EVALUATION OF GLUCOCORTICOID-INDUCED HYPERGLYCEMIA WITH DIFFERENT ROUTES OF ADMINISTRATION IN TERTIARY CARE HOSPITAL

Saranya Ponraj[1,3]Ragul Ezhumalai[2,3], Raja Poomalai[2,3], Subhaharini Sathish kanchana[2,3], Suresh Saravanan[2,3], Yazhini Selvam[2,3]

[1]Assistant professor, Department of Pharmacy Practice, Karpagam College of Pharmacy, Coimbatore, Tamil Nadu, India
[2]VI Pharm.D. Student, Karpagam College of Pharmacy, Coimbatore, Tamil Nadu, India.
[3]Affiliated to The Tamil Nadu Dr. MGR Medical University, Chennai, Tamil Nadu, India.

ABSTRACT

Background: The primary aim of this study is to evaluate the hyperglycaemic effects induced by glucocorticoids through various routes of administration and to identify key factors contributing to elevated blood sugar levels in patients receiving glucocorticoid therapy. **Methodology:** A prospective observational study was conducted with 60 patients as per the study criteria at Karpagam hospital, Coimbatore in duration of 6 months. Demographic data, different routes of glucocorticoid administration, and drug action (short, intermediate, long acting) in the development of hyperglycaemia. Random Blood Sugar level was monitored. **Results**: Out of 60 patients, 29 (48.3%) exhibited elevated RBS levels. The highest prevalence of hyperglycemia was observed in patients receiving glucocorticoids via nebulizer (73%) and IV (60%) routes. Short-acting glucocorticoids induce the highest rate of hyperglycemia (75%). Male patients (60%) and 55–75-year age group were more prone to elevated blood sugar levels. Obese patients (BMI > 30) had a high incidence of hyperglycemia (89%). Hypertension (23%) and chronic obstructive pulmonary disease (16.6%) are the Common comorbidities among study patients. **Conclusion**: This study indicates that the significant hyperglycemic effects are induced by glucocorticoid therapy. The route of administration plays a critical role in the risk of hyperglycemia. Nebulizer and IV routes, as well as short-acting glucocorticoids, showed the highest association with elevated RBS levels. These findings emphasize the need for careful monitoring of blood glucose in patients undergoing glucocorticoid treatment, especially who are with risk factors such as older age, obesity, and comorbidities.

KEYWORDS: Glucocorticoids, Hyperglycemia, Routes of administration, Random blood sugar, Glucocorticoid therapy.

1. INTRODUCTION

Glucocorticoids (GCs) are widely used anti-inflammatory and immunosuppressive medications that have been an essential part of medical treatment since the mid-20th century. These drugs are prescribed for a broad range of acute and chronic inflammatory conditions, including asthma, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, and inflammatory bowel diseases [12]. Their ability to suppress inflammation and regulate immune responses makes them a cornerstone of treatment in many medical disciplines. Studies suggest that approximately 0.9% of the general population uses GCs at any given time, with usage increasing to around 2.5% among older adults aged 70 to 79 years. Additionally, up to 25% of patients prescribed GCs may require prolonged therapy lasting more than six months [14,35].

Oral GCs are most frequently used in respiratory conditions, accounting for nearly 40% of prescriptions, while the remaining prescriptions are distributed across musculoskeletal disorders, skin diseases, and immunosuppressive therapy. Despite their therapeutic benefits, long-term GC use is associated with significant adverse effects, including weight gain, osteoporosis, hypertension, and hyperglycemia. One of the most concerning metabolic complications of GC therapy is glucocorticoid-induced hyperglycemia (GIH), which can contribute to the development of diabetes or worsen existing diabetes [19,20,41].

1) Glucocorticoid-Induced Hyperglycemia (GIH)

GIH is a well-documented consequence of GC therapy that has been recognized for more than six decades. GCs are among the most frequently implicated drugs in medication-induced hyperglycemia and diabetes. Their role in disrupting glucose homeostasis is particularly concerning for patients who already have pre-existing diabetes, as GCs can significantly worsen glycemic control [3,4]. Additionally, GCs can reveal undiagnosed diabetes in susceptible individuals and may lead to the development of new-onset diabetes, referred to as glucocorticoid-induced diabetes mellitus (GIDM) [1,2].

In non-diabetic individuals, glucose levels are generally expected to return to normal after discontinuing GC therapy. However, studies indicate that in some cases, persistent hyperglycemia can occur, necessitating long-term monitoring and intervention to prevent the onset of diabetes. Research shows that continuous administration of high-dose GCs over two to three months significantly raises the risk of developing diabetes [5,6]. Furthermore, patients on prolonged GC therapy are more likely to experience fasting hyperglycemia compared to those receiving cyclic or intermittent GC regimens [1,2].

In organ transplant recipients undergoing steroid-based immunosuppressive therapy, the prevalence of hyperglycemia ranges between 17% and 32%. This highlights the impact of GCs on glucose metabolism, particularly in high-risk patient populations.[8]

Additionally, stress-induced hyperglycemia (SIH) in hospitalized patients receiving GCs has an estimated incidence of 40% to 50%, further emphasizing the need for careful monitoring [7]. SIH can manifest as either the worsening of pre-existing type 2 diabetes, the unmasking of previously undiagnosed diabetes, or transient hyperglycemia in individuals without a prior history of diabetes [10]. The likelihood of developing SIH increases with higher GC doses and longer treatment durations, although it does not appear to be influenced by the specific type of GC used [40].

2) Mechanism and Etiology of GIH

The hyperglycemic effects of GCs are primarily due to their profound influence on glucose metabolism [9,11]. These effects mimic the metabolic disturbances seen in type 2 diabetes mellitus (T2DM). Several mechanisms contribute to GIH, including:

1. Inhibition of Insulin Secretion: GCs suppress insulin release from pancreatic β-cells, reducing the body's ability to regulate blood glucose levels effectively.

2. Increased Glucagon Secretion: GCs stimulate pancreatic α-cells to release glucagon, a hormone that raises blood glucose levels by promoting hepatic glucose production.

3. Hepatic Glucose Overproduction: GCs enhance glucose production in the liver by increasing gluconeogenesis and glycogenolysis, resulting in elevated blood sugar levels.

4. Peripheral Insulin Resistance: GCs impair glucose uptake in skeletal muscles and adipose tissue, reducing insulin sensitivity and promoting hyperglycemia.

5. Direct Pancreatic Toxicity: Prolonged GC use is associated with β-cell dysfunction and destruction, further impairing insulin production [4,5,11,13,15].

Additionally, GCs exacerbate hyperglycemia by enhancing the actions of counter-regulatory hormones such as glucagon and adrenaline. These hormones activate pathways that increase insulin resistance, further complicating glucose control. Some evidence also suggests that GCs affect intestinal glucose absorption by modifying enterocyte receptor activity, further contributing to hyperglycemia [7-16].

3) Epidemiology of GIH

The prevalence of GIH varies depending on the population studied, the type of GC used, and the treatment duration. Globally, approximately 1% of the general population and 2.5% of older adults are prescribed oral GCs. The incidence of GIH among patients receiving long-term GC therapy ranges between 20% and 30%, with the risk increasing significantly in hospital settings[16-19].

A study conducted among primary care patients with diabetes estimated that 2% of individuals on oral GCs developed GIH. In hospitalized patients without prior diabetes, 50% experienced hyperglycemia (blood glucose ≥200 mg/dL) during GC treatment. Furthermore, a retrospective study analyzing 2,424 hospitalized patients over four years reported a 34% incidence of GIH [17,18].

In transplant recipients receiving methylprednisolone and prednisone, 87% of non-diabetic patients developed hyperglycemia, with two-thirds requiring insulin therapy upon discharge. Another study focusing on hospitalized patients with community-acquired pneumonia treated with 50 mg of prednisone daily for one week observed a 20% incidence of hyperglycemia, with an odds ratio (OR) of 1.96 compared to placebo-treated patients [15,16].

A meta-analysis involving approximately 35,000 participants from 13 studies found that 32% of non-diabetic patients treated with GCs for at least one month developed GIH. Another recent meta-analysis of 118 randomized controlled trials reported a GIH prevalence of 10%, with severe hyperglycemia occurring in 5% of cases [17-20].

A. Risk Factors and Predictors of GIH

Several factors contribute to the development of GIH, including:

1) **Higher GC Dose:** The risk of hyperglycemia increases with higher cumulative doses.

2) **Longer Duration of Therapy:** Prolonged GC use is associated with a greater incidence of GIH.

3) **Older Age:** Elderly patients are at a higher risk due to reduced insulin sensitivity.

4) **Pre-existing Diabetes or Insulin Resistance:** Individuals with T2DM or metabolic syndrome are more likely to develop GIH.

Hospitalization and Stress: Patients receiving high-dose GCs in hospitals, particularly those in critical care settings, have an increased risk [20-25].

B. Clinical Implications and Management

Given the significant risk of hyperglycemia associated with GC therapy, regular blood glucose monitoring is crucial for patients undergoing treatment. The management of GIH includes:

1. Lifestyle Modifications: Patients should follow a balanced diet, engage in physical activity, and maintain a healthy weight to mitigate the risk of hyperglycemia.
2. Pharmacologic Intervention:

Oral Hypoglycemic Agents: Metformin and DPP-4 inhibitors can be used in mild to moderate hyperglycemia.

Insulin Therapy: In patients with severe hyperglycemia, insulin is the preferred treatment option.

3. Tapering GC Therapy:

Whenever possible, clinicians should use the lowest effective GC dose and consider alternative therapies to reduce metabolic complications [23-28].

2. MATERIALS AND METHODS

This prospective observational study was conducted in the Departments of General Medicine, General Surgery, Dermatology, Pulmonology, and Orthopedics at Karpagam Faculty of Medical Sciences and Research, Coimbatore. Before initiation, ethical approval was obtained from the Institutional Ethics Committee. The study was carried out over six months, from March to August 2024. Patients admitted to the respective departments during the study period were included based on predefined inclusion and exclusion criteria. A structured patient data collection form was used to gather relevant clinical information from medical records daily. The collected data included demographic details such as age and gender, past medical and medication history, laboratory investigations, diagnosis, and current treatment regimens. The study focused on evaluating patient profiles, disease patterns, and treatment outcomes. All collected data were recorded systematically and analyzed to identify trends and correlations in disease management across different specialties. Any missing or unclear information in patient records was clarified with healthcare professionals to ensure accuracy and completeness. Confidentiality and ethical considerations were strictly maintained throughout the study. Patient data were anonymized, and no personally identifiable information was used in data analysis or reporting. The findings from this study aimed to contribute to improving clinical decision-making and optimizing treatment strategies in the studied departments**.**

3. STUDY CRITERIA

Inclusion Criteria

- Age of 18 years and above.
- Patient receiving any dosage form of glucocorticoids.
- Patient with non-diabetic conditions.
- Patients receiving glucocorticoid therapy in departments such as General Medicine, General Surgery, Dermatology, and Pulmonology.

Exclusion Criteria

- Patient below the age of 18 years.
- Lactating and pregnant women.
- Patients with diabetes mellitus and psychiatric disability.
- Outpatient.

Methodology

This study was a prospective observational analysis conducted over six months at Karpagam Faculty of Medical Sciences and Research. The primary objective was to assess the incidence of corticosteroid-induced hyperglycemia using Cochran's formula. A total of 60 patients who were prescribed glucocorticoids during their treatment were enrolled in the study.

Patient data were collected through direct interactions, during which demographic details such as age, gender, medical history, and current medications were documented in a structured data collection form. Informed consent was obtained from all participants before data collection.

To evaluate the impact of glucocorticoid therapy on blood glucose levels, patients underwent a random blood glucose test after receiving six doses of corticosteroids. The test was performed using a standard glucometer, ensuring accuracy and consistency in measurements. The collected glucose levels were then compared with baseline values to determine any significant changes.

Descriptive statistical analysis was conducted using Microsoft Excel to interpret the data. The results were categorized based on the degree of hyperglycemia observed, and trends were analyzed to understand the correlation between glucocorticoid use and blood sugar fluctuations.

This methodology ensured a systematic approach to identifying corticosteroid-induced hyperglycemia and provided valuable insights into its occurrence in a clinical setting. The findings from this study contribute to better monitoring strategies and the management of hyperglycemia in patients receiving corticosteroid therapy.

4. RESULTS

Prevalence of glucocorticoids in induced hyperglycemia (n = 60)

Prevalence = no. of population affected the study (n = 29) \Total no. of population in study (n = 60) x100 = 48.3%

The study found a substantial incidence of GCIH, affecting 29 out of 60 patients (48.3%), who showed elevated RBS levels, highlighting the need for close monitoring and management of blood sugar levels in patients undergoing glucocorticoid treatment.

Gender distribution among the study population (n=60)

Among the study population, 60 patients were included in this study, the majority of the patients were males (60%).

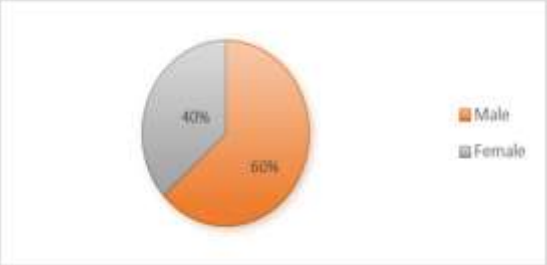

Fig 1. Gender distribution among the study population

Table 1. Age Distribution among the study population

Age (years)	No. of Patients	Percentage
18 - 35	09	15%
36 - 55	16	27%
56 - 75	33	55%
>75	02	3%

Table 2: Comorbidities Associated with Study Population

Comorbidity	No. of patients	Percentage
Hypertension	14	23%
Chronic obstructive pulmonary disease	10	16.6%
Coronary artery disease	1	1.7%
Nephrotic syndrome	2	3.3%
Rheumatoid arthritis	1	1.7%
No comorbidities	32	53.3%

Table 3: RBS Level Distribution Among the Study Population Based on BMI

BMI	RBS ELEVATED	PERCENTAGE
Underweight n=07	07	100%
Normal weight n=28	09	32.1%
Overweight n=16	05	31%
Obese n=09	08	89%

Distribution of Route of Administration Among the Study Population (n=60)

In majority of patient elevated RBS levels were observed in 11 out of 15 patients (73.3%) the medication received nebulizer route, 9 out of 15 patients (60%) the medication through the IV route, 6 out of 15 patients (40%) the medication received by oral route and 3 out of 15 patients (20%) the medication received topical route showed elevated RBS levels.

Distribution based on duration of action of drugs among the study population (n=60)

The study found that among 4 patients who received short-acting drugs, 3(75%) had elevated RBS levels. Out of 17 patients who received intermediate-acting drugs, 8(47.1%) showed elevated RBS levels. Among 39 patients who received long-acting drugs, 18(46.2%) had elevated RBS levels

5. DISCUSSION

The study found that 48.3% of patients undergoing glucocorticoid therapy experienced elevated Random Blood Sugar (RBS) levels, highlighting a significant risk of hyperglycemia in non-diabetic individuals receiving these medications. This finding aligns with previous research investigating the incidence of hyperglycemic episodes following glucocorticoid administration [29].

A notable trend observed in the study was that most patients affected by glucocorticoid-induced hyperglycemia (GCIH) were in the 55–75 age group, suggesting that older adults are more susceptible to hyperglycemia due to glucocorticoid therapy. This increased vulnerability could be attributed to age-related metabolic changes and decreased insulin sensitivity, which heightens the risk of glucose dysregulation. Previous studies on elderly patients receiving glucocorticoids have reported similar patterns, emphasizing the need for close monitoring of blood sugar levels in this age group to prevent complications [30].

Another significant finding was the high prevalence of comorbidities among affected patients, particularly hypertension (23%), chronic obstructive pulmonary disease (COPD) (16.6%), and less common conditions such as nephrotic syndrome and rheumatoid arthritis. Despite these associations, an interesting observation was that more than half (53.3%) of the study population had no pre-existing comorbidities but still developed hyperglycemia during glucocorticoid treatment. This suggests that glucocorticoid therapy alone can be a strong independent factor in raising blood glucose levels, irrespective of pre-existing metabolic disorders [31].

The study also identified a clear association between body mass index (BMI) and elevated RBS levels. Both underweight (100%) and obese (89%) patients exhibited a higher incidence of GCIH compared to those with normal or overweight BMIs. This suggests that both extremes of body weight may contribute to glucose intolerance in the presence of glucocorticoid therapy. The metabolic vulnerability of underweight

individuals could be due to lower muscle mass and reduced insulin reserves, while obesity is already a well-established risk factor for insulin resistance. Research has previously highlighted this relationship, indicating that BMI plays a critical role in the incidence and severity of hyperglycemia in patients on glucocorticoids [32].

Understanding the pharmacodynamics of glucocorticoid drugs is crucial when prescribing them, as different formulations and durations of action may impact the risk of hyperglycemia. Short-acting glucocorticoids were found to pose a higher immediate risk for elevated blood sugar levels, necessitating more frequent glucose monitoring. This is particularly important for individuals with additional risk factors, such as obesity or pre-existing metabolic disorders, as the rapid effects of these medications can lead to acute glucose imbalances [33,40].

The route of administration also played a significant role in determining hyperglycemic risk. The study found that patients receiving glucocorticoids via nebulization (73%) and intravenous (IV) routes (60%) were more likely to develop elevated RBS levels compared to those using oral or topical glucocorticoids. These findings suggest that drug delivery methods significantly influence metabolic side effects. Nebulized glucocorticoids may lead to more rapid systemic absorption, triggering quicker onset of hyperglycemia. Similarly, IV administration delivers the drug directly into the bloodstream, resulting in faster and more potent metabolic effects compared to oral or topical routes. These observations highlight the need for clinicians to carefully consider the route of administration, as certain methods may necessitate closer glucose monitoring to mitigate potential adverse effects [34,39].

The study further explored the relationship between the duration of glucocorticoid action and hyperglycemia. Patients receiving short-acting glucocorticoids (75%) were more likely to experience elevated RBS levels than those on intermediate-acting (47.1%) and long-acting (46.2%) glucocorticoids. While it may be expected that longer-acting glucocorticoids would have a prolonged hyperglycemic effect, the study suggests that the immediate and potent impact of short-acting glucocorticoids may overwhelm the body's glucose regulation mechanisms, leading to acute hyperglycemia. This aligns with findings from previous research, indicating that short-acting glucocorticoids can cause a more immediate spike in blood glucose levels compared to their long-acting counterparts [36-39].

These findings underscore the importance of personalized risk assessment, careful dose selection, and frequent glucose monitoring during glucocorticoid therapy. Healthcare providers should prioritize patient education and adopt tailored strategies to minimize the risk of GCIH, thereby optimizing treatment outcomes.

6. CONCLUSION

This study investigated glucocorticoid-induced hyperglycemia (GCIH) in non-diabetic patients receiving glucocorticoids through various routes, revealing a high

prevalence of hyperglycemic episodes, especially with chronic nebulizer and topical administration. Continuous monitoring of blood glucose levels is crucial for early detection and prevention of prediabetic conditions and diabetes mellitus. Effective management strategies include dose tapering, dosage adjustments, and antihyperglycemic agents.

The study emphasizes the need for routine blood glucose monitoring, personalized risk assessment, and early intervention in non-diabetic patients receiving glucocorticoid therapy. Healthcare professionals and clinical pharmacists play a critical role in educating patients and ensuring appropriate management of GCIH to prevent adverse outcomes.

Given the widespread use of glucocorticoids, proactive measures such as patient education, interprofessional collaboration, and strict glucose monitoring are essential to mitigate the risk of hyperglycemia and optimize patient outcomes. Future recommendations focus on regular assessment of blood glucose levels, early identification of high-risk patients, and prompt intervention to prevent complications.

By implementing these strategies, healthcare providers can significantly reduce the risk of GCIH, improve clinical outcomes, and enhance the overall quality of care in glucocorticoid therapy.

7. CONFLICT OF INTEREST

There was no funding or conflict of interest related to this work.

8. AUTHOR CONTRIBUTION

All the authors have played a significant role in this work.

9. Acknowledgement

The authors express thanks for the facilities provided by the Managing Trustee of Karpagam Charity Trust and Dr. S. Mohan, Principal, Karpagam College of Pharmacy, Coimbatore, India to carry out the experiment.
We express our heartfelt gratitude to our parents and mentors for their constant motivation and unwavering support throughout the completion of this work.

10. REFERENCES

1. Aldibbiat AM, Al-Sharefi A. Do benefits outweigh risks for corticosteroid therapy in acute exacerbation of chronic obstructive pulmonary disease in people with diabetes mellitus. International Journal of Chronic Obstructive Pulmonary Disease, 2020.
2. Chertok Shacham E, Kfir H, Schwartz N, Ishay A. Glycemic control with a basal-

bolus insulin protocol in hospitalized diabetic patients treated with glucocorticoids: a retrospective cohort study. BMC Endocrine Disorders, 2018.

3. Gulliford MC, Charlton J, Latinovic R. Risk of diabetes associated with prescribed glucocorticoids in a large population. Diabetes care, 2006.
4. Hermayer KL, Egidi MF, Finch NJ, Baliga P, Lin A, Kettinger L, Biggins S, Carter RE. A randomized controlled trial to evaluate the effect of glycemic control on renal transplantation outcomes. The Journal of Clinical Endocrinology & Metabolism, 2012.
5. Roberts A, James J, Dhatariya K, Joint British Diabetes Societies (JBDS) for Inpatient Care, Agarwal N, Brake J, Brooks C, Castro E, Gregory R, Higham C, Hobley L. Management of hyperglycaemia and steroid (glucocorticoid) therapy: a guideline from the Joint British Diabetes Societies for Inpatient Care group. Diabetic Medicine, 2018.
6. Tatalovic M, Lehmann R, Cheetham M, Nowak A, Battegay E, Rampini SK. Management of hyperglycaemia in persons with non-insulin-dependent type 2 diabetes mellitus who are started on systemic glucocorticoid therapy: a systematic review. BMJ open, 2019.
7. Waljee AK, Rogers MA, Lin P, Singal AG, Stein JD, Marks RM, Ayanian JZ, Nallamothu BK. Short term use of oral corticosteroids and related harms among adults in the United States: population-based cohort study, 2017.
8. Fathallah N, Slim R, Larif S, Hmouda H, Ben Salem C. Drug-induced hyperglycaemia and diabetes. Drug safety, 2015.
9. Fong AC, Cheung NW. The high incidence of steroid-induced hyperglycaemia in hospital. Diabetes research and clinical practice, 2013. Herman IP. Physics of the human body. Springer, 2016.
10. Hwang JL, Weiss RE. Steroid-induced diabetes: a clinical and molecular approach to understanding and treatment. Diabetes/metabolism research and reviews, 2014.
11. Dobravc Verbič M, Gruban J, Kerec Kos M. Incidence and control of steroid-induced hyperglycaemia in hospitalised patients at a tertiary care centre for lung diseases. Pharmacological Reports, 2021.
12. Perez A, Jansen-Chaparro S, Saigi I, Bernal-Lopez MR, Minambres I, Gomez-Huelgas R. Glucocorticoid-induced hyperglycemia. Journal of diabetes, 2014.
13. Suh S, Park MK. Glucocorticoid-induced diabetes mellitus: an important but overlooked problem. Endocrinology and metabolism, 2017.
14. Van Raalte DH, Diamant M. Steroid diabetes: from mechanism to treatment. Neth J Med, 2014.
15. Wallace MD, Metzger NL. Optimizing the treatment of steroid-induced hyperglycemia. Annals of Pharmacotherapy, 2018.
16. Blackburn D, Hux J, Mamdani M. Quantification of the risk of corticosteroid-induced diabetes mellitus among the elderly,2002.
17. Blum CA, Nigro N, Briel M, Schuetz P, Ullmer E, Suter-Widmer I, Winzeler B, Bingisser R, Elsaesser H, Drozdov D, Arici B. Adjunct prednisone therapy for

patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial. The Lancet, 2015.

18. Chakkera HA, Weil EJ, Castro J, Heilman RL, Reddy KS, Mazur MJ, Hamawi K, Mulligan DC, Moss AA, Mekeel KL, Cosio FG. Hyperglycemia during the immediate period after kidney transplantation. Clinical Journal of the American Society of Nephrology, 2009.
19. Chan HW, Cheung CY, Liu YL, Chan YH, Wong HS, Chak WL, Choi KS, Chau KF, Li CS. Prevalence of abnormal glucose metabolism in Chinese renal transplant recipients: a single centre study. Nephrology Dialysis Transplantation, 2008.
20. Delfs N, Struja T, Gafner S, Muri T, Baechli C, Schuetz P, Mueller B, Blum CA. Outcomes of hospitalized patients with glucocorticoid-induced hyperglycemia a retrospective analysis. Journal of clinical medicine, 2020.
21. Donihi AC, Raval D, Saul M, Korytkowski MT, DeVita MA. Prevalence and predictors of corticosteroid-related hyperglycemia in hospitalized patients. Endocrine Practice, 2006.
22. Kleinhans M, Albrecht LJ, Benson S, Fuhrer D, Dissemond J, Tan S. Continuous glucose monitoring of steroid-induced hyperglycemia in patients with dermatologic diseases. Journal of Diabetes Science and Technology, 2024.
23. Kulkarni S, Durham H, Glover L, Ather O, Phillips V, Nemes S, Cousens L, Blomgran P, Ambery P. Metabolic adverse events associated with systemic corticosteroid therapy a systematic review and meta-analysis. BMJ open, 2022.
24. Li JX, Cummins CL. Fresh insights into glucocorticoid-induced diabetes mellitus and new therapeutic directions. Nature Reviews Endocrinology, 2022.
25. Liu XX, Zhu XM, Miao Q, Ye HY, Zhang ZY, Li YM. Hyperglycemia induced by glucocorticoids in nondiabetic patients: a meta-analysis. Annals of nutrition and metabolism, 2014 .
26. Gonzalez-Gonzalez JG, Mireles-Zavala LG, Rodriguez-Gutierrez R, Gomez-Almaguer D, Lavalle-Gonzalez FJ, Tamez-Perez HE, Gonzalez-Saldivar G, Villarreal-Perez JZ. Hyperglycemia related to high-dose glucocorticoid use in noncritically ill patients. Diabetology & metabolic syndrome, 2013.
27. Linssen MM, Van Raalte DH, Toonen EJ, Alkema W, Van der Zon GC, Dokter WH, Diamant M, Guigas B, Ouwens DM. Prednisolone-induced beta cell dysfunction is associated with impaired endoplasmic reticulum homeostasis in INS-1E cells. Cellular signalling, 2011.
28. Tamez-Perez HE, Quintanilla-Flores DL, Rodriguez-Gutierrez R, Gonzalez-Gonzalez JG, Tamez-Pena AL. Steroid hyperglycemia: prevalence, early detection and therapeutic recommendations: a narrative review. World journal of diabetes, 2015.
29. Bock G, Chittilapilly E, Basu R, Toffolo G, Cobelli C, Chandramouli V, Landau BR, Rizza RA. Contribution of hepatic and extrahepatic insulin resistance to the pathogenesis of impaired fasting glucose: role of increased rates of gluconeogenesis. Diabetes, 2007.
30. Ha YJ, Lee KH, Jung SJ, Lee SW, Lee SK, Park YB. Glucocorticoid-induced

diabetes mellitus in patients with systemic lupus erythematosus treated with high-dose glucocorticoid therapy. Lupus, 2011.

31. Kong X, Yu J, Bi J, Qi H, Di W, Wu L, Wang L, Zha J, Lv S, Zhang F, Li Y. Glucocorticoids transcriptionally regulate miR-27b expression promoting body fat accumulation via suppressing the browning of white adipose tissue. Diabetes, 2015.
32. Lee MJ, Pramyothin P, Karastergiou K, Fried SK. Deconstructing the roles of glucocorticoids in adipose tissue biology and the development of central obesity. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 2014.
33. Morton NM, Seckl JR. 11β-hydroxysteroid dehydrogenase type 1 and obesity. Obesity and Metabolism, 2008.
34. Pagano G, Cavallo-Perin P, Cassader M, Bruno A, Ozzello A, Masciola P, Dall'Omo AM, Imbimbo B. An in vivo and in vitro study of the mechanism of prednisone-induced insulin resistance in healthy subjects. The Journal of clinical investigation, 1983.
35. Pecoraro N, Reyes F, Gomez F, Bhargava A, Dallman MF. Chronic stress promotes palatable feeding, which reduces signs of stress: feedforward and feedback effects of chronic stress. Endocrinology, 2004.
36. Rafacho A, Cestari TM, Taboga SR, Boschero AC, Bosqueiro JR. High doses of dexamethasone induce increased β-cell proliferation in pancreatic rat islets. American Journal of Physiology-Endocrinology and Metabolism, 2009.
37. Ruzzin J, Wagman AS, Jensen J. Glucocorticoid-induced insulin resistance in skeletal muscles: defects in insulin signalling and the effects of a selective glycogen synthase kinase-3 inhibitor. Diabetology, 2005.
38. Schneiter P, Tappy L. Kinetics of dexamethasone-induced alterations of glucose metabolism in healthy humans. American Journal of Physiology-Endocrinology and Metabolism, 1998.
39. Udden J, Bjorntorp P, Arner P, Barkeling B, Meurling L, Rossner S. Effects of glucocorticoids on leptin levels and eating behaviour in women. Journal of internal medicine, 2003.
40. Vegiopoulos A, Herzig S. Glucocorticoids, metabolism and metabolic diseases. Molecular and cellular endocrinology, 2007.
41. Xu C, He J, Jiang H, Zu L, Zhai W, Pu S, et al. Direct effect of glucocorticoids on lipolysis in adipocytes. Mol Endocrinol, 2009.