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Short-term effect of intravenous methylprednisolone pulse therapy on glycemic control in patients with normoglycemia and pre-diabetes

Katarzyna Mitkowska
Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Warsaw, Poland
https://orcid.org/0000-0003-3772-6174

Katarzyna Pelewicz
Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Warsaw, Poland
https://orcid.org/0000-0002-2333-2337

Izabela Walasik
Student's Scientific Circle "Endocrinus", Department of Internal Medicine and Endocrinology, Medical University of Warsaw
https://orcid.org/0000-0003-2908-0908

Sebastian Szewczyk
Student's Scientific Circle "Endocrinus", Department of Internal Medicine and Endocrinology, Medical University of Warsaw
https://orcid.org/0000-0001-5511-5823

Piotr Miśkiewicz
Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Warsaw, Poland
https://orcid.org/0000-0003-4015-6491

Corresponding author: piotr.miskiewicz@wum.edu.pl

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ABSTRACT

Introduction. Systemic steroid therapy leads to disturbances in carbohydrate metabolism. The effect of immunosuppression with intravenous methylprednisolone (IVMP) pulses on glycaemia is not conclusive.
Aim. This study aimed to assess the short-term effect of IVMP therapy in moderate-to-severe Graves' orbitopathy (GO) on glycaemic control in normoglycaemic patients with and without pre-diabetes.
Material and Methods. Twenty-five GO patients treated with IVMP pulses (at initial dose of 6 x 0.5 g once a week, followed by 0.25 g given for 6 consecutive weeksweekly) were recruited and divided into a normoglycaemic group (n = 15, patients without pre-diabetes) and a pre-diabetic group (n = 10, patients with impaired fasting glycaemia (IFG) and/or impaired glucose tolerance (IGT)). Six daily capillary blood glucose measurements were performed at fixed times the day before and on the day of the first pulse administration.
Results. There was a significant increase in the glucose concentration on the day of IVMP administration in both groups of patients compared to the day before drug administration, with 50% of patients showing an increase in blood glucose above 200 mg/dl. There were no statistically significant differences between the two groups.
Conclusions. Methylprednisolone in a high intravenous dose has a tremendous impact on the blood glucose level in normoglycaemic and pre-diabetic patients on the day of drug administration.

Introduction

Therapy with high-dose intravenous glucocorticoids (GCs) is widely and effectively used to treat a variety of inflammatory and autoimmune diseases [1,2]. It is considered as the first-line treatment for moderate-to-severe and active Graves' orbitopathy (GO) by the European Group on Graves' Orbitopathy (EUGOGO) [3]. Intravenously administered GCs are more effective and better tolerated than oral GCs [2-5], however, there is still a risk of serious side effects, e.g. pulmonary embolism, myocardial infarction, severe cerebrovascular events, acute liver damage and sudden death, as well as changes in coagulation status and blood pressure [2,3,5-9]. One of the described side effects is hyperglycaemia, with the influence of GCs on glucose homeostasis being complex. Mechanisms of glucocorticoid-induced diabetes mellitus (DM) include increased insulin resistance, destruction of pancreatic cells, β-cell dysfunction, impaired insulin release, impaired suppres-

Table 1. Summary of studies that investigated glycaemia during intravenous methylprednisolone pulse therapy

Study	Size of the study group	Diagnosis	IVMP regimen	Glycaemic state before IVMP treatment	Glucose-lowering treatment before treatment	Monitoring of glycaemia	Results
Feldman-Billard et al. [12]	224	AON, SU, OIN, CGR, other	250, 500 or 1000 mg of IVMP a day for 3 consecutive days	Patients with and without known DM history Group of patients without DM consisted of normoglycaemic and pre-diabetic patients	All but 1 patient with DM were treated with either oral glucose-lowering agents or insulin	mFBG was measured in all subjects before and after each pulse. In subjects with DM, self-monitoring of capillary blood glucose was performed at least 3 times per day before each meal	Patients without DM showed a 50% increase in mFBG after 1st pulse Diabetic patients showed a 44% increase in mFBG after the 1st pulse
Perez et al. [14]	50	SLE, ITP, MS, AHA, other	1000 mg of IVMP a day for 3 consecutive days	Patients without known DM history	-	mFBG before and after each pulse	68% increase of mFBG after the 1st pulse
Tanaka et. al. [16]	5	GO	500 mg of IVMP - 3 cycles of 3 days a week	Patients without known DM history and normal glucose tolerance	-	Continuous blood glucose monitoring	Glucose levels increased from 4 hours after the administration of IVMP up to midnight, then gradually decreased until morning. The highest glucose level was after dinner, exceeding 200 mg/dl (240–293 mg/dL) in all patients.
Current study	25	GO	Cumulative dose of 4.5 g of IVMP, divided into 12 weekly infusions (6 x 0.5 g, then 6 x 0.25 g)	Patients without DM Divided into two groups: normoglycaemic and pre-diabetic	-	Analysis performed during 1st pulse of IVMP (500 mg) in patients treated with standard 12 pulses of methylprednisolone. Capillary blood glucose measurements 6 times a day – fasting (6:00), two hours after every main meal (11:00, 15:00, 19:00), at 22:00 and 2:00	Increase in capillary blood glucose levels on the day of pulse administration at 19:00, 22:00 and 2:00 in both groups, also at 15:00 in the pre-diabetic group. The highest increase in capillary blood glucose was at 19:00 (mean 204 mg/dL in the non-diabetic group and 203 in the pre-diabetic group). No significant differences between two groups.

AON acute optic neuritis, *SU* severe uveitis, *OIN* ocular infectious diseases, *CGR* corneal graft rejection, *SLE* systemic lupus erythematosus, *ITP* idiopathic thrombocytopenic purpura, *MS* multiple sclerosis, *AHA* autoimmune haemolytic anaemia, *GO* Graves' orbitopathy, *IVMP* intravenous methylprednisolone pulse, *DM* diabetes mellitus, *mFBG* morning fasting blood glucose

sion of hepatic glucose production and inhibited glycogenesis [10,11]. Only a few studies assessed the influence of intravenous methylprednisolone (IVMP) on glucose tolerance (Table 1) [12-16]. Moreover, most studies did not compare patients without diabetes (non-diabetic) to patients with diabetes [12,14]. Some authors suggest that the effect of the IVMP therapy on glucose tolerance in non-diabetic patients is transient and has no clinical relevance, thus these patients do not need any glucose-lowering treatment [12], while others believe that there is evidence that acute hyperglycaemia is a cardiovascular risk factor, independent of the presence of previous diabetes [14,17-19]. Acute hyperglycaemia is associated with an increase in LDL cholesterol oxidation, impaired endothelial function, activation of the coagulation cascade, increased production of pro-inflammatory cytokines and oxidative stress. Therefore, this study aimed to evaluate the short-term influence of IVMP therapy in moderate-to-severe GO on glucose tolerance in patients with normoglycaemia and those with pre-diabetes (impaired fasting glycaemia (IFG) and/or impaired glucose tolerance (IGT)) prior to treatment.

Material and Methods

Patients

The study was conducted at one academic referral centre in the Medical University of Warsaw (WUM). Patients with active, moderate-to-severe GO according to the EUGOGO classification were admitted to the Department of Endocrinology for IVMP therapy from 2012 to 2016. The study included 25 patients: 20 patients with Graves' disease, 4 patients with Hashimoto's thyroiditis and

Table 2. Basic characteristics of patients (n = 25)

	Number of patients (%) or mean ± SD range		
	Normoglycaemic	**Pre-diabetic**	***p*-value**
Number of patients	15 (60%)	10 (40%)	
Impaired fasting glucose	0 (0%)	10 (100%)	
Fasting plasma glucose (normal range – lower than 100 mg/dl)	90 ± 4.92 (81–98)	110 ± 16.17 (100–152)	0.00003
Impaired glucose tolerance	0 (0%)	5 (50%)	
Blood plasma glucose in 2h oral glucose tolerance test (normal range – lower than 140 mg/dl)	97 ± 20.3 (68–133)	134 ± 47.86 (61–192)	0.1
Thyroid disease			
Graves' disease treated for hyperthyroidism	10 (67%)	6 (60%)	1
Graves' disease after radical treatment on levothyroxine	2 (13%)	1 (10%)	1
Euthyroid Graves'	0 (0%)	1 (10%)	0.4
Hashimoto thyroiditis on levothyroxine	3 (20%)	1 (10%)	0.6
Orbitopathy of unknown aetiology	0 (0%)	1 (10%)	0.4
Sex			
Women	9 (60%)	8 (80%)	0.4
Men	6 (40%)	2 (20%)	0.4
Age (years)	50 ± 10 (35–77)	59 ± 10 (43–74)	0.07
Body mass index (kg/m^2)	25 ± 4 (20–34)	26 ± 5 (16–33)	0.7
Current smokers	7 (47%)	2 (20%)	0.2
Past smokers	5 (33%)	3 (30%)	1
Non-smokers	3 (20%)	5 (50%)	0.2
TSH (normal range: 0.27–4.2 µIU/mL)	2.83 ± 1.63 (0.52–6.25)	1.78 ± 1.68 (0.008–5.81)	0.2
fT4 (normal range 12.0–22.0 pmol/L)	16.28 ± 3.6 (12.1–20.9)	18.64 ± 3.73 (12.91–21.96)	0.1
fT3 (normal range: 3.1–6.8 pmol/L)	4.76 ± 0.93 (3.2–6.6)	5.16 ± 0.86 (3.36–6.48)	0.3
Median CAS	4.0	4.5	0.8
Comorbidity			
Hypertension	5 (33%)	4 (40%)	1
Hypercholesterolemia	1 (6%)	1 (10%)	1
Diabetes mellitus	0 (0%)	0 (0%)	
Oral GCs	0 (0%)	0 (0%)	
Hypoglycaemic drugs	0 (0%)	0 (0%)	

1 patient with orbitopathy of unknown aetiology. In total, 16 patients were treated with antithyroid drugs (alone or according to a "block and replace" schedule) and 7 patients received levothyroxine: 3 patients with Graves' disease who were at least 6 months after the last radical treatment (radioiodine therapy or thyroidectomy) and 4 patients with Hashimoto's thyroiditis, 1 patient had euthyroid Graves' disease. The inclusion criteria consisted of (1) active, moderate-to-severe GO; (2) age≥18 years and (3) euthyroidism for at least 1 month. Exclusion criteria were: (1) treatment with oral GCs within the last six months; (2) any other treatment known to significantly alter carbohydrate metabolism (e.g., glucose-lowering drugs) and (3) a clinical diagnosis of diabetes mellitus. Depending on the state of carbohydrate metabolism, patients were divided into two groups: a normoglycaemic group (n = 15, patients without pre-diabetes) and a pre-diabetic group (n = 10, patients with IFG and/or IGT). Diagnosis of pre-diabetes was based on fasting plasma glucose higher than or equal to 100 mg/dl but lower than 126 mg/dl and/ or blood plasma glucose higher or equal to 140 mg/dl but lower than 200 mg/dl in the second hour of oral glucose tolerance test [20]. Clinical characteristics of both groups are shown in Table 2. The study was approved by the Bioethics Committee of the Medical University of Warsaw.

Study design

All patients received IVMP therapy according to the EUGOGO recommendations: starting at a dose of 0.5 g once weekly for 6 weeks, followed by 0.25 g once weekly for 6 weeks (4.5 g cumulative dose). The analysis was performed during the 1st IVMP administration, with an IVMP pulse infusion of 4 hours from 11:00 to 15:00 for all patients. In both groups, six daily capillary blood glucose measurements (glycaemic profile) were performed at fixed times (6:00, 11:00, 15:00, 19:00, 22:00, 2:00) the day before and on the day of the 1st IVMP pulse administration. Patients received a diet consisting of three meals at 9:00, 13:00 and 17:00, with the measurement at 6:00 indicating fasting glucose and measurements at 11:00, 15:00 and 19:00 indicating the glucose level 2 hours after a meal. Capillary blood glucose measurements were analysed using a Glucomaxx glucose meter (Genexo, Warsaw, Poland).

Statistical analysis

All analyses were performed using STATISTICA software ver. 13.3 (StatSoft Polska, Cracow, Poland). Continuous variables are expressed as mean ± standard deviation (SD) or median values. Categorical data were presented as numbers (n) or percentages (%). Comparisons between blood glucose measurements were performed using paired t-tests. Differences between both groups (normoglycaemic and pre-diabetic) were compared using the Mann-Whitney U test. A p-value <0.05 was deemed statistically significant.

Results

Evaluation before intervention

Baseline mean values of six daily capillary blood glucose measurements on the day before the administration of 500 mg IVMP are shown in Table 3. In all patients in the normoglycaemic group, glycaemia remained lower than 200 mg/dl during the day. In one patient (10%) from the pre-diabetic group, glycaemia higher than 200 mg/dl was observed during the day.

Table 3 Changes in glucose concentrations during intravenous methylprednisolone pulse (0.5 g)

	Normoglycaemic group			Pre-diabetic group		
Time of measurement	**Day before**	**Day of the pulse**	***p*-value**	**Day before**	**Day of the pulse**	***p*-value**
6:00	88 ± 6	89 ± 12	0.77	93 ± 10	90 ± 12	0.5
11:00	110 ± 31	106 ± 21	0.6	95 ± 24	102 ± 26	0.6
15:00	114 ± 26	143 ± 34	0.057	100 ± 14	148 ± 28	0.007
19:00	116 ± 20	204 ± 44 (130–318)	0.00003	104 ± 25	203 ± 35 (161–330)	0.001
22:00	101 ± 20	162 ± 37	0.00003	96 ± 20	167 ± 21	0.00002
2:00	93 ± 17	139 ± 25	0.00004	86 ± 11	152 ± 33	0.001

Results are presented as mean ± SD. Statistically significant results are in bold

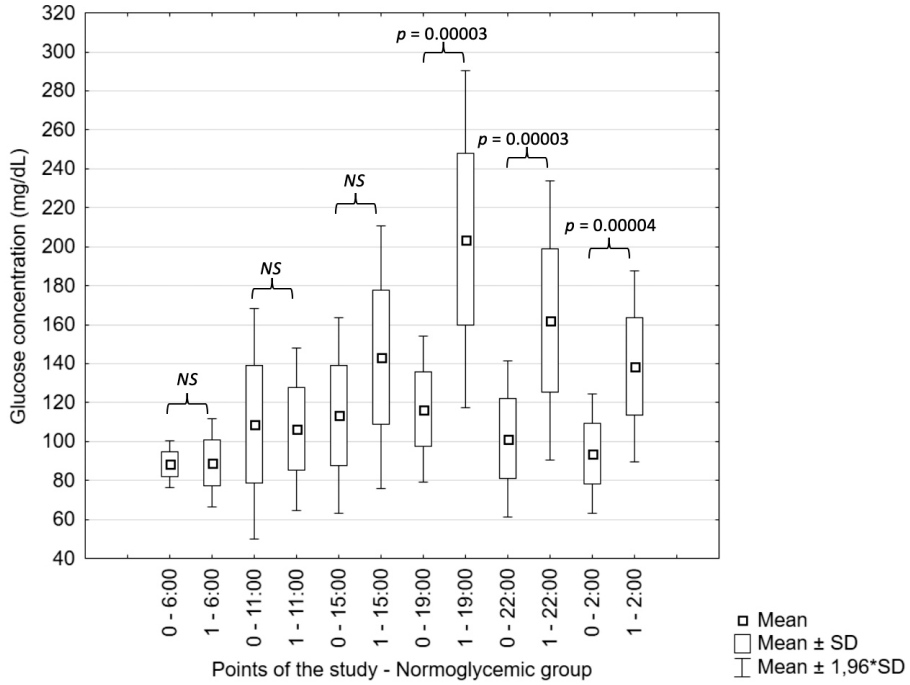

Figure 1. Glucose concentrations during intravenous methylprednisolone pulse (500 mg) in normoglycaemic patients. *NS* non-significant. *0–6:00* day before the pulse, measurement at 6:00, *1–6:00* day of the pulse, measurement at 6:00, *0-11:00* day before the pulse, measurement at 11:00, *1–11:00* day of the pulse, measurement at 11:00, *0-15:00* day before the pulse, measurement at 15:00, *1–15:00* day of the pulse, measurement at 15:00, *0–19:00* day before the pulse, measurement at 19:00, *1–19:00* day of the pulse, measurement at 19:00, *0–22:00* day before the pulse, measurement at 22:00, *1–22:00* day of the pulse, measurement at 22:00, *0–2:00* day before the pulse, measurement at 2:00, *1–2:00* day of the pulse, measurement at 2:00.

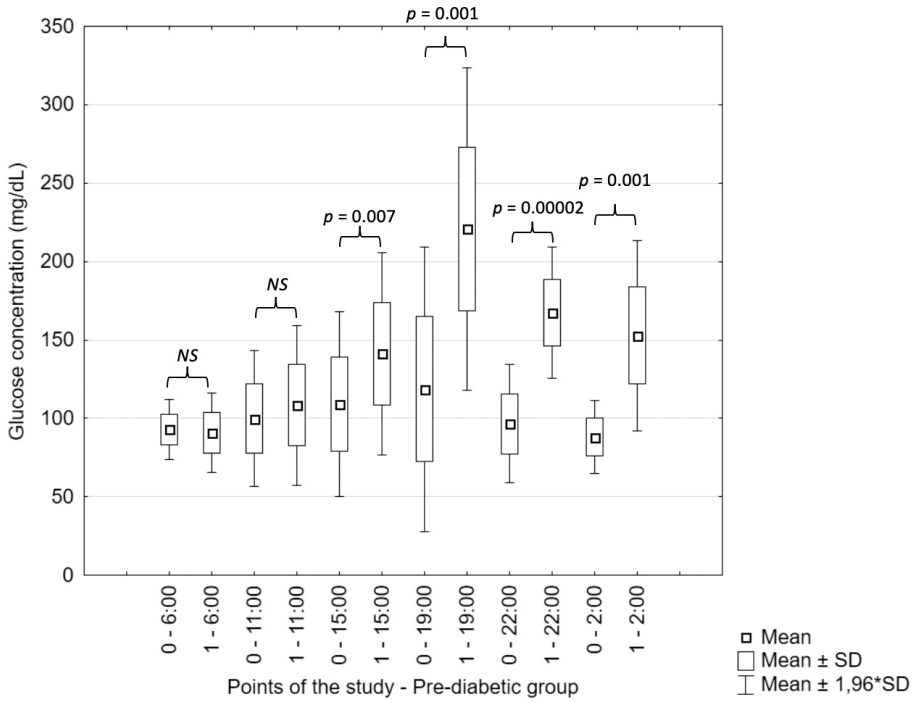

Figure 2. Glucose concentrations during intravenous methylprednisolone pulse (500 mg) in pre-diabetic patients. *NS* non-significant. *0–6:00* day before the pulse, measurement at 6:00, *1–6:00* day of the pulse, measurement at 6:00, *0–11:00* day before the pulse, measurement at 11:00, *1–11:00* day of the pulse, measurement at 11:00, *0–15:00* day before the pulse, measurement at 15:00, *1–15:00* day of the pulse, measurement at 15:00, *0–19:00* day before the pulse, measurement at 19:00, *1–19:00* day of the pulse, measurement at 19:00, *0–22:00* day before the pulse, measurement at 22:00, *1–22:00* day of the pulse, measurement at 22:00, *0–2:00* day before the pulse, measurement at 2:00, *1–2:00* day of the pulse, measurement at 2:00

Short-term influence on single IVMP pulse on glycaemia

Detailed outcomes of capillary blood glucose for the IVMP pulse are shown in Table 3. In the normoglycaemic group, we observed a statistically significant increase in capillary blood glucose levels on the day of pulse administration at 19:00, 22:00 and 2:00 (Figure 1 and Table 3). In the pre-diabetic group, we observed a significant increase in capillary blood glucose levels on the day of pulse administration at 15:00, 19:00, 22:00 and 2:00 (Figure 2 and Table 3). The highest increase in capillary blood glucose compared to the glucose concentration in both groups was observed on the day before the pulse at 19:00, which is 8 hours after the start of the IVMP infusion and 4 hours after its end.

A comparative analysis did not show statistically significant differences between the observed increases in glycaemia between two groups. Detailed outcomes are presented in Table 4 and Figure 3.

Discussion

Hypercortisolism, both endogenous and exogenous, is associated with an increased risk of hyperglycaemia and diabetes mellitus, hence, may occur during the for therapy with oral GCs [21]. However, the influence of therapy with IVMP on glycaemic control is not conclusive, with only a few studies conducted regarding this topic. The results of these studies are summarised in Table 1.

Feldman-Billard et al. [12] and Perez et al. [14] assessed morning fasting glucose one day after IVMP administration, observing a 50% and 68% increase, respectively. Unfortunately, in both studies, the groups of patients were not homogeneous, with patients receiving IVMP due to different indications and varying doses. The studies included patients without diagnosed diabetes mellitus, but they were not divided into two groups (patients with normoglycaemia vs patients with pre-diabetes). Furthermore, both lacked information wheth-

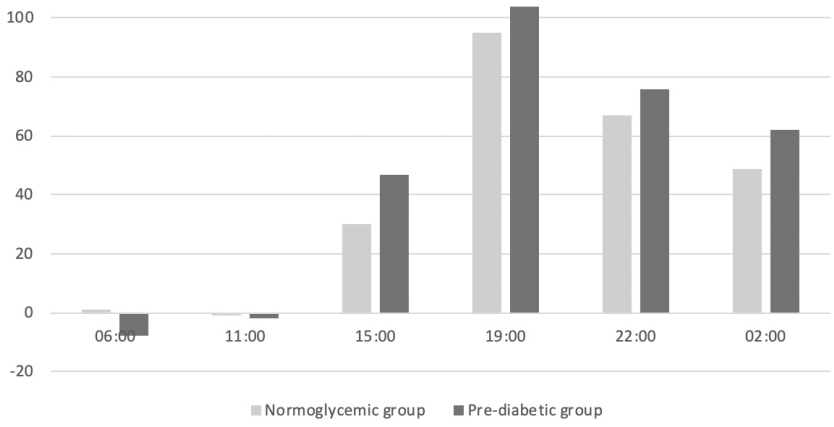

Figure 3. Average increase in glucose concentration at a given measurement point on the day of the intravenous methylprednisolone pulse administration compared to average glucose concentration at the same time of day before

Table 4 Average increase in glucose concentration at a given measurement point on the day of intravenous methylprednisolone pulse (0.5 g) administration compared to average glucose concentration at the same time of day before

	Average increase in glucose concentration		
Time of measurement	Normoglycaemic group	Pre-diabetic group	*p*-value
6:00	1	-7.5	0.2
11:00	-1	-2	0.9
15:00	30	47	0.5
19:00	95	104	0.7
22:00	67	76	0.6
2:00	49	62	0.4

Results are presented as mean. No results were statistically significant

er patients were taking other medications that may affect glycaemia or whether steroids were given at a fixed time. Moreover, in both studies, glycaemia was controlled only in the morning and no measurements were taken during the day.

While Feldman-Billard et al. [12] suggested that the effect of the IVMP therapy on glucose tolerance in patients without DM is transient and has no clinical relevance, thus these patients do not need any monitoring of blood glucose levels or glucose-lowering treatment, Perez et al. [14] stated that there is evidence that acute hyperglycaemia is a cardiovascular risk factor, independently of the presence of previous diabetes, so patients without DM should be monitored and further long-term studies are necessary to identify clinical significance. None of these studies evaluated glucose levels at the time of day when they are most affected, which may explain the controversy.

There is only one study [16] concerning patients without diabetes receiving IVMP pulse therapy in which glucose levels were monitored during the day of the treatment. Unfortunately, the study group was small, consisting of five patients. Regardless, it was noted that glycaemia increased 2–3 hours after IVMP pulse administration, lasting for 12 hours and reaching a peak after dinner, or about 10 hours after administration of the IVMP. Glucose levels exceeded 200 mg/dl after dinner in all patients (ranged from 240 to 293), then gradually decreased until morning.

The present study is unique in that the analysed group of patients was homogenous, with patients receiving IVMP at the same dose due to the same indication. IVMP infusion was administered at the same time and lasted for the same period of time for each patient. Also, patients who received medications that may affect blood glucose levels were excluded. Moreover, six daily capillary blood glucose measurements at fixed times (glycaemic profile) were performed to assess glycaemia at the time that it would be most affected. Furthermore, normoglycaemic and pre-diabetic patients were compared.

In this study, measurements of capillary blood glucose during the day of administration of IVMP pulse in comparison to the day before the drug infusion in both normoglycaemic and pre-diabetic patients showed a significant increase of glucose levels 4 hours after the start of IVMP pulse administration, reaching a peak at about 8 hours. At its peak, the mean levels of glucose were 200 mg/dl in both subsets (ranging from 130 to 318 and 161 to 330 in the normoglycaemic and pre-diabetic groups, respectively). Then, after this glucose peak, glucose levels in subsequent measurements gradually decreased, suggesting that the hyperglycaemic effect of IVMP pulse therapy develops at least 4 hours after the beginning of IVMP pulse administration, achieving a peak 4 hours later, then gradually decreasing. There was no difference between non-diabetic and pre-diabetic patients.

The most important question, however, is whether such a high increase in glucose is of clinical importance, especially considering the whole cycle of IVMP therapy with 12 weekly repeated infusions. Is the administration of glucose-lowering agents required?

The present study has some limitations. First, glucose measurements were derived from capillary blood using a glucose meter and not from serum glucose measurements. Moreover, the study was designed with a relatively small number of patients and included overweight and obese patients, patients did not receive standardised meals, and HOMA-IR was not determined prior to treatment to exclude patients with insulin resistance, all of which may affect glucose levels. Finally, we assessed only the short-term effect of one IVMP pulse administration on glucose levels, not the long-term impact of a whole cycle of IVMP therapy, which consists of 12 pulses. Also, we did not measure HbA1c and glucose tolerance with OGTT after therapy, hence, further research is required to assess the long-term impact.

In conclusion, methylprednisolone in a high intravenous dose has a tremendous impact on blood glucose levels in normoglycaemic and pre-diabetic patients on the day of drug administration.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflict of interest statement
The authors declare no conflict of interest.

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