Glycopenia-Induced Sympathoadrenal Activation in Diabetes Mellitus And Uncontrolled Arterial Hypertension: An Observational Study.

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Abstract

Background: Aim of this study is to investigate a possible association of hypoglycemic episodes and arterial hypertension. We hypothesize that hospitalized insulin-treated diabetes patients with hypertensive crisis have more hypoglycemic episodes than their counterparts without hypertensive crisis on admission.

Methods: In a prospective, observational cohort study, 65 insulin-treated diabetes patients (type 1, type 2, type 3c) were included in Group 1, when a hypertensive crisis was present, as control patients in Group 2 without hypertensive crisis or hypoglycemia, in Group 3, when a symptomatic hypoglycemia was present on admission. All patients were subjected to open-label continuous flash glucose monitoring, to 24-hour blood-pressure and Holter electrocardiogram recordings, and to laboratory tests including plasma catecholamines.

Results: 53 patients, thereof 19 Group-1, 19 Group-2, 15 Group-3 patients, completed this study. Group-1 patients had the highest maximum systolic blood pressure, a higher daily cumulative insulin dose at admission, a higher body-mass index, and a higher plasma norepinephrine than control patients of Group 2. Group-3 patients had more documented hypoglycemic episodes (0.8 ± 0.5 per 24 hours) than Group-2 patients (0.2 ± 0.3 per 24 hours), however, they were not different to the ones in Group-1 patients (0.4 ± 0.4 per 24 hours). Plasma norepinephrine and mean arterial blood pressure were not different between Group-1 and Group-3 patients, though higher than in Group-2 patients. At discharge, the daily cumulative insulin dose was reduced in Group-1 (-18.4 ± 24.9 units) and Group-3 patients (-18.6 ± 22.7 units), but remained unchanged in Group-2 patients (-2.9 ± 15.6 units).

Conclusions: An association between hypoglycemic events and uncontrolled hypertension was found in this study.

Background

Randomized clinical trials have proven that the use of intensive insulin therapy to target normal glycated hemoglobin A1c (HbA1c) did not offer cardiovascular benefits (1) and have been shown to even increase the cardiovascular mortality for type-2-diabetes patients (2). The reason for this lack of benefit or even excess mortality seen may relate to hypoglycemia and its sequelae. This includes a neurohormonal stimulation leading to a posthypoglycemic hyperglycemia, a term previously coined as “Somogyi effect” (3). Specifically, neuroglycopenia translates into a neurohumoral activation involving both a hypothalamic-pituitary-axis activation and sympatho-activation. The latter includes sympathetic-nervous-system (SNS) activation and the release of adrenal catecholamines (4). An association between hypoglycemia and arterial hypertension has been demonstrated in a small cohort study of type-1- and type-2-diabetes patients on a continuous glucose monitoring, while concurrently performing a 24-hour ambulatory blood pressure monitoring (ABPM) (5). Hypoglycemic events were less frequently found in type-2 diabetics in comparison to type-1 diabetes patients, the hypoglycemia-related mortality risk was higher in type-2 diabetes patients though (6). Given the correlation between hypoglycemia and arterial hypertension (5), we hypothesized that consecutively hospitalized insulin-treated diabetes patients with hypertensive crisis on admission have a propensity for hypoglycemic episodes in post-admission flash-glucose monitoring (FGM). As a secondary hypothesis, plasma norepinephrine concentrations are expected to be elevated both in insulin-treated diabetes patients

with hypertensive crisis and in diabetes patients with hypoglycemia on admission. To check these hypotheses, we recruited hospitalized insulin-treated diabetes patients presenting with hypertensive crisis at admission. As negative-control group, insulin-treated diabetics with neither hypoglycemia nor hypertensive crisis at admission were included. Diabetes patients, who presented with symptomatic hypoglycemia, served as positive-control group. Overall, the results of this study may highlight a possible association between uncontrolled arterial hypertension and propensity of hypoglycemic events.

Methods

65 Insulin-treated diabetes patients (type 1, type 2, type 3c), hospitalized in the University Hospital Halle (Saale) between 1.6.2017 and 31.12.2019 were screened and enrolled for participation in this observational cohort study based on the inclusion and exclusion criteria. The number of recruited study participants was limited by in- and exclusion criteria and by the scheduled time frame of study, a power calculation for study size was not possible. All patients provided written informed consent. Staff physicians treating the patients were unaware whether or not patients participated in this study. In addition, staff physicians did not participate in this study in any way. Thus all decisions made in study patients reflected the staff physician`s opinion and were not influenced by the organizers or by persons conducting this observational study. The ethics committee of the Medical Faculty of the Martin-Luther University Halle-Wittenberg approved this study protocol (Study number 2017-28). Data acquisition was performed according to the principles of the Declaration of Helsinki and Good Clinical Practice (E6, revision 2) from 2015.

Inclusion criteria

- Insulin-treated diabetes patients (type 1, type 2 or Type 3c Diabetes mellitus), diagnosed for at least one year before study enrollment,

- age: 18 - 99 years

- male or female

Cohort specific inclusion criteria:

- Group 1: hypertensive crisis at admission (systolic blood pressure > 180 mmHg)
- Group 2: absence of hypertensive crisis or symptomatic hypoglycemia at admission.
- Group 3: symptomatic hypoglycemia at admission

Exclusion criteria

- age below 18 years or more than 99 years

- an active tumour disease or curative care within 5 years,

- gravidity or women with child-bearing potential with no safe forms of contraception,

- severe pain (visual analogue scale from 1-10: >3),

- known secondary cause o arterial hypertension,

- septicaemia,

- allergies to adhesives, inability to use FGM

- current use of glucocorticoids,

- psychiatric disorders and all forms of dementia with lack of ability to provide an informed consent, - stage-5 chronic kidney disease (defined by estimated GFR < 15ml/min)

- acute kidney injury (AKI) with need for renal-replacement therapy

- acute or chronic heart failure (New York Heart Association class higher than 2).

Study Visits

Visit 1: Within 24 hours after admission for study recruitment and group allocation. Medical history was taken, clinical examination was carried out. Patients received instructional materials and behavioral counseling regarding diabetes care, a FGM sensor (FreeStyle libre, Abbott Diabetes Care, Abbott GmbH, Wiesbaden, Germany). A 24-hour ABPM and Holter electrocardiogram were placed.

Visit 2: Within 48 hours after admission, venous blood glucose, plasma catecholamines, serum cortisol, and routine laboratory parameters including serum creatinine and HbA1c were determined.

Visit 3: Prior to discharge or 14 days after Visit 2 (whatever applied first), the FGM sensor was removed, data were retrieved and analyzed. Concomitant medication including daily cumulative insulin dose and laboratory parameters including serum creatinine, estimated glomerular filtration rate (eGFR), if applicable, were recorded. In case of an evolving AKI as shown by an increase (>0.3 mg/dL) of serum creatinine by discharge, eGFR was not calculated. In case of an AKI prior to hospitalization as shown by a decrease (>0.3 mg/dL) of serum creatinine by discharge or in case of no change (>0.3 mg/dL) of serum creatinine by discharge, eGFR at discharge was provided.

Analysis

If applicable, both the hypertensive crisis and symptomatic hypoglycemia events at admission were used for cohort allocation and were not considered as an event for analysis. In addition, information on missing data was provided in the Tables. Continuous data were given as mean ± standard deviation. To test for normality, Kolmogorov-Smirnov test was used. For group-wise comparisons, an ordinary one-way Analysis of Variance test was used as a parametric test, Kruskal-Wallis test was used, if data showed no Gaussian distribution. As post-hoc tests, Tukey or Dunn`s test were used, where appropriate.

Primary Outcome parameters:

Number of post-admission hypoglycemic episodes (tissue glucose level < 3.9 mmol/L) per 24h of FGM

Secondary Outcome parameters:

- Change in concomitant classes and defined daily dose (DDD) of antihypertensive medications, by discharge,

- Change in daily cumulative insulin dose by discharge

- Comparison of plasma catecholamines, heart rate variability (the standard deviation of RR intervals derived from Holter electrocardiogram), HbA1c among groups

Results

53 diabetes patients on insulin therapy completed this prospective observational study (Fig. 1). The key baseline characteristics are represented in Table 1. Group-1 patients were more obese than Group-2 or Group-3 patients, and they had an impaired renal function when compared to the negative control Group 2. The concomitant antihypertensive medication did not differ between groups at admission (Table 1). However, the average daily cumulative insulin dose was higher in Group-1 patients than in the control patients Group 2 (Table 2).

Table 1. Baseline characteristics of hospitalized diabetes patients with a hypertensive crisis (Group 1), without a hypertensive crisis or a symptomatic hypoglycemia (Group 2), with symptomatic hypoglycemia (Group 3) at admission. aFinal number of diabetes patients subjected to statistical analysis, if data were lacking.

	Group 1			Group 2			Group 3			
	n	Mean ± SD	n[a]	n	Mean ± SD	n[a]	n	Mean ± SD	n[a]	p
Men/Women (n)	7/12	NA	NA	9/10	NA	NA	6/9	NA	NA	NA
Diabetes Type 1/2/3c	0/19/0	NA	19	1/17/1	NA	19	6/8/1	NA	15	NA
Age (years)	19	69.9 ± 9.8	19	19	64.1 ± 15.8	19	15	62.2 ± 21.9	15	0.3449
Body mass index (kg/m^2)	19	38.1 ± 14.0	19	19	28.5 ± 10.5	19	15	27.4 ± 6.0	15	0.0028
Antihypertensive classes per patient at admission (n)	19	3.9 ± 1.6	19	19	2.3 ± 1.6	19	15	2.5 ± 1.6	15	0.1435
Antihypertensive DDD at admission (n)	19	6.2 ± 5.4	19	19	3.0 ± 3.4	19	15	4.7 ± 6.0	15	0.0662
Daily cumulative insulin dose (units/d)	19	60.9 ± 41.5	19	19	30.5 ± 27.6	19	15	46.5 ± 23.3	15	0.0229
HbA1c (%)	19	8.6 ± 2.8	19	19	8.9 ± 2.8	19	15	7.7 ± 1.5	15	0.8592
Urea (plasma; mmol/L)	19	10.5 ± 5.1	19	19	6.6 ± 5.0	19	15	6.9 ± 4.2	15	0.0105
Creatinine (serum; µmol/L)	19	132.8 ± 55.3	19	19	89.5 ± 37.2	19	15	110.5 ± 55.2	15	0.0106
Cortisol (plasma; pg/mL)	19	395.4 ± 156.9	17	19	331.1 ± 126.7	18	15	387.6 ± 176.1	13	0.4079
Epinephrine (plasma; pg/mL)	19	34.9 ± 26.1	18	19	32.6 ± 20.4	18	15	32.6 ± 24.4	14	0.9326
Norepinephrine (plasma; pg/mL)	19	788.6 ± 411.9	17	19	437.5 ± 239.3	17	15	644.3 ± 378.7	14	0.0191

	Group 1			Group 2			Group 3			
	n	Mean ± SD	n[a]	n	Mean ± SD	n[a]	n	Mean ± SD	n[a]	p
Heart rate variability, standard deviation of heart-beat intervals (ms)	19	68.5 ± 53.0	13	19	55.5 ± 36.7	12	15	61.5 ± 34.3	8	0.8446

Table 2. Outcomes of hospitalized diabetes patients with a hypertensive crisis (Group 1), without a hypertensive crisis or a symptomatic hypoglycemia (Group 2), with symptomatic hypoglycemia at admission (Group 3). aFinal number of diabetes patients subjected to statistical analysis, if data were lacking.

	Group 1			Group 2			Group 3			
	n	Mean ± SD	n[a]	n	Mean ± SD	n[a]	n	Mean ± SD	n[a]	p
Renal function										
Creatinine at discharge (serum; µmol/L)	19	114.5 ± 36.6	17	19	89.8 ± 32.6	19	15	100.2 ± 46.5	13	0.0754
Change of serum creatinine (baseline versus discharge; µmol/l)	19	-17.9 ± 41.6	17	19	0.3 ± 44.1	19	15	-12.4 ± 65.4	13	0.6705
Estimated glomerular filtration rate (ml/min/1.73m²) at discharge	19	55.2 ± 18.6	16	19	76.7 ± 14.9	16	15	67.3 ± 22.4	12	0.0068
Blood pressure during hospitalization										
Systolic blood pressure (maximum, day-time; mmHg)	19	191.6 ± 20.7	19	19	157.7 ± 20.2	18	15	172.8 ± 22.2	15	< 0.0001
Systolic blood pressure (mean, day-time; mmHg)	19	142.5 ± 13.8	19	19	124.6 ± 16.1	19	15	138.7 ± 18.2	15	0.0030
Diastolic blood pressure (maximum, day-time; mmHg)	19	98.7 ± 13.4	19	19	88.6 ± 11.4	18	15	98.9 ± 20.0	15	0.0749
Diastolic blood pressure (mean, day-time; mmHg)	19	75.3 ± 9.4	19	19	71.3 ± 8.3	19	15	79.1 ± 15.4	15	0.1340
Mean arterial pressure (day-time; mmHg)	19	97.7 ± 8.9	19	19	85.9 ± 9.5	16	15	98.9 ± 15.3	15	0.0035
Systolic blood pressure (maximum, night-time; mmHg)	19	167.7 ± 30.4	19	19	135.6 ± 15.1	15	15	151.5 ± 23.2	15	0.0021
Systolic blood pressure (mean, night-time; mmHg)	19	141.7 ± 18.6	19	19	117.9 ± 12.1	16	15	125.1 ± 17.8	15	0.0003
Diastolic blood pressure (maximum, night-time; mmHg)	19	90.9 ± 15.7	19	19	81.3 ± 8.2	16	15	90.8 ± 15.7	15	0.1339
Diastolic blood pressure (mean, night-time; mmHg)	19	72.9 ± 11.3	19	19	68.7 ± 8.6	16	15	71.7 ± 12.9	15	0.5279

	Group 1			Group 2			Group 3			
	n	Mean ± SD	n[a]	n	Mean ± SD	n[a]	n	Mean ± SD	n[a]	p
Mean arterial pressure (night-time; mmHg)	19	95.9 ± 11.9	19	19	85.9 ± 9.5	16	15	89.5 ± 13.8	15	0.0507
Antihypertensive classes per patient at discharge (n)	19	4.1 ± 1.6	19	19	2.2 ± 1.6	19	15	2.2 ± 1.2	15	0.0011
Change of antihypertensive classes (baseline versus discharge; n)	19	1.1 ± 1.1	19	19	0.2 ± 1.1	19	15	-0.3 ± 1.0	15	0.0017
Antihypertensive DDD at discharge (n)	19	11.0 ± 8.7	19	19	3.0 ± 3.3	19	15	4.9 ± 6.5	15	0.0012
Change of antihypertensive DDD (baseline versus discharge; n)	19	4.8 ± 6.1	19	19	0.1 ± 1.9	19	15	0.2 ± 3.8	15	0.0028
Diabetes-related parameters										
Length of FGM (d)	19	5.1 ± 0.7	19	19	5.3 ± 1.5	19	15	6.2 ± 0.9	15	0.0004
Hypoglycemic episodes[a] (during FGM, n)	19	2.2 ± 1.9	19	19	0.7 ± 1.4	19	15	4.5 ± 2.3	15	< 0.0001
Hypoglycemic episodes per night[a] (during FGM, n)	19	0.8 ± 1.0	19	19	0.2 ± 0.5	19	15	1.5 ± 1.4	15	0.0051
Daily cumulative insulin dose at discharge (units/d)	19	42.5 ± 33.0	19	19	27.6 ± 24.3	19	15	27.9 ± 19.0	15	0.2960
Change of daily cumulative insulin dose (baseline versus discharge; units/d)	19	-18.4 ± 24.9	19	19	-2.9 ± 15.6	17	15	-18.6 ± 22.7	15	0.0479
Primary Outcome										
Hypoglycemic episodes (tissue glucose < 3.9 mmol/l) per 24 h (n)	19	0.4 ± 0.4	19	19	0.2 ± 0.3	17	15	0.8 ± 0.5	15	< 0.0001

1) Insulin-treated diabetes patients with hypertensive crisis (Group 1) and with symptomatic hypoglycemia (Group 3) were not different in terms of hypoglycemic burden during hospitalization.

The number of hypoglycemic episodes per 24 hours of FGM was highest in the positive-control Group 3, Group-1 and Group-3 patients did not differ with regard to hypoglycemic episodes per 24 hours though (Fig. 2). When comparing the average number of nocturnal hypoglycemic episodes per 24 hours of FGM, the same proportion of hypoglycemic episodes was found (Fig. 3). Again, patients of Group 1 and Group 3 did not differ. In other words, diabetes patients both with a hypertensive crisis (Group 1) and with symptomatic hypoglycemia at admission (Group 3) had a high number of hypoglycemic episodes during hospitalization.

By discharge, the daily cumulative insulin dose decreased to the same extent in Group-1 and Group-3 patients (Fig. 4). By discharge, insulin therapy was abandoned completely in 3 or 15.8% of Group-1 patients, in 2 or 10.5% of Group-2 patients and in 2 or 13.3% of Group-3 patients.

2) Plasma norepinephrine, a surrogate of sympathetic tone, was elevated in hypertensive diabetes patients.

Plasma norepinephrine was higher in Group-1 patients when compared to control patients of Group 2 (Fig. 5). Of note, there was no difference in plasma norepinephrine concentration between Group-1 and Group-3 patients. Heart-rate variability, a surrogate of vagal tone (8), was not different among all patient groups (Table 1).

3) Mean systolic arterial blood pressure at daytime was not different in diabetes patients with hypertensive crisis compared to the ones with hypoglycemia on admission

Maximum systolic blood pressure was highest in Group-1 patients both at daytime and at nighttime (Fig. 6, upper panel). Conversely, the average systolic arterial blood pressure was not different between Group 1 and Group 3 both at daytime and at nighttime (Fig. 6, lower panel). By discharge, the use of antihypertensives was intensified in Group 1, while there was no change of both antihypertensive classes and antihypertensive DDD in Group 2 and Group 3, when compared to admission (Table 2). Within 24 hours before discharge, the average mean arterial pressure was well controlled in all study patients: Group 1: 95.3 mmHg, Group 2: 89.3 mmHg, Group 3: 97.1 mmHg (p = 0.12).

4) Renal function was impaired in diabetics with hypertensive crisis at admission.>

By discharge, group-wise changes of serum creatinine were not different among groups (Table 2). During hospitalization, 1 out of 19 Group-1 patients, 3 out of 19 Group-2 patients, and 1 out of 15 (38.5%) Group-3 patients had an evolving AKI. After exclusion of serum creatinine of patients with an evolving AKI, eGFR at discharge was less in Group-1 patients than in Group-2 patients. However, Group-1 and Group-3 patients were not different in terms of eGFR at discharge.

Discussion

As a selection criterion, the maximum systolic arterial pressure was highest in Group-1 patients. Likewise, hypoglycemic episodes per 24 hour FGM were more often detected in the overtly hypoglycemic Group-3 patients when compared to control patients of Group 2. Of note, the first symptomatic hypoglycemia occurring at admission was the inclusion criterion for Group-3 patients and did not count as a result. As a limitation, FGM and ABPM results were not blinded and could have influenced therapy decisions. In addition, regarding daily cumulative insulin dose, within-day dosing issues were not considered in this study. Nevertheless, once hypoglycemic episodes became evident, therapeutic decisions likely led to an insulin reduction. Therefore, the yielded hypoglycemic rate during FGM was unlikely to be increased by the open-label FGM used in this study. Nevertheless, the high number of hypoglycemic episodes in hypertensive Group-1 patients and the elevated mean arterial blood pressure detected in initially hypoglycemic Group-3 patients were unexpected.

Evidence for a higher-than-optimal daily cumulative insulin dose in diabetes patients both with hypoglycemia and hypertensive crisis at admission

As the primary outcome, the number of hypoglycemic episodes per 24 hours of FGM, suggests, this pilot study focused on the hypoglycemic burden in insulin-treated diabetes patients of any causality. In Group-3 patients, the hypoglycemic burden is evident by the proven hypoglycemic episodes during FGM, and by the reduced daily cumulative insulin dose by discharge. Therefore, we conclude that Group-3 patients had a higher-than-optimal daily cumulative insulin dose at admission. Surprisingly, hypertensive Group-1 patients and initially hypoglycemic Group-3 patients showed no difference with respect to hypoglycemic burden in the FGM results. Likewise, as evidence for a higher-than-optimal insulin dosage, the daily cumulative insulin dose was decreased in Group-1 patients by discharge as well.

Hypoglycemia-induced catecholamine release may represent one cause for hypertensive crisis in insulin-treated diabetes patients

In case of a higher-than-optimal daily cumulative insulin dose, the reduction of insulin may reduce both hypoglycemic events and an ensuing hypertensive crisis as a consequence of neurohormonal activation occurring in the framework of the Somogyi effect. If not, patients with an individually higher than optimal daily cumulative insulin dose are more likely to suffer from repetitive hypoglycemic events, or, if hypoglycemia still is compensated for, from hypertensive events. Group-1 and Group-3 patients had comparable norepinephrine-plasma levels. In addition, Group-1 and Group-3 patients had a similar phenotype with respect to the mean arterial blood pressure. These results support the hypothesis that Group-1 patients have an activated SNS with higher norepinephrine-plasma levels in comparison to Group-2 patients. For Group-1 patients, it is tempting to speculate that hypoglycemia triggered the norepinephrine release within the framework of the Somogyi effect. If this hypothesis holds true, the higher maximum systolic blood-pressure and the hypertensive crisis at admission may be, in part, due to a pronounced Somogyi effect in terms of norepinephrine release and SNS activation as a consequence of hypoglycemia. Alternative explanations may relate to the body-mass index being elevated in Group-1 patients. A propensity for arterial hypertension may be assumed, if a metabolic syndrome is present.

Limitations

The main limitation of this pilot study was the small study size. Randomized clinical trials assessing surrogates of SNS tone in diabetes patients are needed to gain a better understanding of both the normal and possibly attenuated responsiveness to hypoglycemia in diabetes patients (9). There, the consideration of more surrogate parameters of SNS activity including the low-frequency band intensity of powerspectral analysis of heart rate and, if feasible, direct measurements of sympathetic nerve activity may help differentiate between normal and attenuated responsiveness to hypoglycemia. To gain a comprehensive picture of the hypoglycemia – hypertension relationship, a better coverage of blood-pressure and tissue glucose monitoring is needed. As the use of long-term FGM becomes feasible, future studies may even provide insights on the initial hypoglycemic episode leading to hospitalization.

Conclusions

In this study, we demonstrated an association between hypoglycemic episodes, norepinephrine release and uncontrolled arterial hypertension in diabetes patients on insulin therapy. The results of this pilot study may encourage health-care professionals to put hypoglycemia on the list of causes to check in hypertensive diabetes patients. In addition, given the fact that Germany is a country with a high use of insulin per capita (10), the results of this study may increase the awareness to minimize the incidence of hypoglycemic episodes in insulin-treated diabetes patients.

Abbreviations

ABPM ambulatory blood-pressure monitoring

AKI acute kidney injury

DDD defined daily dose

eGFR estimated glomerular filtration rate

FGM flash glucose monitoring

HbA1c glycated hemoglobin A1c

IU insulin units including units of insulin analogues

n number

SNS sympathetic-nervous system

Declarations

Ethics approval and consent to participate

The ethics committee of the Medical Faculty of the Martin-Luther University Halle-Wittenberg approved this study protocol (Study number 2017-28). All study participants provided written informed consent to participate in this study.

Consent for publication

All study participants provided written consent to publish study results.

Availability of data and materials

All relevant data are provided in the paper. Source data are available on request from the authors.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AA recruited patients, performed the study, contributed to writing of the manuscript draft, participated in analysis, gave critical input to the interpretation of data

AW analyzed data, gave expert advice to statistical issues and to the interpretation of data

MG provided funding, gave critical input to data analysis and discussion

RP conceived this study, participated in analysis, wrote the manuscript draft, gave final approval to the version to be published. He serves the role of a guarantor, taking full responsibility for the work and for the conduct of the study, had access to the data, and controlled the decision to publish.

All authors reviewed data and participated in the revision of the manuscript.

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Figures

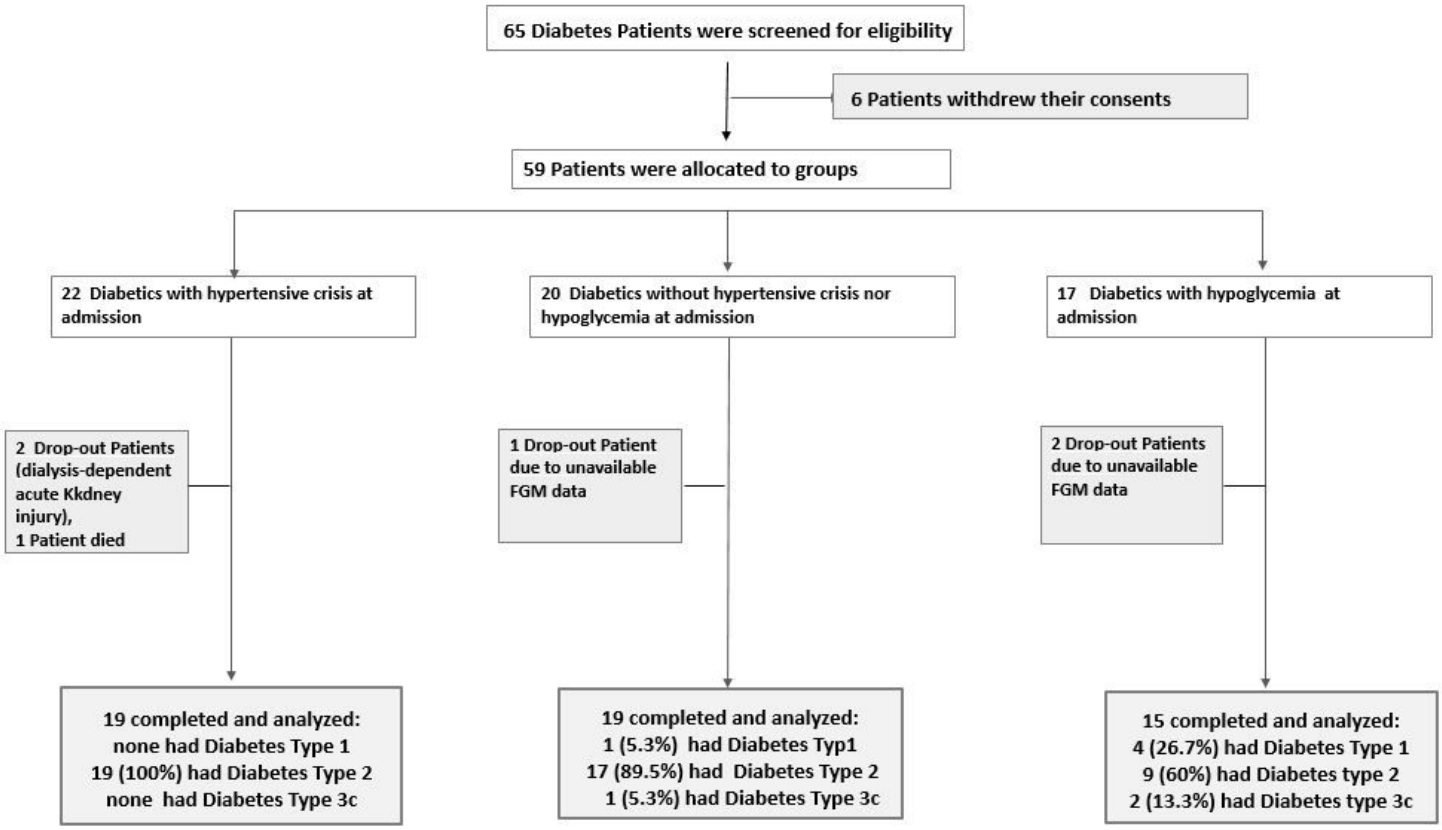

Figure 1

Flow chart which demonstrates screening and study recruitment of diabetes patients to this study.

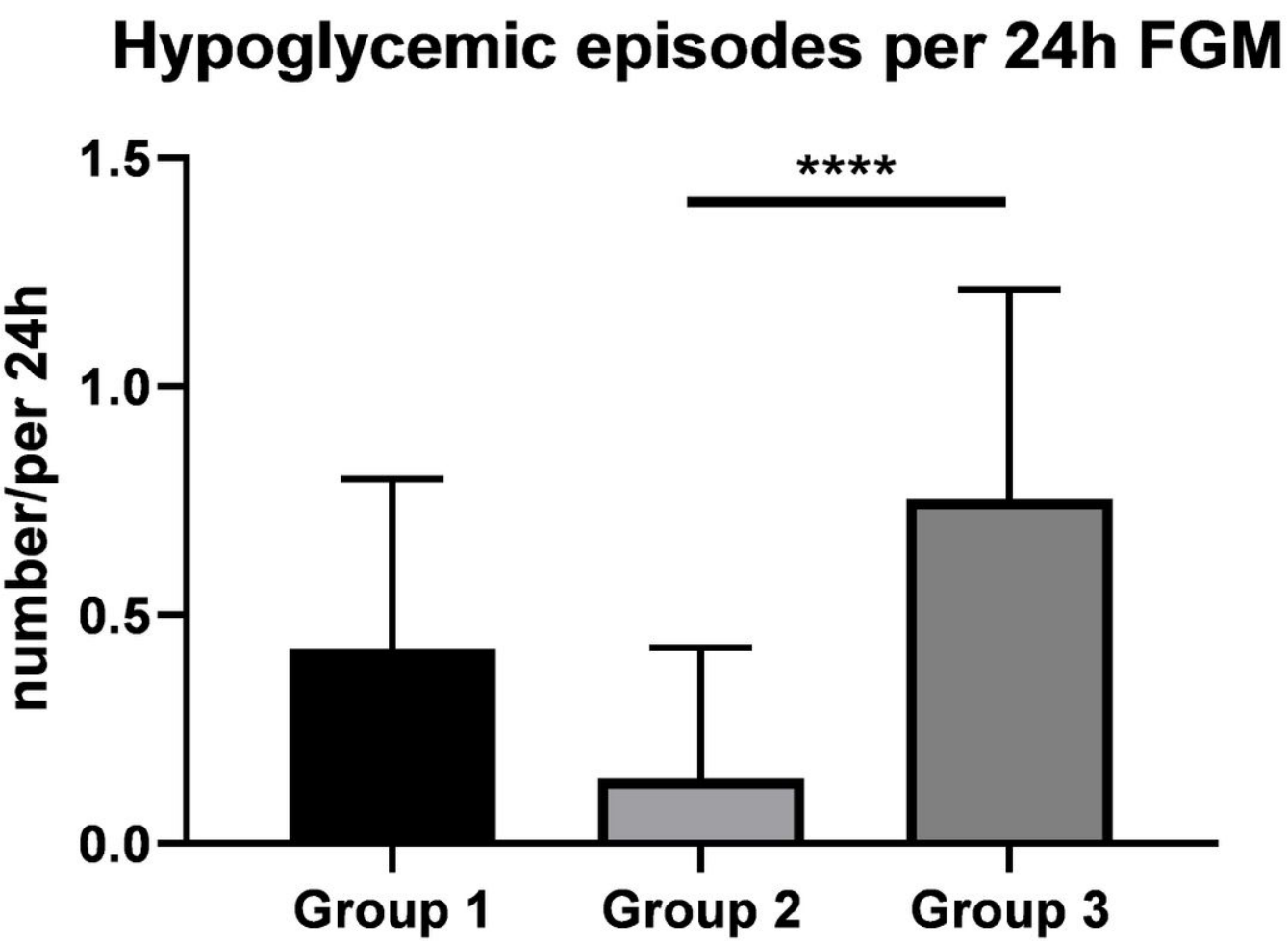

Figure 2

Hypoglycemic episodes per 24h flash glucose monitoring (FGM) among groups. Asterisks signify relevant differences according to post-hoc analysis.

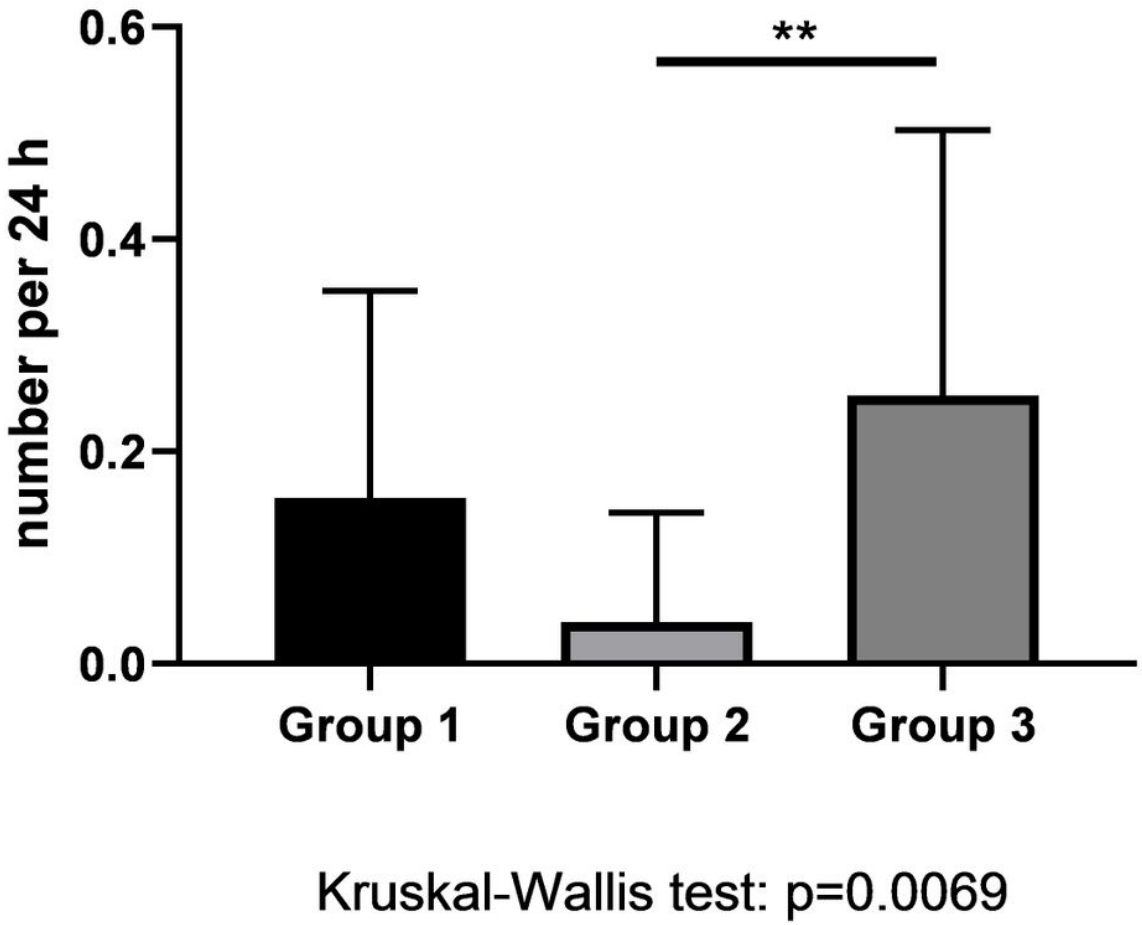

Figure 3

Nocturnal hypoglycemic episodes per 24h flash glucose monitoring (FGM) among groups. Asterisks signify relevant differences according to post-hoc analysis.

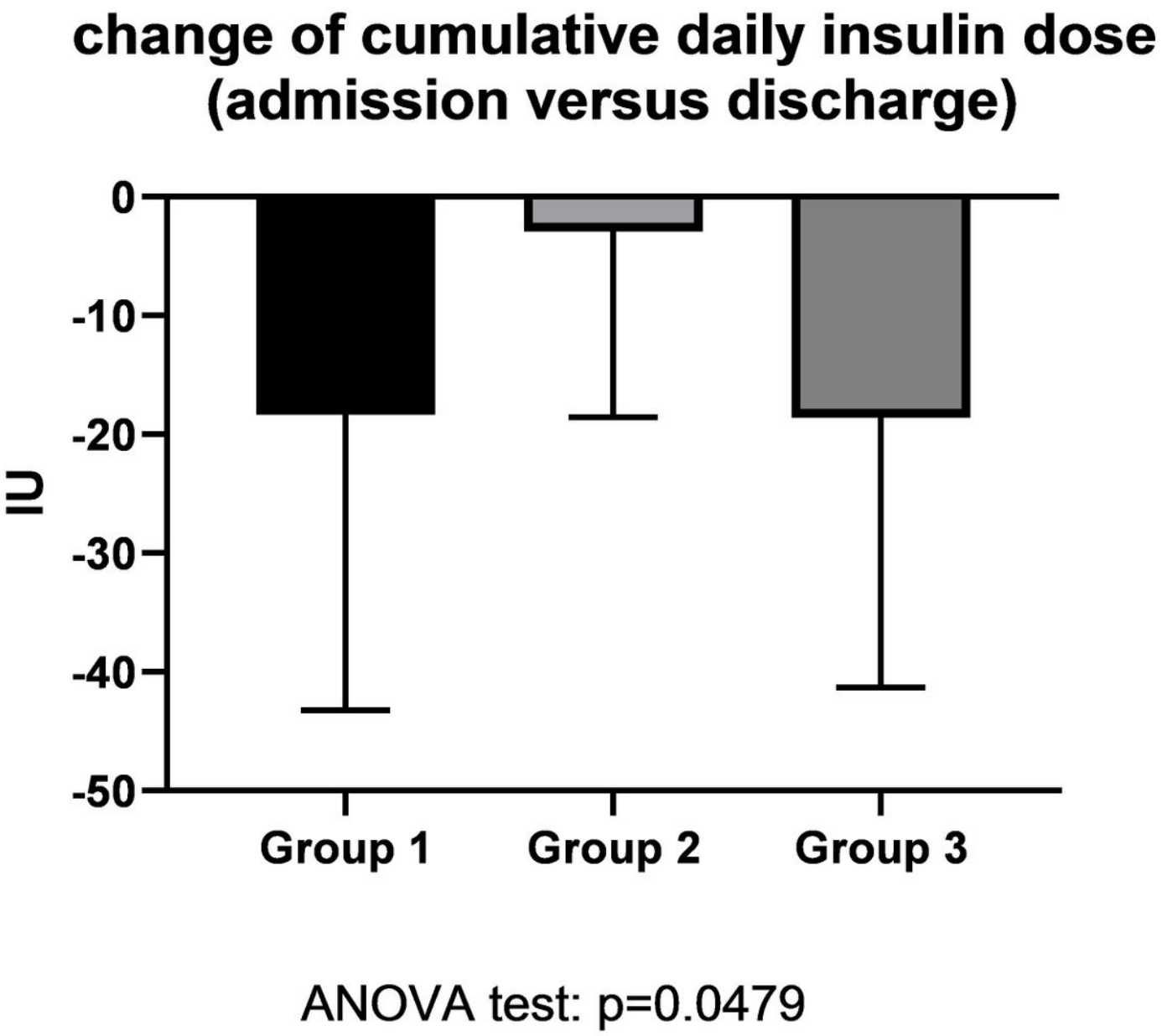

Figure 4

Change of cumulative daily insulin units (IU) from the time of admission versus discharge. Asterisks signify relevant differences according to post-hoc analysis.

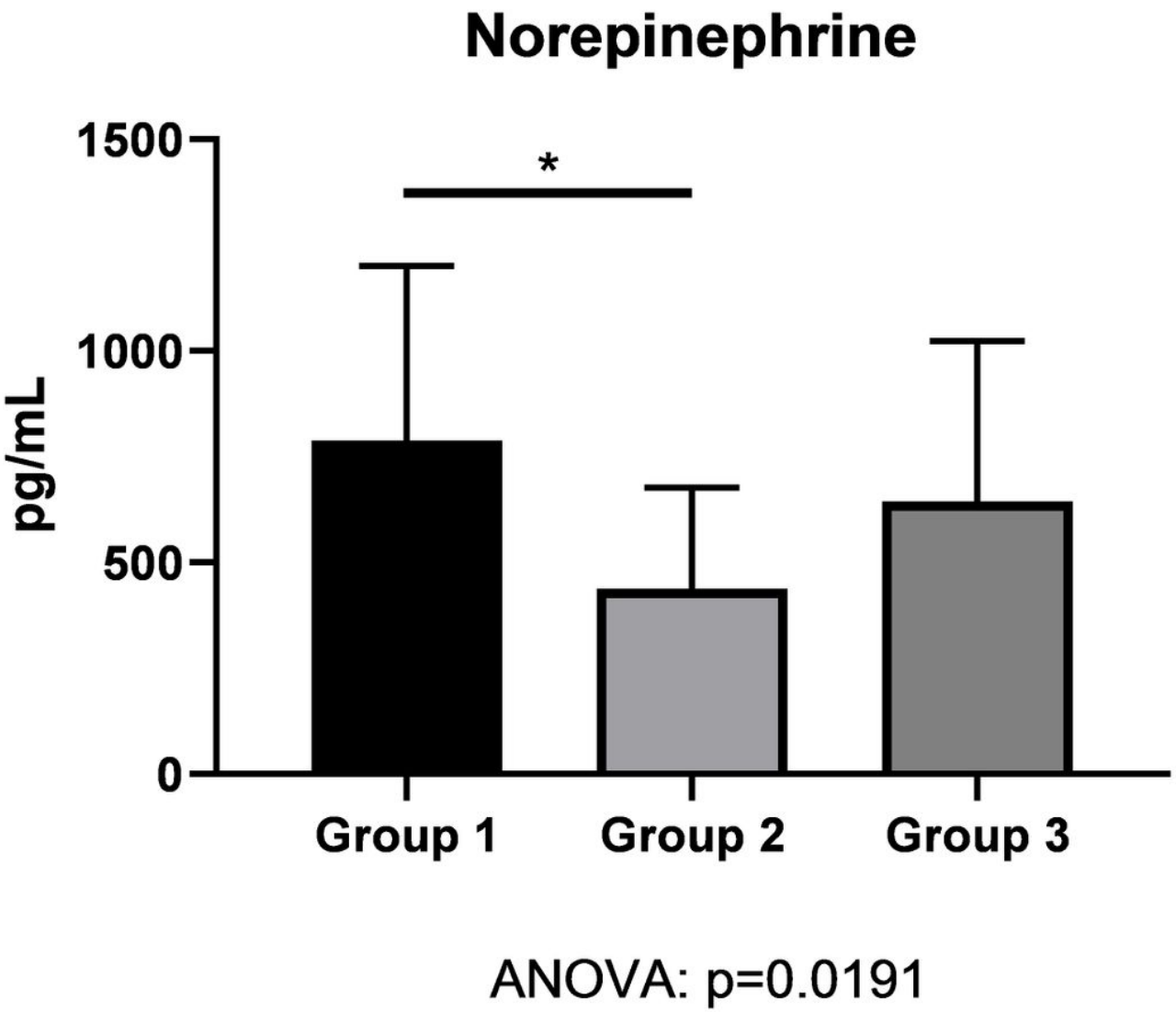

Figure 5

Plasma Norepinephrine levels at admission among groups. Asterisks signify relevant differences according to post-hoc analysis.

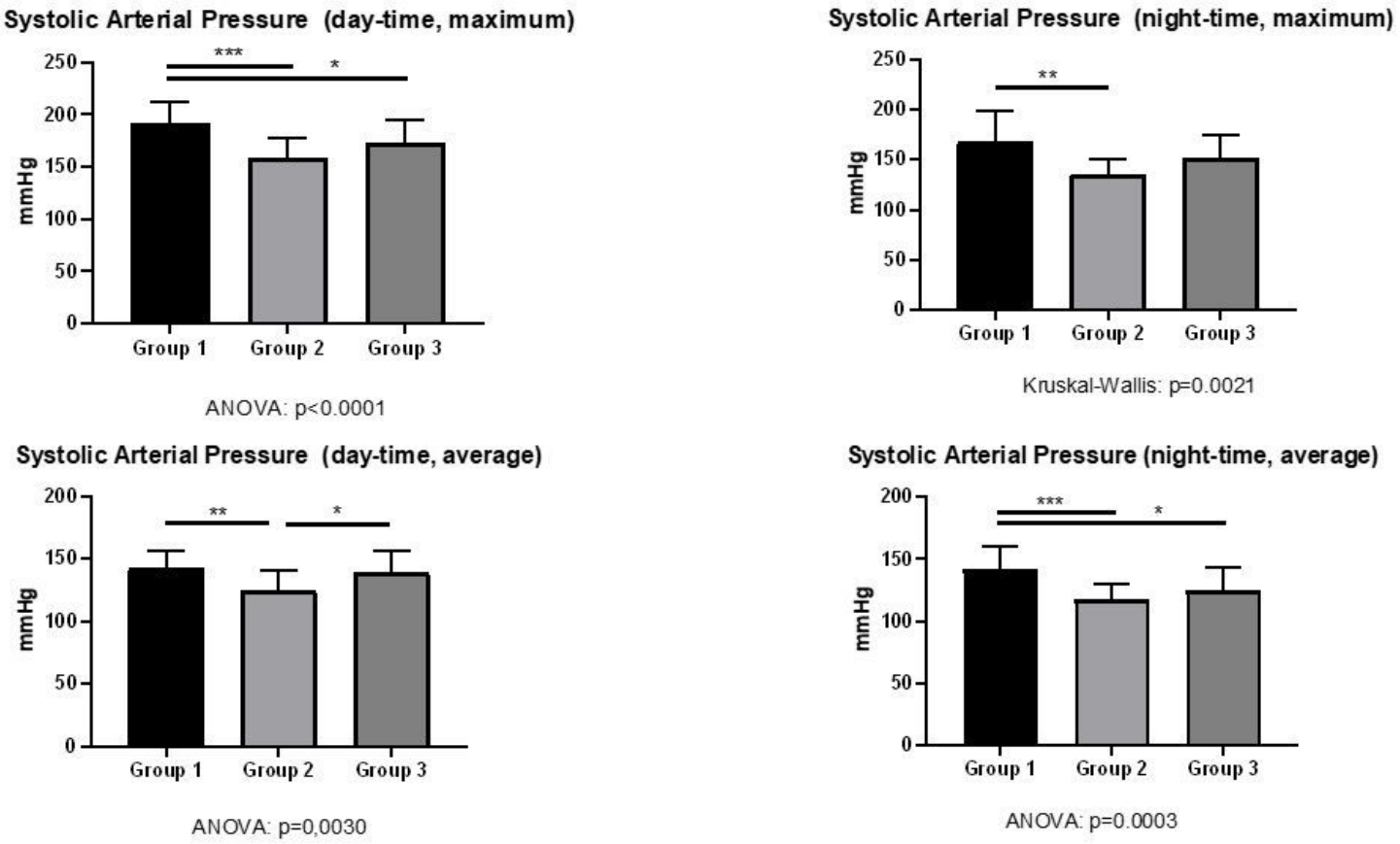

Figure 6

Maximum systolic blood pressure both at daytime and at nighttime (upper panel) and average systolic arterial blood pressure both at daytime and at nighttime (lower panel). Asterisks signify relevant differences according to post-hoc analysis.