-8 am periods[17].

Formulas for calculating β -cell function and IR from a previous publication were used[14].

RESULTS

Twenty patients diagnosed with hypopituitarism, including nine with Sheehan's syndrome, four with empty sella, six with hypophysectomy, and one with pituitary hypoplasia, and receiving Pred replacement were enrolled in this study. Of these patients, 16 had suffered acute hypopituitarism, presenting symptoms of hyponatremia, hypotension, hypoglycemia, *etc.*, and four of them were diagnosed by corticotropin stimulation test (stimulated cortisol < 500 nmol/L). Significantly reduced levels of 24-h urinary free cortisol were detected in all of the patients during the course of the disease. Twelve patients were treated with doses of > 5 mg/d Pred and eight patients were treated with doses of \leq 5 mg/d. There were also 12 patients undergoing concurrent thyroid hormone replacement therapy. The general characteristics and laboratory results of PG, subgroups, and NCs, including age, sex, disease duration (duration since hypopituitarism had been definitely diagnosed), blood pressure, plasma sodium, and endocrine hormone levels, are listed in the Table 1. Blood pressure, plasma sodium, and hormone levels were within the normal range in PG under the recommended replacement regimen.

Glucose-target-rate

Significantly increased PT1 ($P = 0.018$) and PT3 ($P = 0.002$) along with decreased TIR ($P < 0.001$) were identified in PG when compared with that of NCs (Figure 1A).

Remarkable elevations in PT1 ($P = 0.02$) and PT3 ($P < 0.001$) along with reduction in TIR ($P < 0.001$) were identified in Pred > 5 mg/d group when compared with those of NCs (Figure 1B). Comparable PT1, PT3, and TIR were found between Pred \leq 5 mg/d group and NCs (Figure 1B).

GV

In PG, parameters of general GV were identified significance in CV ($P = 0.003$) compared with that of NCs. With regard to within-day GV, a notable elevation was found in SD ($P = 0.003$) when compared to those of NCs. There were no significant differences found in indices of day-to-day GV (Figure 2A).

In Pred > 5 mg/d group (Figure 2B), remarkable elevations were identified in parameters of general GV (CV, $P < 0.001$), within-day GV (SD, $P < 0.001$) and day-to-day GV (MODD, $P = 0.019$; area of IQR, $P = 0.002$), compared to that of NCs. However, no significant difference was observed in GV parameters between Pred \leq 5 mg/d group and NCs (Figure 2B).

Period glucose level

For PG, period glucose level analysis indicated that glucose level was significantly lower at period of 3-8 am ($P = 0.004$) than that of NCs (Figure 3). Consistent results were found in the analysis of hypoglycemia occurrence with a remarkable elevation during this period ($P = 0.012$, Figure 4A). In addition, significantly increased glucose levels were identified at postprandial phase of PG (after lunch, $P = 0.028$; after dinner, $P < 0.001$) when compared to that of NCs (Figure 3).

In Pred > 5 mg/d group, notable alterations were found during the 3-8 am period with decreased glucose level ($P = 0.025$, Figure 5A) and increased hypoglycemia occurrence ($P = 0.008$, Figure 4B) in comparison with those in NCs. In addition, a remarkable elevation in glucose level was observed at postprandial phase (after lunch, $P = 0.015$; after dinner, $P < 0.001$) when compared with that of NCs (Figure 6A).

In Pred \leq 5 mg/d group, a significant reduction of glucose level at 3-8 am period ($P = 0.021$) were found in comparison with NCs (Figure 5B), whereas, hypoglycemia occurrence was comparable to that of NCs (Figure 4B). Comparable postprandial glucose levels were also identified at postprandial periods between Pred \leq 5 mg/d group and NCs (Figure 6B).

Islet function assessment

In PG, glucose metabolism indicators showed a significant difference in HOMA- β ($P = 0.003$) compared with that of NCs (Table 2).

Glucose metabolism indicators showed a notable difference in HOMA- β ($P = 0.021$) in Pred > 5 mg/d group when compared with those of NCs (Table 2). As for Pred \leq 5 mg/d group, significant difference was found in HOMA- β ($P < 0.001$), and G/I ($P = 0.018$) in comparison with that in NCs (Table 2).

Table 1 General characteristics and laboratory results of patient groups and normal controls

Parameters	PG	Pred (> 5 mg/d)	Pred (≤ 5 mg/d)	NCs	Reference range
Age (year-old)	52.85 ± 3.49	51.5 ± 4.78	49.88 ± 5.33	50.75 ± 3.05	-
Male:female	5:15	3:9	2:6	5:15	-
BMI (kg/m ²)	19.46 ± 1.39	20.02 ± 1.44	18.61 ± 0.81	20.5 ± 1.58	18.5-23.9
Disease duration (day)	730 (88.75, 1095)	730 (50, 1642.5)	730 (638.75, 1095)	-	-
Blood pressure (mmHg)	(108.65 ± 1.15)/(74.85 ± 0.89)	(108.25 ± 1.62)/(75.08 ± 1.36)	(109.25 ± 1.65)/(74.5 ± 0.98)	(111.95 ± 1.17)/(73.5 ± 0.7)	-
Pred dose (mg/d)	6.19 ± 1.54	7.29 ± 0.48	4.53 ± 0.93	-	-
ACTH (pmol/L)	3.5 ± 0.33	3.58 ± 0.51	3.37 ± 0.33	4.40 ± 0.41	1.6-13.9
Cortisol at 8 am (nmol/L)	228.01 ± 4.42	230.24 ± 6.84	224.66 ± 4.44	372.90 ± 16.69	171-536
Cortisol at 4 pm (nmol/L)	153 ± 11.99	165.93 ± 17.48	133.6 ± 12.87	159.10 ± 14.62	64-327
Cortisol at 0 am (nmol/L)	111.55 ± 8.85	113.31 ± 12.01	108.91 ± 13.76	-	-
UFC (nmol/24h)	141.33 ± 11.34	131.80 ± 10.41	155.61 ± 23.86	-	100-279
FT3 (pmol/L)	4.25 ± 0.13	4.24 ± 0.15	4.27 ± 0.25	5.20 ± 0.14	3.1-6.8
FT4 (pmol/L)	14.11 ± 0.55	13.45 ± 0.50	15.09 ± 1.10	12.98 ± 0.92	10-23
TSH (μIU/ml)	1.076 ± 0.16	1.1 ± 0.19	1.04 ± 0.28	2.30 ± 0.19	0.27-4.2
Plasma sodium (mmol/L)	141.95 ± 0.86	140.3 ± 0.65	142.63 ± 1.07	140.6 ± 0.55	137-147

Pred: Prednisone; NCs: Normal controls; BMI: Body mass index; ACTH: Adrenocorticotrophic-hormone; UFC: Urine free cortisol; FT3: Free triiodothyronine; FT4: Free thyroxine; TSH: Thyroid stimulation hormone. The laboratory tests were conducted in patient group during prednisone treatment.

Table 2 Glucose metabolism indicators in patient groups and normal controls

Parameters	PG	Pred (> 5 mg/d)	Pred (≤ 5 mg/d)	NCs	Reference range
HbA1c (%)	5.61 ± 0.101	5.71 ± 0.15	5.47 ± 0.11	5.46 ± 0.06	4.8-5.9
FBG (mmol/L)	4.71 ± 0.12	4.81 ± 0.19	4.56 ± 0.11	5.01 ± 0.13	3.9-6.1
FINS (μU/mL)	7.10 ± 0.64	6.82 ± 0.98	7.52 ± 0.72	5.76 ± 0.62	2.6-24.9
HOMA-β	130.22 ± 13.43 ^a	113.511 ± 16.18 ^a	155.28 ± 21.37 ^a	81.02 ± 6.83	-
HOMA-IR	1.52 ± 0.17	1.52 ± 0.27	1.54 ± 0.17	1.32 ± 0.16	-
G/I	0.79 ± 0.09	0.898 ± 0.14	0.64 ± 0.048 ^a	1.02 ± 0.082	-
QUICKI	0.69 ± 0.03	0.71 ± 0.04	0.66 ± 0.02	0.73 ± 0.03	-

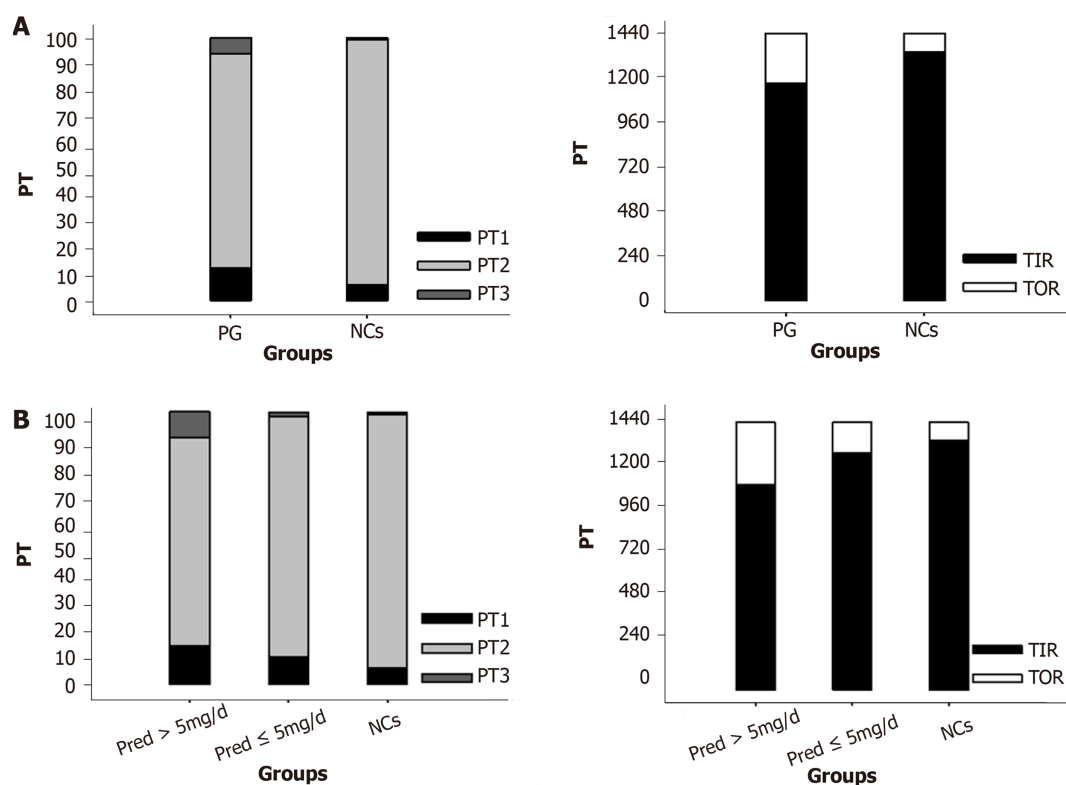
^a*P* < 0.05.

Pred: Prednisone; NCs: Normal controls; HbA1c: Glycosylated hemoglobin; FBG: Fasting blood glucose; FINS: Fasting insulin; HOMA-IR: Homeostasis-insulin resistance; G/I: Fasting glucose/fasting insulin ratio; QUICKI: Quantitative insulin check index.

DISCUSSION

In this study, we investigated the glucose metabolism profile in patients with hypopituitarism receiving GCs treatment. Significantly decreased glucose-target-rate and glucose level at nocturnal period, along with increased GV, hypoglycemia occurrence, and glucose level at postprandial phase were identified in PG when compared with those of NCs. These results demonstrated that glucose metabolism homeostasis was perturbed in patients with hypopituitarism receiving Pred replacement, despite careful administration. This disturbance may carry a risk of leading to cardiovascular diseases.

A dose of > 5 mg/d Pred was associated with a notable reduction in glucose-target-rate and glucose level at nocturnal period, along with elevation in GV, hypoglycemia occurrence, and glucose level at postprandial phase. However, only glucose level at 3-8 am period was changed significantly in Pred ≤ 5 mg/d group. Accordingly, we concluded that a dose



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Figure 1 Glucose-target-rate profile. A: Comparison of patient group to normal controls (NCs); B: Comparison of prednisone (Pred) > 5 mg/d group and Pred ≤ 5 mg/d group to NCs. Data are denoted as means. PG: Patient group; NCs: Normal controls; Pred: Prednisone; PT: Percentile time; TIR: Time in range; TOR: Time out of range.

of > 5 mg/d Pred may have a more adverse impact on glucose metabolism.

Given the essential role of GCs in maintaining normal life, authoritative guidelines strongly endorse the paramount importance of exogenously GCs replacement in those patients with endogenous insufficiency[3,18]. In this context, GCs replacement has been recognized as a fundamental therapeutic paradigm for patients with hypopituitarism. The diurnal rhythm of physiological cortisol secretion has been recognized for many years[19]. It is challenging for a GCs replacement regimen to accurately mimic this endogenously rhythmic pattern[20,21], usually leading to nonphysiological and subtly excess cortisol levels.

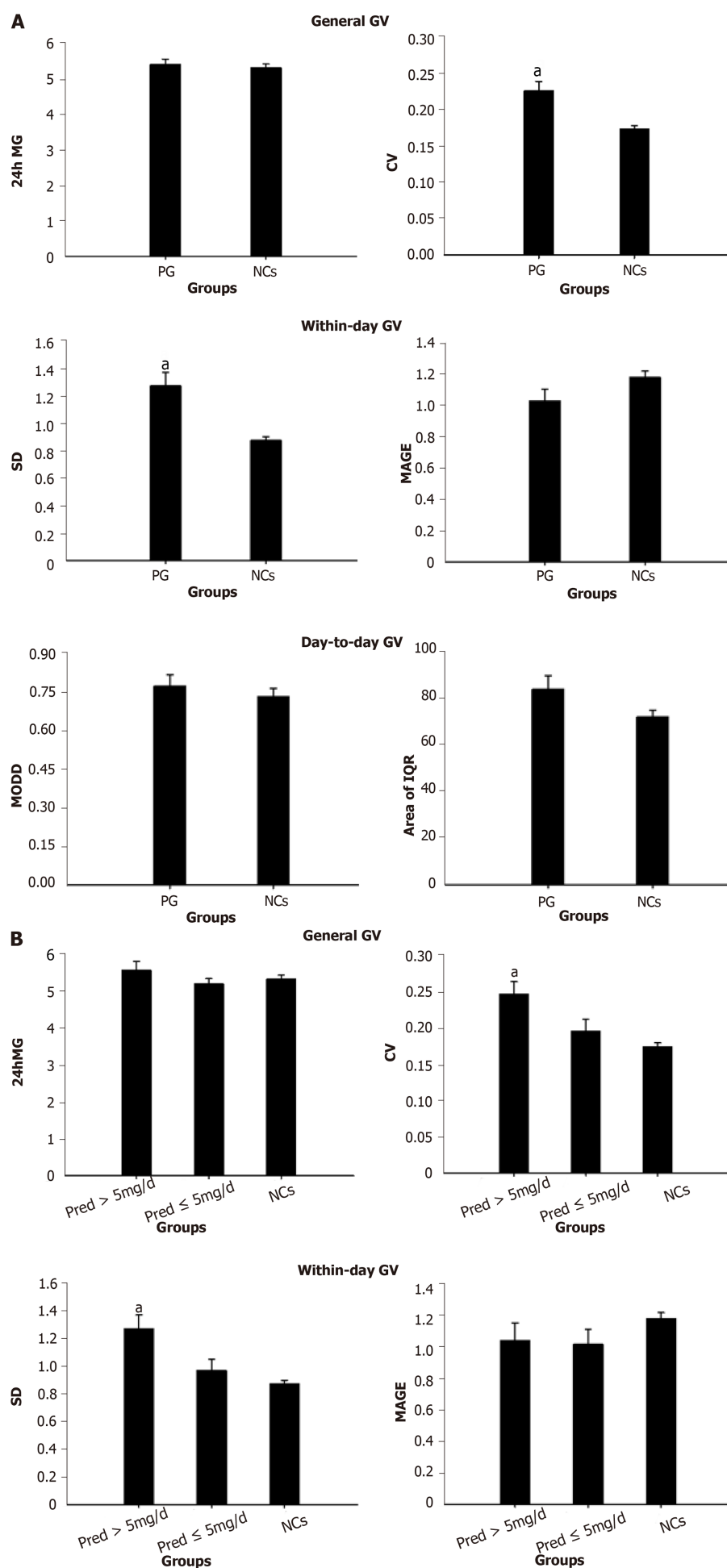
There is a growing awareness of highly dynamic synchronization in cortisol secretion into the blood circulation and its binding to GCs receptor (GR) in peripheral tissues[22]. Non-physiological GCs replacement fails to achieve a circadian rhythmic pattern, and further disturbs the tissue response mode, ensuing compromised hormone action, such as impaired glycometabolism and water-electrolyte metabolism. Pred is a kind of synthetic steroids, endowed with a great and enduring stimulatory effect on GR[23], and by continuously acting on the target tissues of glycometabolism, it can lead to metabolic disturbance.

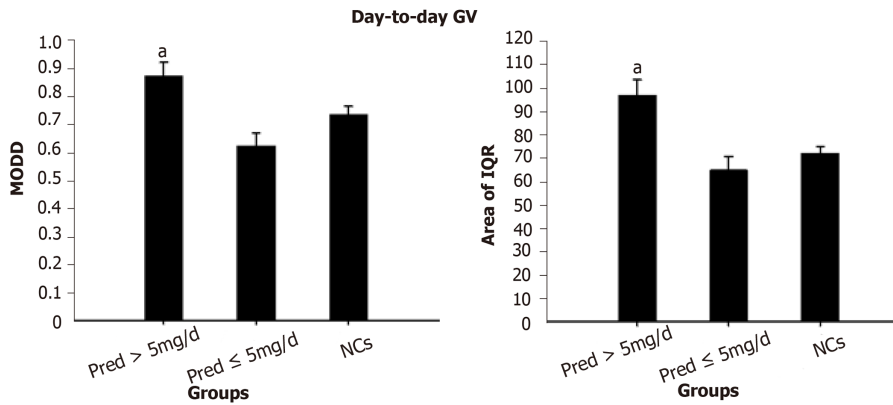
In this study, significantly altered PT and TIR were identified in PG when compared with that of NCs. The significantly increased prevalence of hyperglycemia and hypoglycemia led to poor TIR. As an emerging indicator for blood glucose control in diabetic patients, TIR has been demonstrated to be inversely correlated with the risk of cardiovascular events [24,25]. The statistically decreased TIR identified in Pred group may herald a higher risk of cardiovascular events in these patients.

The results of significantly increased GV than that of NCs suggested that Pred replacement brought about an adverse impact on glycometabolism. GV is known to be positively associated with incidence of cardiovascular events in patients with diabetes[26,27]. Accordingly, we hypothesized that this notable elevation of GV found in PG implied that these patients would be prone to developing cardiovascular diseases during the long-term replacement therapy regimen.

The average glucose level throughout the whole day in PG was within the normal range. Nonetheless, a notable reduction was indicated at period of 3-8 am. Increased hypoglycemia occurrence was also identified at this period but not at 0-3 am period. Taken together, one could postulate that there existed relatively insufficient cortisol level at 3-8 am period, which was responsible for the elevated occurrence of hypoglycemia.

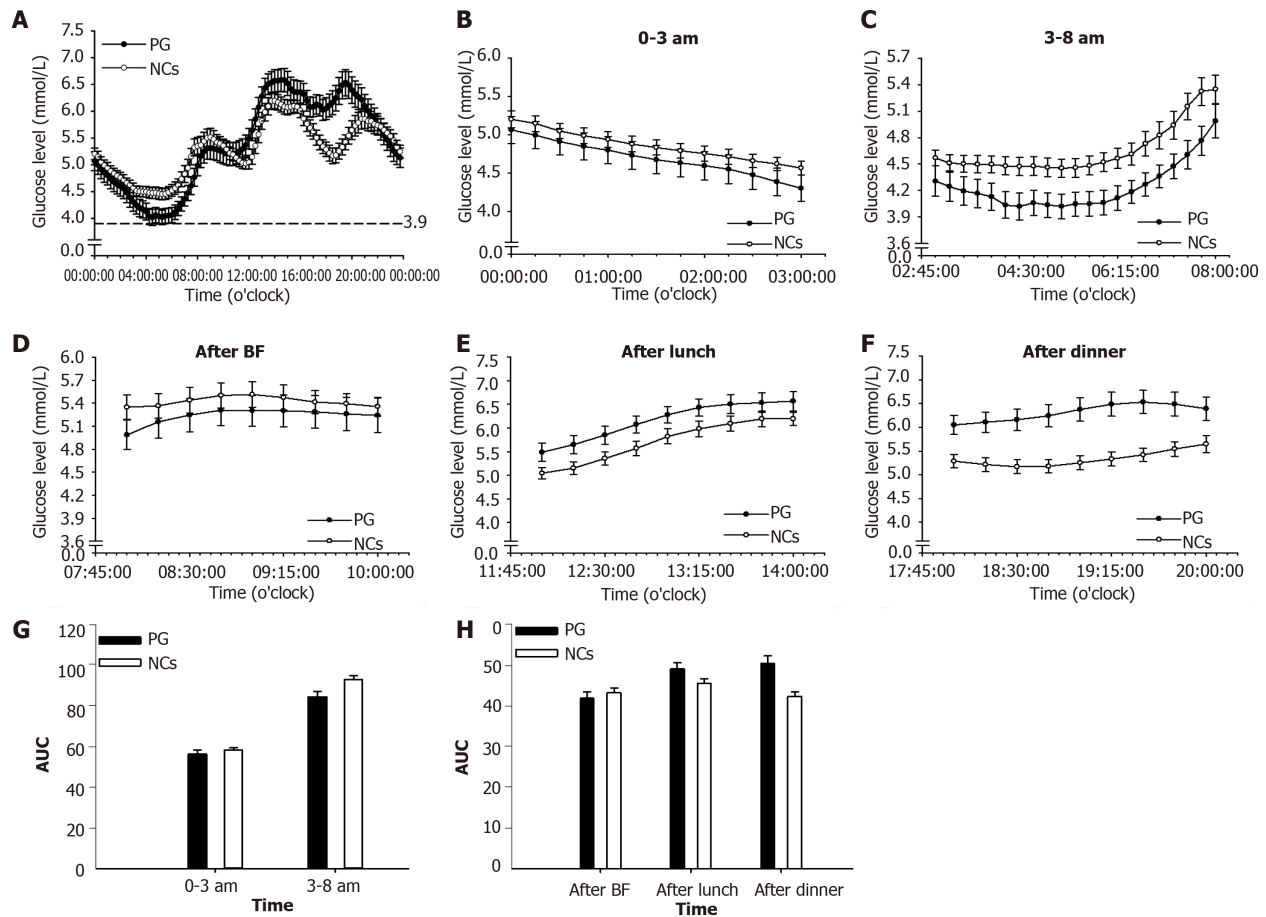
It is crucial to reiterate the basic fact that cortisol secretion follows a circadian rhythm in normal subjects, which commences with a rise at approximately 3 am, reaches a peak at around 8-9 am, and then progressively decreases towards a nadir at around midnight[16]. The cortisol trough level seemed sufficient in PG according to the comparable glucose level and hypoglycemia occurrence observed at 0-3 am period, when compared to those of NCs, which allowed us to hypothesize that Pred produced long-term steroids effects due to its delayed disassociation from GR. The applied Pred regimen was enough to maintain sufficient a trough level, although it failed to adequately and synchronously





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Figure 2 Glucose variability profile. A: Comparison of patient group to normal controls (NCs); B: Comparison of prednisone (Pred) > 5 mg/d group and Pred ≤ 5 mg/d group to NCs. Data are denoted as mean ± SE. ^a*P* < 0.05. PG: Patient group; NCs: Normal controls; Pred: Prednisone; GV: Glucose variability; MG: Mean glucose; CV: Coefficient of variance; MODD: Mean of daily difference; IQR: Interquartile range.

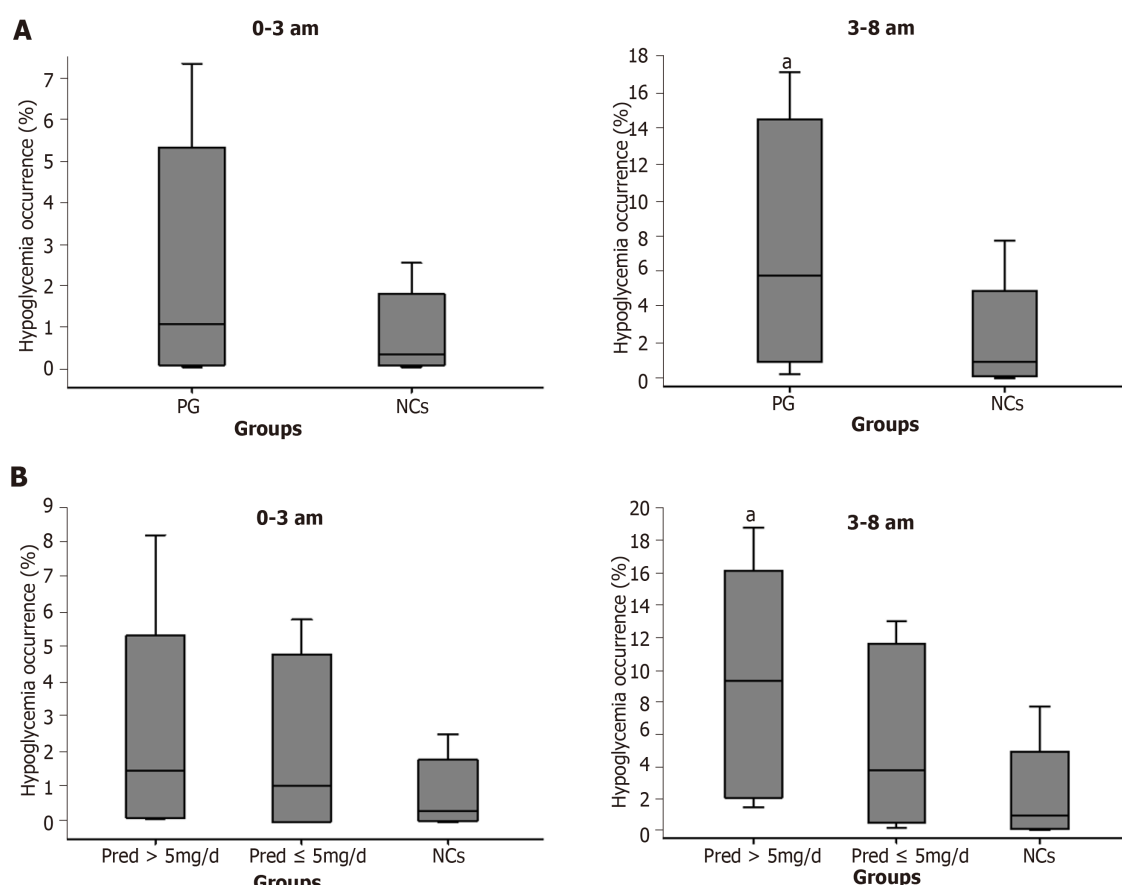


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Figure 3 Comparison of glucose level and area under the curve between patient group and normal controls. A: Glucose level during whole day; B: Glucose level at 0-3 am period; C: Glucose level at 3-8 am period; D: Glucose level after breakfast; E: Glucose level after lunch; F: Glucose level after dinner; G: Area under the curve (AUC) at 0-3 am period and 3-8 am period; H: AUC at postprandial periods. Data are denoted as mean ± SE. ^a*P* < 0.05. AUC: Area under the curve; PG: Patient group; NCs: Normal controls; BF: Breakfast.

maintain cortisol elevation from 3 am to 8 am compared to the normal cases in NCs. Consequently, there may have existed a pre-dose cortisol insufficiency at period of 3-8 am when the steroids effect of the last administration had been washed out, leading to decreased glucose level and increased hypoglycemia occurrence.

A significantly increased postprandial glucose level was found in PG compared with that of NCs, seemingly indicating a subtly excess cortisol level during the daytime. As an allegedly long-acting GCs preparation, Pred possesses a great affinity for GR, occupying and stimulating the GR over a lengthy period until it is finally degraded[23]. Prolonged



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Figure 4 Hypoglycemia occurrence. A: Comparison of patient group to normal controls (NCs); B: Comparison of prednisone (Pred) > 5 mg/d group and Pred ≤ 5 mg/d group to NCs. Data are showed as median, interquartile range, and interdecile range. ^a*P* < 0.05. PG: Patient group; NCs: Normal controls; Pred: Prednisone; IQR: Interquartile range.

exposure to steroids allows continuous accesses to target tissues, eliciting unfavorable side effects such as increased postprandial glucose level, as discovered in this study.

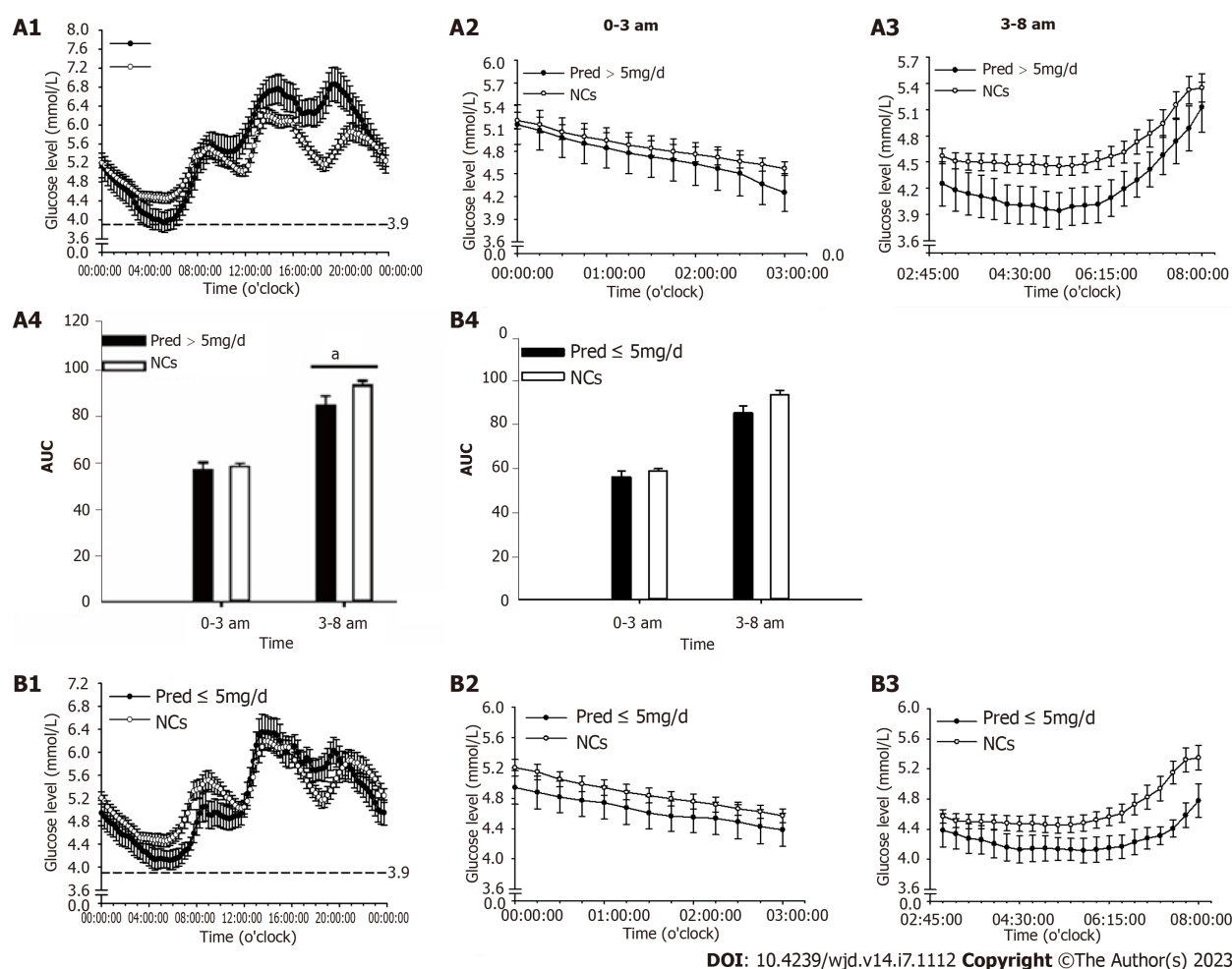
An important consideration when interpreting the influence of GCs replacement on glucose metabolism is whether the daily dose matches with the measured cortisol secretion rate over the course of an entire day in a normal subject. The physiological cortisol production rate is lower than the traditionally recommended GCs replacement dose[28,29]. Clinical evidence suggests that a dose of > 20 mg/d HC correlates with increased incidence of adverse events[11,12,30]. A dose of 5 mg Pred is equivalent to 20 mg HC. Assuming that patients under a replacement regimen of > 5 mg/d Pred were associated with a higher risk of adverse metabolic profile, PG was distributed into two subgroups: Pred > 5 mg/d and Pred ≤ 5 mg/d.

Significantly altered PT and TIR were found in Pred > 5 mg/d group, revealing that poor TIR was attributed to increased hyperglycemia and hypoglycemia occurrence. However, all indicators of glucose-target-rate showed no significant difference between Pred ≤ 5 mg/d group and NCs. According to TIR results, Pred > 5 mg/d group may have a predisposition towards developing cardiovascular diseases.

Significantly increased GV was detected in Pred > 5 mg/d group, while no statistical difference was identified in these parameters when Pred ≤ 5 mg/d group and NCs were compared. It is tempting, therefore, to speculate that patients in Pred > 5 mg/d group experienced more aggressive glycometabolism impairment and a great tendency to experience adverse cardiovascular events.

The average daily glucose level was normal in both Pred > 5 mg/d group and Pred ≤ 5 mg/d group. In Pred > 5 mg/d group, a notable reduction of glucose level was documented at 3-8 am period, highlighting the possibility of insufficient nocturnal hormone level. Moreover, a remarkable elevation of hypoglycemia occurrence was identified at this period, adding credence to the speculation of insufficient nocturnal hormone level. The Pred ≤ 5 mg/d group exhibited a significantly decreased glucose level at 3-8 am period, however, hypoglycemia occurrence at this period was comparable to that in NCs, prompting the assumption that insufficient nocturnal hormone level was relatively mitigated in comparison with the situation in Pred > 5 mg/d group. In addition, the glucose level and hypoglycemia occurrence at 0-3 am period were comparable to those of NCs in Pred > 5 mg/d group and Pred ≤ 5 mg/d group, demonstrating that a sufficient trough level may have been achieved in these two group.

A significantly increased glucose level at postprandial phase was identified in Pred > 5 mg/d group, but not in Pred ≤ 5 mg/d group. The underlying mechanism was assumed to be continuous hormone accessing to the target tissue due to



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Figure 5 Glucose level and area under the curve during the day, at 0-3 am, period and at 3-8 am period. Comparison of prednisone (Pred) > 5mg/d group to normal controls (NCs): A1, during the day; A2, at 0-3am; A3, at 3-8am; A4, AUC. Comparison of prednisone (Pred) ≤ 5mg/d group to normal controls (NCs): B1, during the day; B2, at 0-3am; B3, at 3-8am; B4, AUC. Data are denoted as mean ± SE. * $P < 0.05$. AUC: Area under the curve; NCs: Normal controls; Pred: Prednisone.

the long-acting property of Pred during the daytime. This continuous stimulation may have disturbed glucose regulation in the relevant organs, leading to reduced glucose disposal and elevated glucose production. The present data allowed us to hypothesize that a Pred dose of > 5 mg/d posed a more profound effect on glucose regulation during the efficacy period than a dose of ≤ 5 mg/d.

Impaired β -cell function was indicated by relevant parameters in PG when compared to that of NCs. Summarizing the yet published literature, there are no consistent data supporting the presence of impaired β -cell function in patients with hypopituitarism undergoing GCs treatment[31-33]. Results generated in this study allowed us to hypothesize that the physiological Pred replacement regimen may exert adverse effects on glucose metabolism, leading to compromised β -cell function.

Of special note is that adrenocorticotrophic-hormone (ACTH) levels measured in all the groups were within the normal range, probably indicating partial ACTH deficiency. The normal ACTH levels were suggestive of a reasonable Pred treatment because an excess dose of Pred might suppress the ACTH secretion. However, the usage of FGMS identified impaired glucose metabolism, which is relevant to higher risks of cardiovascular diseases. In this light, FGMS attests its importance in providing reliable information for evaluating a suitable Pred replacement regimen.

CONCLUSION

Pred replacement in patients with hypopituitarism impaired glucose metabolism, leading to an increased risk of cardiovascular events. A dose of > 5 mg/d Pred had a more significant influence on glucose metabolism than a dose of ≤ 5 mg/d. A suitable Pred replacement regimen necessitates comprehensive and accurate evaluation, for which FGMS is a kind of promising and reliable assessment device. Altogether, the integration of results in this study adds weight to the existing knowledge, and further provides new reference and guidance for future clinical work to effectively avoid the risk of cardiovascular events and improve well-being in patients with hypopituitarism.

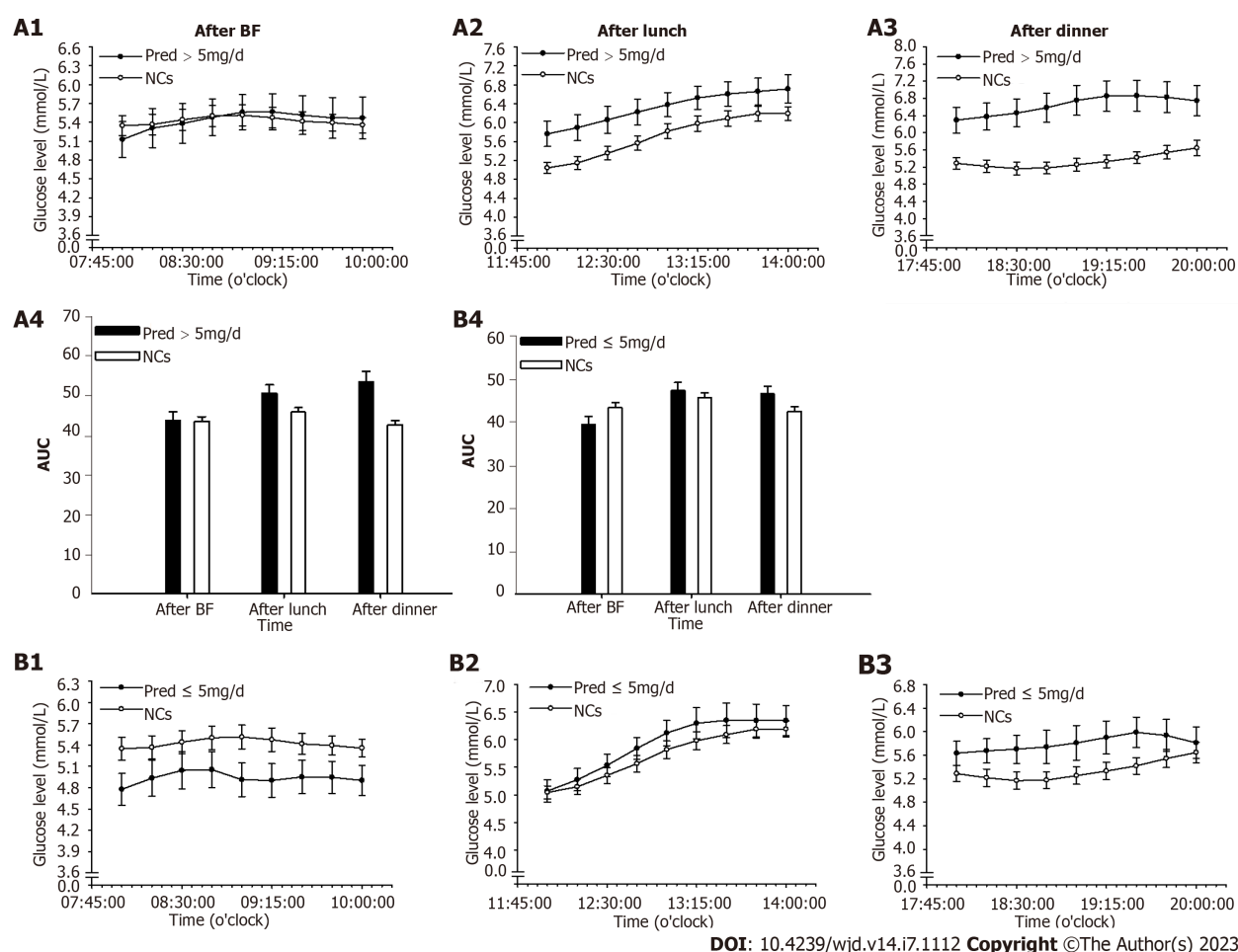


Figure 6 Glucose level and area under the curve at postprandial phase. Comparison of prednisone (Pred)>5mg/d group to normal controls (NCs): A1, after BF; A2, after lunch; A3, after dinner; A4, AUC. Comparison of prednisone (Pred) ≤ 5mg/d group to normal controls (NCs): B1, after BF; B2, after lunch; B3, after dinner; B4, AUC. Data are denoted as mean ± SE. * $P < 0.05$. AUC: Area under the curve; NCs: Normal controls; Pred: Prednisone; BF: Breakfast.

ARTICLE HIGHLIGHTS

Research background

As the growing amount of information consolidated in the field of glucocorticoids' (GCs) hyperglycemia effect, whether GCs replacement therapy disturbs glycometabolism homeostasis in patients with hypopituitarism has garnered considerable interest. Timely and adequate GCs replacement has been commonly recognized as a lifesaving prescription for those patients with hypopituitarism, which aims to restore hormone deficiency and improve well-being. Choosing an optimum GCs replacement regimen for patients with hypopituitarism continues to be a challenging problem as the physiological cortisol rhythm is difficult to replicate. An inability to mimic physiological cortisol rhythms or over-treatment may make those patients receiving GCs replacement susceptible to metabolic disturbances and subsequent cardiovascular events.

Research motivation

Commonly used glucocorticoids replacement regimens in hypopituitarism patients have difficulty mimicking physiological cortisol rhythms and are usually accompanied with risks of over-treatment, which will pose adverse effects on glucose metabolism. Disorders associated with glucose metabolism are established risk factors of cardiovascular events, one of the life-threatening ramifications. As the increasing prevalence of adverse events occurs in hypopituitarism patients under GCs replacement, greater emphasis has been placed on choosing a suitable replacement regimen with as little influence on glycometabolism as possible.

Research objectives

This study was designed to assess the glucose metabolism profile recorded by a flash glucose monitoring system in patients with hypopituitarism, illuminating the impact of GCs preparation (Pred) and prescription doses on glucose metabolism. In doing so, we hope to add novel insights into the existing body of evidence and provide references to guide the treatment choices for those patients with hypopituitarism, in order to reduce the incidence of cardiovascular events.

Research methods

In this study, patients with hypopituitarism treated with Pred were enrolled as patient group (PG), and regrouped into Pred > 5 mg/d group and Pred ≤ 5 mg/d group based on the recommended Pred dose per day. Age- and sex-matched normal controls (NCs) without known hypopituitary dysfunction or glycometabolic disorders were enrolled. At baseline, all the recruited patients underwent hypopituitary-adrenal/thyroid function assessment, along with electrolyte and glucose metabolism evaluation, including plasma sodium, glycosylated hemoglobin, fasting blood glucose, and fasting insulin. The NCs received laboratory tests similar to those of PG. Flash glucose monitoring system (FGMS) was used to record glucose profile of both PG and the NCs. Parameters of glucose-target-rate, glucose variability (GV), and period glucose level were analyzed. β -cell function and insulin resistance (IR) were assessed by calculating the homeostasis model assessment (HOMA)- β along with HOMA-IR, fasting glucose/insulin ratio, and quantitative insulin sensitivity check index.

Research results

Twenty patients diagnosed with hypopituitarism receiving Pred replacement were enrolled in this study. Of these, twelve patients were treated with doses of > 5 mg/d Pred and eight patients were treated with doses of ≤ 5 mg/d. Significantly decreased glucose-target-rate and glucose level at nocturnal period, along with increased GV, hypoglycemia occurrence, and glucose level at postprandial phase were identified in PG when compared with those of NCs. These results demonstrated that glucose metabolism homeostasis was perturbed in patients with hypopituitarism receiving Pred replacement, despite careful administration. This disturbance may carry a risk of leading to cardiovascular diseases. A dose of > 5 mg/d Pred was associated with a notable reduction in glucose-target-rate and glucose level at nocturnal period, along with elevation in GV, hypoglycemia occurrence, and glucose level at postprandial phase. However, only glucose level at 3-8 am period was changed significantly in Pred ≤ 5 mg/d group. Accordingly, we concluded that a dose of > 5 mg/d Pred may have a more adverse impact on glucose metabolism. Impaired β -cell function was indicated by relevant parameters in PG when compared to that of NCs.

Research conclusions

Pred replacement in patients with hypopituitarism impaired glucose metabolism, leading to an increased risk of cardiovascular events. A dose of > 5 mg/d Pred had a more significant influence on glucose metabolism than a dose of ≤ 5 mg/d. A suitable Pred replacement regimen necessitates comprehensive and accurate evaluation, for which FGMS is a kind of promising and reliable assessment device. Altogether, the integration of results in this study adds weight to the existing knowledge, and further provides new reference and guidance for future clinical work to effectively avoid the risk of cardiovascular events and improve well-being in patients with hypopituitarism.

Research perspectives

The integration of results in this study adds weight to the existing knowledge, and further provides new reference and guidance for future clinical work to effectively avoid the risk of cardiovascular events and improve well-being in patients with hypopituitarism.

FOOTNOTES

Author contributions: Liu YF was the guarantor and designed the study; Liu ZA, Xu LX, Bai T, Xiang CY, Zhang J, Lv DQ, Liu YF, Wei YH, and Wu BF participated in the acquisition of the data; Han MM, Zhang JX, and Liu ZA analyzed and interpreted the data; Han MM and Zhang JX drafted the initial manuscript; Liu YF, Zhang Y, and Han MM revised the article critically for important intellectual content.

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Informed consent statement: Written informed consent was obtained from all the subjects after explanation of study design and purpose.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: The analyzed data presented in the study are included in the article, further inquiries can be directed to the corresponding authors.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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