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Observational Study

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

Glycometabolism profile in hypopituitarism patients

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Abstract

BACKGROUND

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.

AIM

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

METHODS

Twenty patients with hypopituitarism receiving prednisone replacement (patient group) and 20 normal controls 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, period glucose level, and hypoglycemia occurrence at certain periods. Islets β -cell function was also assessed. Based on the administered prednisone dose per day, the patient group was then regrouped into prednisone $>5\text{mg/d}$ and prednisone $\leq 5\text{mg/d}$ subgroups; Comparative analysis was carried out between the patient group and normal controls.

RESULTS

Significantly altered glucose metabolism profile were identified in the patient group. Wherein, remarkable reductions in glucose-target-rate and nocturnal glucose level, along with elevations in glucose variability, hypoglycemia occurrence and postprandial glucose level were identified when compared with those in normal controls. Subgroup analysis indicated more significant glucose metabolism impairment in the prednisone

>5mg/d group, including significantly decreased glucose-target-rate and nocturnal glucose level, along with increased glucose variability, hypoglycemia occurrence, and postprandial glucose level. With regard to Islets β -cell function, patient group showed significant difference in homeostasis model assessment- β compared with that of normal controls; A notable difference in homeostasis model assessment- β was identified in prednisone >5mg/d group when compared with those of normal controls; As for prednisone \leq 5mg/d group, significant difference was found in homeostasis model assessment- β , and fasting glucose/insulin ratio in comparison with that in normal controls.

CONCLUSION

Our results demonstrated that prednisone replacement disrupted glycometabolic homeostasis in patients with hypopituitarism. A prednisone dose of >5mg/d seemed to cause more adverse effects on glycometabolism than a dose of \leq 5mg/d. Comprehensive and accurate evaluation is necessary to consider a suitable prednisone replacement regimen, wherein, FGMS 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 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 replacement, using a flash glucose monitoring system, in order to clarify impacts of different glucocorticoids preparations and prescriptions on glycometabolism, along with the resultant risks of consequent cardiovascular events. According to the results generated in this study, prednisone replacement disturbed glycometabolic homeostasis in patients with hypopituitarism. A dose of >5mg/d prednisone caused more adverse effects on glycometabolism than that of ≤5mg/d, contributing to the higher risks of cardiovascular events.

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 high 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 excess 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 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. 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 (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.

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 received Pred replacement were recruited in this study as patient group (PG). The hypopituitarism was diagnosed by the following criteria^[3]: medical history (postpartum hemorrhage, hypophysectomy, pituitary crisis, and *etc.*); clinical manifestations (hyponatremia, hypotension, hypoglycemia, and *etc.*); pituitary MRI (empty sella, pituitary hypoplasia, pituitary stalk interruption, and *etc.*); 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 (HbA1c), fasting blood glucose (FBG), and fasting insulin (FINS). 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 difficult availability of HC in China, most of hypopituitarism patients received Pred replacement regimen instead. In this study, we enrolled patients with hypopituitarism treated with Pred as PG, and regrouped PG into Pred >5 mg/d group and Pred ≤5 mg/d group based on the recommended prednisone dose per day.

FGMS

FGMS (FreeStyle Libre, Abbott Diabetes Care, Witney, United Kingdom) was used to record glucose profile of both PG and the NCs. Due to unexpected dropping of the sensor or other unpredictable interferences, we failed to obtain a complete two-week monitoring data. The data from the first-day of monitoring were removed due to poor accuracy. In the end, 222 days of monitoring data were collected from patients in PG (134 days for the Pred >5 mg/d group, and 88 days for the Pred ≤5 mg/d group), while NCs provided 184 day of glucose data. The FGMS required a real-time scanned value within 8-hour 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.

Islets 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 Microsoft Excel datasheet. Data analysis and graph plotting were performed using SPSS 21.0 and Sigmaplot 12.5. All data are shown as mean \pm 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 (TOR, the time of

sensor glucose values less than 3.9 mmol/L and above 7.8 mmol/L during the day). GV was analyzed from the following perspectives: general GV including 24-hour mean glucose (24hMG) and coefficient of variance (CV); within-day GV consisting of standard deviation (SD) and mean amplitude of glycemic excursion (MAGE); 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 3am 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 0-3am and 3-8am. Glucose levels and area under the curve (AUC) of glucose level at 0-3am, 3-8am, and postprandial periods were analyzed. In addition, hypoglycemia occurrence (glucose value less than 3.9 mmol/L) was analyzed during 0-3am and 3-8am 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 Sheehan's syndrome, four empty sella, six hypophysectomy, and one pituitary hypoplasia, receiving Pred replacement were enrolled in this study. Of these patients, 16 of them have ever suffered acute hypopituitarism, presenting symptoms of hyponatremia, hypotension, hypoglycemia, and *etc.*; four of them were diagnosed by corticotropin stimulation test (stimulated cortisol<500nmol/L); significantly reduced levels of 24-hour urinary free cortisol were detected in all of the patients during the course of disease. Twelve patients were treated with doses of >5mg/d Pred and eight patients were treated with doses of \leq 5mg/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 has 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 $> 5\text{mg/d}$ group when compared with those of NCs (Figure 1B). Comparable PT1, PT3, and TIR were found between Pred $\leq 5\text{mg/d}$ group and NCs (Figure 1B).

Glucose variability

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 $> 5\text{mg/d}$ group (Figure 2B), a remarkable elevation was 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, $P = 0.002$) than that of NCs. However, no significant difference was observed in GV parameters between Pred $\leq 5\text{mg/d}$ group and NCs (Figure 2B).

Period glucose level

For PG, period glucose level analysis indicated that glucose level was significantly lower at period of 3-8am ($P = 0.004$) 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). Besides, significantly increased glucose level was identified at postprandial phase (after lunch, $P = 0.028$; after dinner, $P < 0.001$) when compared to that of NCs (Figure 3).

In Pred >5mg/d group, notable alterations were found during 3-8am 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 ≤ 5 mg/d group, significant reduction of glucose level at 3-8am 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 level was identified at postprandial periods between Pred ≤ 5 mg/d group and NCs (Figure 6B).

Islets function assessment

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

Glucose metabolism indicators showed notable difference in HOMA- β ($P = 0.021$) in Pred >5mg/d group when compared with those of NCs (Table 2). As for Pred ≤ 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).

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 considerate and prudent administration. This disturbance may carry a risk of leading to cardiovascular diseases.

A dose of >5mg/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 3-8am period was changed significantly in Pred ≤5mg/d group. Accordingly, we concluded that a dose of >5mg/d Pred may have a more adverse impact on glucose metabolism.

Given the essential role of GCs in maintaining normal life, authoritative guidelines strongly endorsed 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 classical view propounded several years ago referred to the diurnal rhythm of physiological cortisol secretion [19], pushing barrier towards GCs replacement regimen choice. Nowadays' GCs administrations are hard to accurately mimic the 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], continuously acting on the target tissues of glycometabolism, leading 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 hyper- and hypoglycemia led to poor TIR. As an emerging indicator for blood glucose control in diabetic patients, TIR has been demonstrated to 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 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 were 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 3-8am. Increased hypoglycemia occurrence was also identified at this period but not at 0-3am period. Taken together, one could postulate that there existed relatively insufficient cortisol level at 3-8am period, which were 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 3am, reaches a peak at around 8-9am, 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 0-3am 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 maintain cortisol elevation from 3am to 8am compared to the normal cases in NCs. Consequently, there may have existed a pre-dose cortisol insufficiency at period of 3-8am when the steroids effect of the last administration had been washed out, leading to decreased glucose level and increased hypoglycemia occurrence.

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

Prolonged exposure to steroids continuously accesses to target tissue, eliciting unfavorable side effects such as increased postprandial glucose level, as discovered in this study.

In addition, 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. It is also important to mention that the physiological cortisol production rate is lower than the traditionally recommended GCs replacement dose [28,29]. Clinical evidence suggests that a dose of >20mg/d HC correlates with increased incidence of adverse events [11,12,30]. A dose of 5mg Pred is equivalent to 20mg HC. Assuming that patients under a replacement regimen of >5mg/d Pred were associated with a higher risk of adverse metabolic profile, PG was distributed into two subgroups: Pred >5mg/d and Pred ≤5mg/d.

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

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

The average daily glucose level maintained normal in both Pred >5mg/d group and Pred ≤5mg/d group. In Pred >5mg/d group, a notable reduction of glucose level was documented at 3-8am 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 ≤5mg/d group exhibited significantly decreased glucose level

at 3-8am 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 >5mg/d group. In addition, glucose level and hypoglycemia occurrence at 0-3am period were comparable to those of NCs in Pred >5mg/d group and Pred ≤5mg/d group, demonstrating that a sufficient trough level may have been achieved in these two group.

Significantly increased glucose level at postprandial phase was identified in Pred >5mg/d group, but not in Pred ≤5mg/d group. The underlying mechanism was assumed to be continuous hormone accessing to the target tissue due to 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 Pred dose of >5mg/d posed more profound effect on glucose regulation during the efficacy period than that of ≤5mg/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 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 overdose 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 $>5\text{mg/d}$ Pred had a more significant influence on glucose metabolism than a dose of $\leq 5\text{mg/d}$. 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.

ARTICLE HIGHLIGHTS

Research background

As the growing amount of information consolidated in the field of glucocorticoids' 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 PG into Pred >5mg/d group and Pred ≤5mg/d group based on the recommended prednisone 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 (HbA1c), fasting blood glucose (FBG), and fasting insulin (FINS). The NCs received laboratory tests similar to those of PG. 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. ²β-cell function and insulin resistance (IR) were assessed by calculating the homeostasis model assessment (HOMA)-β along with HOMA-IR, ¹fasting glucose/insulin ratio (G/I), and quantitative insulin sensitivity check index (QUICKI).

Research results

Twenty patients diagnosed with hypopituitarism receiving Pred replacement were enrolled in this study. Of these, 12 patients were treated with doses of $>5\text{mg/d}$ Pred and eight patients were treated with doses of $\leq 5\text{mg/d}$. 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 considerate and prudent administration. This disturbance may carry a risk of leading to cardiovascular diseases. A dose of $>5\text{mg/d}$ 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 3-8am period was changed significantly in Pred $\leq 5\text{mg/d}$ group. Accordingly, we concluded that a dose of $>5\text{mg/d}$ 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 $>5\text{mg/d}$ Pred had a more significant influence on glucose metabolism than a dose of $\leq 5\text{mg/d}$. 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.

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