BLOOD PRESSURE PROFILE AND GLYCEMIC PROFILE IN TYPE 1 DIABETES MELLITUS

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Abstract

Background: *The main objective of this study is to analyze the blood pressure profile of patients with type 1 diabetes mellitus and the aspect of the glycemic profile in order to identify the correlations between blood pressure and glycemia at a 24 hours' monitoring interval, as well as the blood pressure modifications in the context of hypo and hyperglycemic episodes.* ***Material and method***: *The study included 112 patients with type 1 diabetes mellitus, with disease duration of at least 10 years, from the Diabetes, Nutrition and Metabolic Disease Center Iasi and Suceava. The patients were evaluated both in terms of automatic blood pressure monitoring (ABPM) and continuous glucose monitoring system (CGMS) simultaneously for 24 hours.* ***Results***: *The dynamic analysis of the glycemia during the day (active period) reveals an increase of the average values of the glycemia during the prandial period. At night, starting with 0.00 h, one may notice a progressive decrease of the average values of glycemia. In patients without arterial blood pressure, the blood pressure parameters are correlated, to a small extent, with the glycemia values. The risk of high blood pressure is 3.14 times bigger during the hypoglycemic period, in comparison with the normal glycemia period. The ongoing record of arterial blood pressure during hypoglycemia revealed high values for systolic, as well as for diastolic blood pressure, values considered significant from a statistical perspective (p <0.05). The risk of rise of the blood pressure values during the hyperglycemic period is 4.87 times bigger in comparison with the blood pressure values from the normal glycemia period. A slight, physiological decrease in arterial blood pressure (systolic blood pressure from 136.2 ± 21.2 mmHg to 132.3 ± 14.2 mmHg, p NS [not significant]; diastolic blood pressure from 87.3 ± 13.8 mmHg to 86.4 ± 12.6 mmHg, p NS) was observed in the group that showed a lower postprandial increase of blood glucose (<43.6 mg/dl). On the contrary, a significant postprandial increase of arterial blood pressure was observed (systolic blood pressure from 132.1 ± 17.7 mmHg to 148.6 ± 26.4 mmHg, p<0.05; diastolic blood pressure from 73.4 ± 14.3 mmHg to 82 ± 12 mmHg, p<0.05) in the group that showed a higher postprandial increase of blood glucose (>43.6 mg/dl). Conclusions: Hypoglycemia, but also postprandial hyperglycemia, a typical feature of type 1 diabetes mellitus, may increase the blood pressure values, causing higher hemodynamic stress. In type 1 diabetes mellitus patients, without high blood pressure, the blood pressure parameters are weakly correlated with the values of the glycemia.*

key words: *Type 1 diabetes mellitus, CGMS, ABPM.*

High blood pressure in type 1 diabetes mellitus is a topic of extreme actuality in the context of the increase of the prevalence of the two diseases. Diabetes mellitus and high blood pressure are deeply inter-correlated and act in a synergic manner, causing macro and microvascular lesions [1]. Type 1 diabetes mellitus, in combination with blood pressure, worsens the prognosis of these patients and increases the mortality rate, shortening life span; hence, a crucial modality of improving the prognosis, as important as good glycemia control, is the reduction, in as many patients as possible, of the values of blood pressure below 130/80 mmHg [2].

In type 1 diabetes mellitus, the prevalence of high blood pressure is small (approximately 5%) after 10 years of disease, of 33% after 20 years and of 70% after 40 years. In the presence of diabetic nephropathy, high blood pressure is present in 75-85% of the cases. On the other hand, high arterial blood pressure often reflects the onset of nephropathies (between 10 and 30% of the patients with a history of over 10 years) [3].

High blood pressure is considered a major risk factor for the advancement of terminal kidney disease in diabetic patients. The lack of decrease of blood pressure at night, observed during the analysis of the circadian blood pressure profile, could be an additional risk factor for the advancement of diabetic nephropathy. According to the current definitions of high blood pressure (≥14/90 mmHg), persons with type 1 diabetes mellitus, likely to develop kidney diseases, will suffer from high blood pressure after the occurrence of microalbuminuria.

The circadian glycemic oscillations may lead to modifications of blood pressure, influencing the blood pressure parameters of these patients.

In the context of these characteristics of high blood pressure in type 1 diabetes mellitus, the main objective of this study is to analyze the blood pressure profile of patients with type 1 diabetes mellitus and the aspect of the glycemic profile in order to identify the correlations between arterial blood pressure and glycemia at a 24 hours' monitoring interval, as well as blood pressure modifications in the context of hypo and hyperglycemic episodes.

Material and method

This study included 112 patients with type 1 diabetes mellitus, who have had the disease for at least 10 years, found in the records of the Diabetes, Nutrition, Metabolic Diseases Centers of Iasi and Suceava, 52 of them suffering from high blood pressure. The patients were assessed both from the perspective of blood pressure (automatic blood pressure monitoring) and from the perspective of their glycemia (continuous glucose monitoring), simultaneously, for a 24 hours' period. The exclusion criteria were secondary high blood pressure, complications of diabetes or of high blood pressure, which make the use of glycemia or blood pressure monitoring devices impossible, the patient's refusal. Type 1 diabetes mellitus was defined according to the ADA criteria, acknowledged by international forums.

Continuous glucose monitoring was conducted with the help of the Continuous

Glucose Monitoring System (CGMS) MiniMed Medtronic. The MiniMed (CGMS) continuous glucose monitoring system is conceived in such a manner as to continuously and automatically monitor the glycemia values at the level of the hypoderm at every 10 seconds and to cache them at every 5 minutes, thus ensuring up to 288 measurements per day. In the selected group, the glycemic assessment was performed at 15 minutes' intervals, simultaneously with the automatic recording of the blood pressure parameters. Thus, 96 determinations were performed for each patient. As the study group is comprised of 112 patients, a number of 10752 determinations were obtained.

For the selected group of patients, we described, from the perspective of glucose monitoring, 3 periods per patient [4]:

- period of hypoglycemia (values < 70 mg/dl),
- period of normal glycemia (values between 70 and 180 mg/dl),
- period of hyperglycemia (values > 180 mg/dl).

The continuous monitoring of the values of blood pressure was conducted with the help of a mobile oscillometer of the Automatic Blood Pressure Monitoring (ABPM) type, periodically calibrated and verified. Two different periods were defined: the daytime (active) period, from 6 am to 10 pm, and the nighttime (passive) period, which included measurements from 10 pm to 6 am. The arterial blood pressure was registered at 15 minutes intervals, during the day, and at 30 minutes' intervals at night. The average values of systolic arterial blood pressure and of diastolic arterial blood pressure registered during a day or a night were stored as SBS and DBS values for the respective period. A ratio of 0.9 or even smaller between the SBS night value and the SBS day value was defined as a normal decrease during the night. The phenomenon called "non-dipper" is defined as a relative decrease of nocturnal arterial blood pressure, smaller than 10% of the daytime value, both for systolic and for diastolic blood pressure.

Results and discussions

Of the 112 patients with type 1 diabetes mellitus, 62 were males and 50 females. The average age of the subjects was 38.3 ± 11 years, with variations between 18 and 50 years. The patients have had diabetes mellitus for 5 up to 15 years, with an average of 12.96 ± 3.92 years (table 1).

Table 1. Group characteristics

	N = 112
Sex (m/f)	62/50
Age	38.3 ± 11 years
BMI	24.08 ± 3.51 kg/m2
Duration of type 1 DM	12.96 ± 3.92 years

As concerns the number and percentage of glucose values according to glycemia fields, following continuous glucose monitoring (CGMS), the following results were obtained:

– the numerical distribution of the values of interstitial glucose predominantly registered values between 70 - 180 mg/dl (62.05%), followed by values > 180 mg/dl (36.1%). A small percentage was registered by the values < 70 mg/dl (1.84%),
– hypoglycemia episodes were frequently associated with physical effort (table 2).

The average duration of the hypoglycemia episodes was 30 ± 5.5 minutes, the average duration of the hyperglycemia periods was

6.44 ± 0.92 hours, and the duration of the normal glycemia was 61.72 ± 5.6 (table 3).

Table 2. Repartition according to the position of the glycemia values in the glycemic field

Glycemic fields	No. of determinations	%
Episodes of hypoglycemia (values< 70 mg/dl)	198	1.84%
Episodes of normal glycemia (values between70 and 180 mg/dl)	6672	62.05%
Episodes of hyperglycemia (values > 180 mg/dl)	3882	36.10%
	10752	

Table 3. Average duration of glycemia periods per patient

Parameter	Value
Average duration of hypoglycemia per patient	30 ± 5.5 minutes
Average duration of hyperglycemia per patient	6.44 ± 0.92 hours
Average duration of normal glycemia per patient	61.72 ± 5.6 hours

The dynamic analysis of glycemia during the day (active period) reveals an increase in the average values of the glycemia during the prandial period, values that are significantly bigger in comparison with other glycemia values registered during the day (figure 1). During the day, the values of the glycemia have significant oscillations in patients with high blood pressure (F=1.21, p=0.1193, 95%CI), as well as in patients without high blood pressure. (F=1.75, p=0.0002, 95%CI).

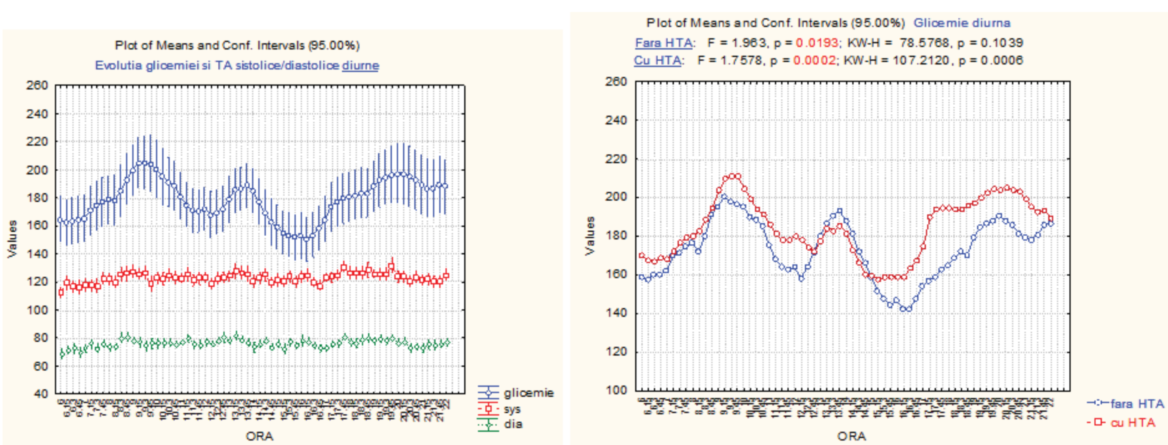

Figure 1. Average values of daytime glycemia depending on the moment of the measurement

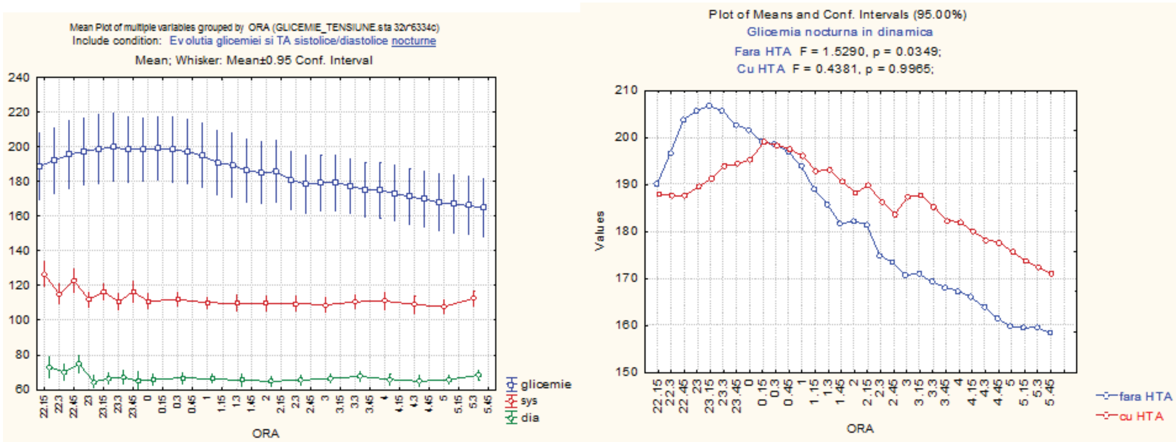

Figure 2. Average values of night time glycemia depending on the moment of the measurement

Significant variations are registered during the night – it is worth mentioning that, starting with 0.00 hours, one may notice a progressive decrease of the average values of glycemia (figure 2). During the night, the values of the glycemia register significant decreases in patients who do not suffer from high blood pressure (F=1.52, p=0.034, 95%CI), whereas the decreases are not significant in patients with high blood pressure (F=0.43, p=0.99, 95%CI).

The correlation between night time glycemia and the magnitude of nocturnal modifications of SBS and DBS was very significant. This high correlation proves that the lack of glycemic balance in hypertensive patients with type 1 diabetes mellitus can be estimated based on the magnitude of the decrease of nocturnal blood pressure and that the significant decrease of nocturnal blood pressure is associated with a better response of the action of insulin, postprandially.

In patients without high blood pressure, the blood pressure parameters are correlated to a very small extent with the values of the glycemia, fact proven by the small value of the correlation coefficients and the high values of the significance level of the Pearson test. The considerations are mode for a confidence interval of 95% (table 4, figure 3).

Table 4. Values of the correlation coefficient daytime/night/time glycemia vs. arterial blood

Glycemia vs.	Systolic blood pressure	Average blood pressure	Diastolic blood pressure	Heart frequency
Patients without high blood pressure				
During the night	0.0047	0.0513	0.0565	0.0549
	0.921	0.275	0.229	0.243
	ns	ns	ns	ns
During the day	0.0180	0.0320	0.0135	0.4939
	0.446	0.175	0.568	0.000
	ns	ns	ns	ss

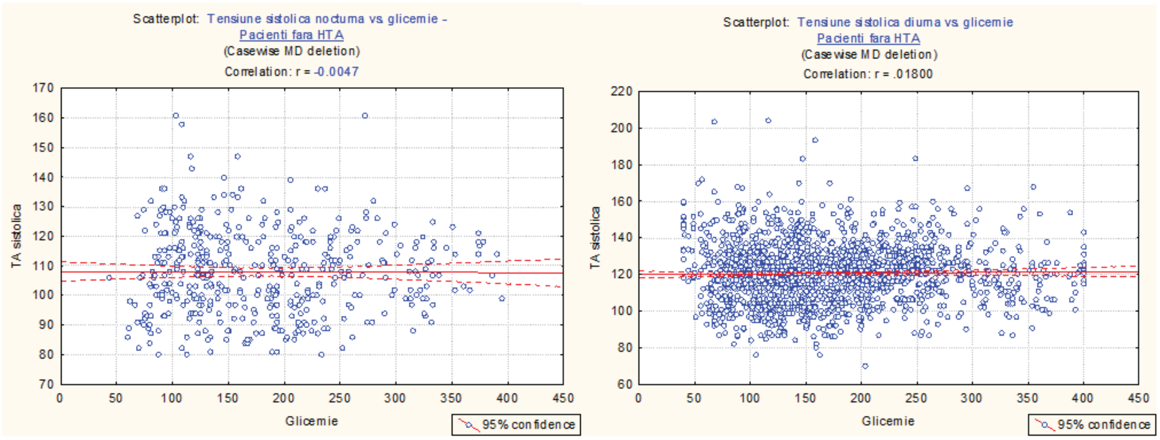

Figure 3. Regression right line glycemia vs. systolic arterial blood pressure in patients without high blood pressure

Of the 198 moments when hypoglycemia was registered, at times these constituted consecutive moments (more than 15 minutes, which is the interval between 2 determinations), thus leading to periods of hypoglycemia. Thus, the analysis outlined the fact that the hypoglycemia periods were present in 14 patients (96 determinations were conducted for a patient during a 24 hours' interval). The 14 patients who suffered from these hypoglycemia episodes were distributed as follows: 9 cases of hypertensive patients and 5 cases of patient with normal blood pressure. (figure 4)

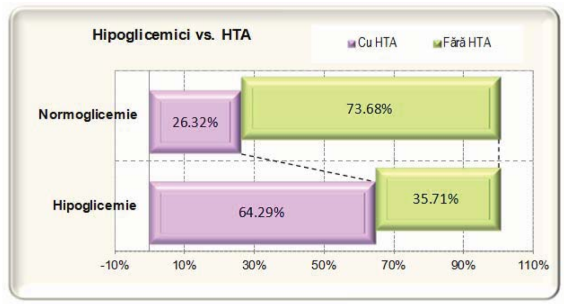

Figure 4. High blood pressure vs. glycemic profile (hypoglycemia)

The risk of high blood pressure is 3.14 times bigger during the period of hypoglycemia, in comparison with the period of normal glycemia. (table 5)

Table 5. Assessment of chance and risk parameters high blood pressure vs. hypoglycemia

Chance PARAMETERS	**Estimated value**	*95% Confidence interval*	
		Minimum	**Maximum**
Chance ratio	3.48	0.05	29.27
Risk PARAMETERS			
Risk ratio	3.14	0.22	7.42

The continuous recording of blood pressure during hypoglycemia revealed high values of systolic blood pressure, as well as of diastolic blood pressure, values that were considered statistically significant ($p<0.05$). The blood pressure behavior during hypoglycemia intervals was characterized by increases of the blood pressure parameters. The cardiovascular modifications caused by hypoglycemia were similar in terms of magnitude, but late in hypertensive patients.

Of the 3882 moments when the hyperglycemia was determined, one could notice that these constituted, at times, consecutive moments (more than 15 minutes, which is the interval between two determinations), and thus hyperglycemia periods occurred. Thus, the analysis revealed that these episodes were present in 67 patients (96 determinations were conducted for a patient). The 67 patients who registered these episodes of hyperglycemia were distributed as follows: 41 cases of hypertensive patients and 26 cases of patients with normal blood pressure (figure 5).

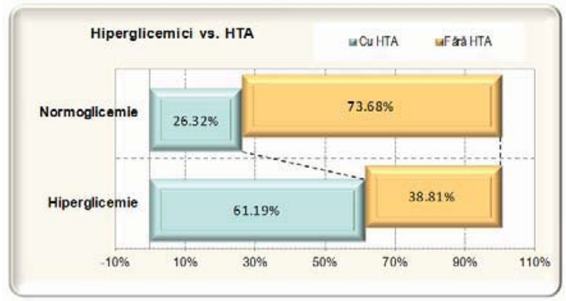

Figure 5. High blood pressure vs. glycemic profile (hyperglycemia)

The risk of increase of blood pressure values during hyperglycemia is 4.87 times bigger in comparison with the blood pressure values from the normal glycemia period (table 6).

Table 6. Assessment of the chance and risk parameters high blood pressure vs. hyperglycemia

	Estimated value	*95% Confidence interval*	
		Minimum	**Maximum**
Chance PARAMETERS			
Chance ratio	4.87	2.77	8.21
Risk PARAMETERS			
Risk ratio (RR)	4.43	2.83	6.65

The analysis of the hyperglycemia interval at night, as well as during daytime, reveals significant increases of the blood pressure parameters. It is worth mentioning the fact that during hypoglycemia periods, the increases of blood pressure parameters are much bigger in comparison with the increases registered during the hyperglycemia period.

During the postprandial, blood pressure usually decreases and reaches a minimum between 30 and 60 minutes after the meal [5]. Giugliano et al. showed that acute hyperglycemia in normal subjects determines significant increases of systolic and diastolic blood pressure [6]. In order to define the relation between postprandial glycemia excursions and arterial blood pressure in type 1 diabetes mellitus, one conducted a dynamic analysis of the blood pressure and glycemic profiles. The distribution of the cases depending on the postprandial glycemic excursions is presented in the analysis below.

Table 7. Distribution of the cases depending on glycemic amplitude

Glycemic amplitude	No. of cases	%
0<x<=50	32	28.57%
50<x<=100	42	37.50%
100<x<=150	23	20.54%
150<x<=200	15	13.39%
Total	112	

Postprandial glycemia increases had values of 85.6 ± 49.5 mg/dl [variation interval 11.28 – 188.7 mg/dl]). The establishing of the *cut off level* enables the assessment of the capacity of a parameter to classify the status of a disease. In order to assess the effect of postprandial glycemia modifications on arterial blood pressure, the postprandial glycemic profiles were divided into two groups, according to the maximum growth level of the glycemia, the proven *cut off level* point (43.6 mg/dl). A slight, physiological decrease of systolic and diastolic blood pressure, without any statistical significance, was registered in the group with a small increase of postprandial glycemia (up to 43.6 mg/dl). On the other hand, in the group with a higher increase of postprandial glycemia, one could notice significant statistical increases of systolic and diastolic blood pressure, values that were preserved throughout the entire duration of the hyperglycemic period. (table 8)

Table 8. Blood pressure modifications during postprandial hyperglycemia

Parameter		Before a meal	After a meal	P value
Group 1 (< 43.6 mg/dl)	SBS	136.2 ± 21.2 mm Hg	132.3 ± 14.2 mm Hg	insignificant
	DBS	87.3 ± 13.8 mm Hg	86.4 ± 12.6 mm Hg	insignificant
Group 2 (>43.6 mg/dl)	SBS	132.1 ± 17.7 mm Hg	148.6 ± 26.4 mm Hg	$p < 0.05$
	DBS	73.4 ± 14.3 mm Hg	82 ± 12 mmHg	$p < 0.05$

SBS=systolic blood pressure DBS=diastolic blood pressure

Discussions

In agreement with the gathered data, Bode et al (2005) noticed that persons with type 1 diabetes mellitus present higher glycemia variations than those with type 2 diabetes mellitus [4]. Statistical analysis revealed direct correlations between the aspect of the glycemic profile and the presence of high blood pressure in type 1 diabetes. Hyperglycemia most often occurs after meals. Studies that made use of CGMS monitoring also identified episodes of significant postprandial hyperglycemia, despite the prandial glycemia in therapeutic targets [7]. This phenomenon was underappreciated by using traditional glucose monitoring. There is evidence which certifies the fact that these postprandial increases in diabetic patients are an important factor which contributes to the occurrence of cardiovascular diseases, and especially atherosclerosis [8, 9].

The acknowledgement of the association of high blood pressure with type 1 diabetes mellitus led to the hypothesis that the modifications of the metabolism of carbohydrates have something to do with high blood pressure and its complications. As the etiology of high blood pressure is heterogeneous, there is no sure criterion which can reveal what subgroup of hypertensive patients will have more pregnant glycemia variations. The identification of such a group can help us understand the relation between glycemia oscillations and high blood pressure and can contribute to the development of some future strategies in order to prevent high blood pressure complications. In this study, glycemic variability had higher prevalence in nondipper hypertensive patients. The magnitude of the lack of glycemic balance can be estimated with the help of the magnitude of the decrease of nocturnal blood pressure. These results create the possibility that a reduction of nocturnal blood pressure may be useful for the stratification of the degree of lack of glycemic balance in hypertensive patients.

Intensive treatment of type 1 diabetes mellitus slows down the progression towards specific microvascular complications, but determines a marked increase of the hypoglycemia risk induced by insulin treatment [10]. Intensive insulin treatment is associated with a diminished response of catecholamines to the decrease of the glycemia values, which can modify the behavior of the cardiovascular system under these circumstances [11, 12]. Cardiac debit normally increases in the presence of hypoglycemia, but the diminution of this augmentation may lead to the decrease of the supply of glucose and of other metabolic sublayers to the periphery [13]. The cardiovascular response to hypoglycemia was examined in healthy subjects, without diabetes mellitus, after the intravenous bolus injection of insulin [14, 15]. Severe hypoglycemia induced by insulin determines a transitory increase of the cardiac debit, of the heart frequency, with an associated decrease of peripheral resistance. One could also notice a significant increase of the ejection fraction of the left ventricle, suggesting an increase of the myocardial systolic activity. These previous studies did not present the effects of hypoglycemia on the diastolic function, which is an important component of cardiac performance [16].

The increase of cardiac activity as a response to hypoglycemia per se is diminished in patients with type 1 diabetes mellitus. Previous studies have proven the decreased catecholamine response in the presence of recurrent hypoglycemia [17, 12]. As expected, in this study the response to counter-regulation was modified and manifested itself via ample blood pressure modifications, but with a moment of occurrence at a distance from the onset of hypoglycemia. In most patients with type 1 diabetes mellitus, the response of glucagon to hypoglycemia decreases and even disappears a couple of months after the onset of diabetes. On the other hand, over 45% of the long term patients with type 1 diabetes mellitus register the alteration of the glucagon and adrenalin secretion, which is triggered at a smaller than normal level of glycemia, the level decreasing even more after recent hypoglycemia [18]. The cardiovascular response is thus impaired, the blood pressure values registering significant increases, although not at the same time with the hypoglycemia period. Blood pressure modifications occur during the day, as well as during the night, and statistical analysis shows more marked blood pressure increases during the day for the same magnitude of hypoglycemia.

The possibility for hypoglycemia to determine blood pressure increase via the osmotic effect per se must not be excluded. Acute hyperglycemia also induces the increase of platelet aggregation and of blood viscosity. The analysis showed a significant delay between the onset of the hyperglycemic period and the occurrence of blood pressure modifications. This can be explained via the time necessary for the hyperglycemia to activate the metabolic pathways which supposedly mediate vascular effects: the self-oxidation of glucose, of the polyol pathway and of cyclooxygenase. All these pathways are strictly associated with hyperglycemia and may augment the production of oxygen-reactive substances, mainly superoxide anions, which inactivate the endogenous nitric oxide. [19] Moreover, the plasma concentration of insulin may attenuate the vascular effects of hyperglycemia, possibly via the ability of insulin to induce vasodilatation mediated by the nitric oxide [20].

The collected data show a positive correlation between the high values of glycemia and blood pressure values. The DCCT study proved the role of adequate durable control, expressed via the HbA1c values, in the prevention of the occurrence of specific chronic complications. Nevertheless, the investigators of the DCCT trial discovered that, by itself, HbA1c does not suffice for explaining the occurrence of specific chronic complications, suggesting that postprandial hyperglycemic excursions may favor the occurrence of chronic complications of diabetes [21].

Conclusions

Circadian glycemic modifications, hypo and hyperglycemia determine increases of blood pressure values, with significant consequences on hemodynamic stress. An adequate therapeutic regime, which enables the obtaining of euglycemia, without significant oscillations of plasma glucose, ensures a long evolution, without the occurrence of specific chronic complications.

In patients with type 1 diabetes mellitus, without high blood pressure, the blood pressure parameters are weakly correlated with the values of the glycemia. In type 1 diabetes mellitus, the hypertension risk is 3.14 times bigger during the hypoglycemia period, in comparison with the period of normal glycemia.

Postprandial hyperglycemia influences blood pressure behavior: a slight, physiological decrease of systolic and diastolic arterial blood pressure was registered in the group with a small rise of postprandial glycemia (up to 43.6 mg/dl). In the group with a bigger rise of postprandial glycemia, one could notice statistically significant increases of systolic and diastolic arterial blood pressure.

This study has clearly shown that acute hyperglycemia determines significant hemodynamic modifications during the day, as well as during the night. The relevance of the influence of these modifications on vascular chronic complications in type 1 diabetes mellitus is only speculative at present, but our findings can provide an additional mechanism via which hyperglycemia acts as an independent factor in the occurrence of specific cardiovascular complications.

ABPM and CGMS monitoring outline the blood pressure and glycemic profiles in type 1 diabetes mellitus, with obvious advantages in comparison with the intermittent measurement of blood pressure and glycemia, and establish the premises for adequate therapeutic intervention.

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