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STUDY OF METFORMIN'S EFFECTIVENESS IN PREVENTING GLUCOCORTICOIDS-INDUCED HYPERGLYCEMIA IN HEMATOLOGICAL DISEASES

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ABSTRACT

Introduction: Glucocorticoids are the most common cause of drug-induced hyperglycemia, but there is no international consensus on screening for the incidence of hyperglycemia following the treatment. In vitro studies have shown that glucocorticoids modulate the activity of AMP-activated protein kinase (AMPK), one of the enzymatic mediators of metformin, in different tissues in a tissue-specific manner, while metformin reverses these effects in adipose tissue. **Objective:** To study the effectiveness of metformin in preventing hyperglycemia following the use of glucocorticoids in the treatment of hematological diseases. **Methods:** A randomized controlled trial (RCT). The study included 37 patients; who visited Tishreen University Hospital during the period between 2023-2024 and candidates for starting treatment with glucocorticoids for hematological indications. They were randomly divided into two groups. The control group: (18 patients): received glucocorticoids without metformin. The second group: (19 patients): metformin was added with glucocorticoids (metformin group) (we did not find any statistically significant differences between the two groups). **Results:** The incidence of Glucocorticoids-induced hyperglycemia in the control group was: 55.6% using fasting plasma glucose (FPG) and 77.8% using the 2-h post-prandial glucose (PPG). In the other hand, it was in the metformin group: 10.5% using the (FPG) and 15.8% using the (PPG) We found a very significant statistical difference between the two groups (P = 0.001, P = 0.0001). **Conclusions:** The addition of metformin at the start of glucocorticoid therapy reduced the incidence of hyperglycemia from 55.6% (FPG) and 77.8% (PPG) to 10.5% (FPG) and 15.8% (PPG).

KEYWORD:- Hyperglycemia, Metformin, Glucocorticoids, Activated protein kinase monophosphate, AMPK.

INTRODUCTION

Glucocorticoids (GCs) are steroid hormones that play a vital role in the daily physiological functioning of mammals. These hormones are primarily synthesized in the adrenal gland cortex.[1] GCs are widely used for the treatment of inflammation, autoimmune diseases and cancer.[1] The predominant role of glucocorticoids in cancer is in the treatment of lymphoid malignancies, building on an observation that there is an inverse relationship between the size of the adrenal cortex and thymus. Beneficial effects were observed specifically in lymphoid, but not myeloid disease, ranging from symptomatic relief (Multiple myeloma) to complete, but temporary remission in childhood ALL.[2]

In hematological indications for corticosteroid therapy (Table 1), it is essential to administer the lowest effective doses and the shortest course necessary to manage the disease. Typically, starting with prednisolone at 0.5-1 mg/kg is recommended.[3]

Chronic exposure to excess glucocorticoid can lead to iatrogenic Cushing's syndrome, which is associated with increased morbidity, especially from cardiovascular diseases and infections.[4]

Different side effects (Table 2) are common, affecting up to 90% of patients receiving glucocorticoid treatment for over 60 days. These side effects can manifest across a broad range of doses and are influenced by the method of administration.[5] Glucocorticoids-induced hyperglycemia **(**GIH**)** is defined as an abnormal increase in blood glucose associated with the use of glucocorticoids in a patient with or without a history of diabetes mellitus.[6] Corticosteroids exacerbate hyperglycemia in patients with diabetes or may precipitate the appearance of steroid diabetes.[7] The incidence of GIH varies depending on the study design and the threshold set for hyperglycemia.[8]

The effects of corticosteroids on glucose homeostasis are complex and not completely understood. Although glucocorticoids can counteract several effects of insulin such as reduction of appetite at a central level, the main mechanisms that lead to the onset of hyperglycemia include an increase of insulin resistance with increased glucose production, and an inhibition of the production and secretion of insulin by pancreatic β cells.[7] Insulin resistance induced by corticosteroids is essentially postprandial and develops in about 4 hours. However, the variability of blood glucose throughout the day will depend on the type, dose and delivery of the corticosteroid formulation (Table3).[9]

Metformin (N, N-dimethylbiguanide) belongs to the biguanide class of antidiabetic drugs originally derived from galegine (isoamylene guanidine), a guanidine derivative found in the French lilac Galega officinalis.[10] Although metformin has been used in Europe for treatment of hyperglycemia since 1957 (and in the USA since FDA approval in 1994), the exact molecular mechanisms of its therapeutic action remain obscure.[6] Currently, metformin is the frst-line medication to treat type 2 diabetes mellitus (T2DM) in most guidelines and is used daily by >200 million patients.[11]

The benefits of metformin therapy in T2DM have been well documented; it has longterm safety and efficacy data, low risk of hypoglycaemia, cardiovascular benefits, mortality benefits, additive or synergistic effects in combination therapy, low cost and wide availability.[11]

Metformin exerts its glucose-lowering effect primarily by decreasing hepatic glucose production through suppression of gluconeogenesis and enhancing insulin suppression of endogenous glucose production and, to a lesser extent, by reducing intestinal glucose absorption and possibly improving glucose uptake and utilization by peripheral tissues, such as skeletal muscle and adipose tissue.[10]

Early studies highlighted the liver as the major site of metformin action for the control of hepatic glucose production, through both AMP-activated protein kinase (AMPK)-dependent and AMPK-independent mechanisms. However, there is increasing evidence that other sites of action might also be important, including the gastrointestinal tract, the gut microbiota and the tissue-resident immune cells.[11]

Metformin clearance depends on renal function and declines in the presence of renal impairment. Metformin is not recommended if the serum creatinine level is ≥1.4 mg/dl in females and ≥1.5 mg/dl in males due to the rare but fatal lactic acidosis risk. The non-serious side impacts of metformin include nausea, metallic taste, anorexia, flatulence, and diarrhea.[11]

In eukaryotic cells AMP-activated protein kinase (AMPK) plays a major role in regulating cellular energy balance. AMPK responds to changes in intracellular adenine nucleotide levels, being activated by an increase in AMP/ADP relative to ATP. Activation of AMPK increases the rate of catabolic (ATP-generating) pathways and decreases the rate of anabolic (ATP-utilising) pathways.[12] That several metabolic changes associated with glucocorticoid overexposure correspond to metabolic steps regulated by 5'AMP-activated- protein-kinase (AMPK). AMPK is one of the mediators of metformin's action: metformin was able to reverse the glucocorticoid effect on AMPK in vitro and to prevent glycaemic deterioration in non-diabetic patients when initiated simultaneously with glucocorticoid treatment.[13] Metformin was also associated with a favourable immune response in several animal models of autoimmune diseases. It was hypothesised that metformin might alleviate a plethora of metabolic features of glucocorticoid overexposure without adversely affecting their anti-inflammatory benefits.[13]

Table 1: Hematological Indications for corticosteroid therapy.[3]

- Autoimmune haemolytic anaemia
- Idiopathic thrombocytopenic purpura
- Prevention of Graft versus Host Disease
- Thrombotic thrombocytopenic purpura
- Cryoglobulinaemia
- Treatment of lymphoid malignancies
- Infectious mononucleosis

Table 2: Some of glucocorticoids side-effects.[5]

Musculoskeletal	Osteoporosis, avascular necrosis of bone , Myopathy
Endocrine and Metabolic	- Hyperglycemia, Diabetes Mellitus, Dyslipidemia, Weight gain, Cushingoid features, Growth suppression, Adrenal suppression
Cardiovascular	Hypertension, Coronary heart disease, Ischemic heart disease.
Gastrointestinal	Gastritis, Peptic ulcer, Gastrointestinal bleeding.
Dermatologic	Dermatoprosis, Skin atrophy, Ecchymosis, Purpura, Erosions, Striae.
Neuropsychiatric	Mood changes, Depression, Euphoria, mood lability, Irritability Akathisia, Anxiety.
Ophthalmologic	Cataract, Glaucoma, Ptosis.

Table 3: Relative biologic potencies of synthetic steroids in bioassay systems.[12][9]

Steroid	Anti-inflammatory action	Hypothalamic- pitutary-adrenal suppression	Salt retention	Half-live (h)
Cortisol	1	1	1	8-12
Prednisone	3	4	0.75	12-16
Prednisolone	3	4	0.75	12-16
Methylprednisolone	6.2	4	0.5	12-16
Dexamethasone	26	17	0	36-72

METHODS

The study included 42 patients; who visited Tishreen University Hospital during the period between 2023-2024 and candidates for starting treatment with glucocorticoids for hematological indications**. Inclusion criteria:** patients aged 18 or older, receiving a daily prednisone dose of ≥30 mg for at least 4 weeks **Exclusion criteria:** patients on prednisone treatment for any other different indication, preexisting diagnosed diabetes mellitus, recent exposure (less than one year) to GCs, recent exposure (less than three months) to metformin, use of any other antidiabetic therapy, pregnancy, breast-feeding, renal insufficiency, liver failure, tissue hypoxia or concurrent severe illness, consumption of three or more alcoholic drinks per day, and use of any other antidiabetic therapy.

Thirty-seven patients completed the study. They were randomly divided into two groups. The control group: (18 patients): received glucocorticoids without metformin. The second group: (19 patients): metformin was added with glucocorticoids; 850 mg daily for two weeks then850 mg twice daily. (Metformin group) Written informed consent was obtained from all participating subjects before randomization.

We asked about medical and familial history, checked vital signs (blood pressure – heart rate – Spo2% - Δ) then measured weight and height and calculated BMI.

Blood samples were collected in all patients after an over- night fast. Fasting plasma Glucose (FPG), alanine transaminase (ALT), aspartate transaminase (AST), creatinine (crea), urea and post-prandial glucose (PPG) were measured. Then we measured FPG&PPG weekly during the study period. We stopped the study after 4weeks or after hyperhlycemia was development (FPG≥100 mg\dl, PPG≥140 mg\dl). (Mindray BS 380, China).

Statistical analysis

We used **Descriptive Statistics:** Frequencies and percentages for qualitative variables, measures of central tendency and measures of dispersion for quantitative variables. **Inferential Statistics:** (Independent T-Test to study the differences in means between two independent groups, Paired T-Test to study the differences in means between two related groups and Chi-square test to study the relationship between qualitative variables.)

Results were considered statistically significant with a p-value < 5%. The IBM SPSS Statistics (version 25) software was used to calculate the statistical parameters and analyze the results.

RESULTS

We studied 37 patients; were candidates for treatment with glucocorticoids and met the above-mentioned inclusion criteria. They were randomly divided into two groups. The control group: (18 patients): received glucocorticoids without metformin. The second group: (19 patients): metformin was added with glucocorticoids (metformin group) we did not find any statistically significant differences in demographical characteristics between the two groups) (Table 4).

Table 4: Comparing the two samples (At baseline).

Comparing the two samples (At baseline)		Control group	Metformin group	P value
By sex	Male	8 (44.4%)	11 (57.9%)	0.4
	Female	10 (55.6%)	8 (42.1%)	
By age		42.11 ± 17.5	40.68± 19.4	0.8
By weight		72±11.3	75.26 ± 20.01	0.5
By BMI		25.44 ± 4.02	26.8 ± 6.3	0.4
cumulative dose of GCs		1985.22 ± 497.1	2088 ± 1288.1	0.7
By hematological diagonisis	H.Lymphoma	3 (15.8%)	5 (27.8%)	0.8
	ALL	2 (10.5%)	2 (11.1%)	
	MM	10 (52.6%)	8 (44.4%)	
	ITP	4 (21.1%)	3 (16.7%)	
T2DM family history	Pos	8 (44.4%)	10 (52.6%)	0.6
	Neg	10 (55.6%)	9 (47.4%)	
GCs type	Intermediate action	12 (66.7%)	13 (68.4%)	0.7
	Long action	1 (5.6%)	2 (10.5%)	
	Combined	5 (27.8%)	4 (21.1%)	

The incidence of Glucocorticoids-induced hyperglycemia in the control group was: 55.6% using fasting plasma glucose (FPG) and 77.8% using 2-h post-prandial glucose (PPG). In contrast, it was in the metformin group: 10.5% using FPG and 15.8% using PPG. we found a very significant statistical difference between the two groups (P = 0.001, P = 0.0001). (Table 5)

Table 5: Comparing the two samples (At Endpoint).

Comparing the two samples (Endpoint)		Control group	Metformin group	P-value
FPG	< 100 mg\dl	8 (44.4%)	17 (89.5%)	0.001
	≥ 100 mg\dl	10 (55.6%)	2 (10.5%)	
PPG	< 140 mg\dl	4 (22.2%)	16 (84.2%)	0.0001
	≥ 140 mg\dl	14 (77.8%)	3 (15.8%)	

At the endpoint: We found an increase in the arithmetic mean for FPG and PPG in the control group, with a statistically significant difference (P = 0.0001) within group and compared to the metformin group, where the arithmetic mean remained similar to the baseline for the two values. **(table 6) (table 7)**

Table 6: Comparing the two samples (Arithmetic mean of FPG)

Comparing the two samples (Arithmetic mean of FPG)	Control group	Metformin group	P-value
Baseline	86.77 ± 11.2	89.26 ± 9.3	0.4
Endpoint	111.22 ± 29.5	92.42 ± 20.3	0.03
P-value	0.5	0.001	

Table 7: Comparing the two samples (Arithmetic mean of PPG).

Comparing the two samples (Arithmetic mean of PPG)	Control group	Metformin group	P-value
Baseline	100.38 ± 18.5	112.63 ± 14.2	0.06
Endpoint	184.83 ± 54.2	110.42 ± 48.8	0.0001
P-value	0.0001	0.8	

DISCUSSION

There are some studies on the possible effectiveness of metformin in preventing steroid-induced hyperglycemia. Our study revealed that metformin reduced steroid-induced hyperglycemia from 55.6% using fasting plasma glucose (FPG) and 77.8% using post-prandial glucose (PPG) to 10.5% (FPG) and 15.8% (PPG), also Ochla et al.[15] demonstrated that metformin effectively prevents steroid-induced hyperglycemia, as indicated by incidence rates in their study of 72.7% (FPG) and 54.5% (PPG) in the control group compared to 14.3% (FPG) and none elevated (PPG) in the treatment group. These differences can be attributed to differences in sample sizes, duration of steroid exposure, and dosing regimens (the steroid doses in their study were divided into several doses, up to four times a day, whereas in our study, it was limited to once or twice a day).

At the endpoint: We found an increase in the arithmetic mean for FPG and PPG in the control group, with a statistically significant difference (P = 0.0001) within group and compared to the metformin group, where the arithmetic mean remained similar to the baseline for the two values.

Seelig et al[16] found an improvement in mean fasting plasma glucose levels, while postprandial glucose levels remained similar to baseline in the metformin group. In contrast, the mean values for both fasting and postprandial glucose levels increased in the control group, These differences can be attributed to differences in the diagnosis methods of hyperglycemia and indications for steroids treatment.

Pernicova et al[12] found an improvement in mean fasting blood glucose levels, while postprandial glucose levels remained similar to baseline in the metformin group. Conversely, the mean values of postprandial glucose levels increased while fasting glucose levels remained similar to baseline in the control group,[12] These differences can be attributed to differences in hyperglycemia diagnosis methods and indications for steroids treatment, as well as the fact that they did not exclude patients with impaired glucose tolerance or those previously exposed to steroid treatment from the study.

When reviewing patients data who developed hyperglycemia in metformin group, we found that two of them had a history of prolonged hospitalization and the development of severe sepsis, and the third patient had thyrotoxicosis. It is well-documented that both sepsis[17] and thyrotoxicosis[18] exacerbate insulin resistance, thereby amplifying the impact of glucocorticoids on plasma glucose levels.

CONCLUSION

The addition of metformin at the start of glucocorticoids therapy reduced the incidence of hyperglycemia from

55.6% (FPG) and 77.8% (PPG) to 10.5% (FPG) and 15.8% (PPG).

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