ORIGINAL ARTICLE

The Characteristics of Blood Pressure Variability in Subjects with Chronic Kidney Disease Stage III in Diabetic or Non-diabetic Patients

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Abstract

Aim: The aim of this study was to understand the relationship between circadian rhythm of blood pressure (BP) and renal function characteristics in subjects with chronic kidney disease (CKD) Stage III of diabetic and non-diabetic etiology. **Materials and Methods:** A total of 30 CKD - hypertensive patients without diabetes and 30 Type 2 diabetic patients with overt diabetic nephropathy (DN) were enrolled in this study. The values of BP variability were obtained from 24 h ambulatory BP monitoring. **Results:** As a result of a comprehensive examination of patients and statistical processing of data, it was found that in the group of patients with DN the level of albumin to creatinine in the urine was significantly higher than in the group of patients with non-DN (4.08 ± 6.15) mg/g and (1.43 ± 2.94) mg/g, respectively, significantly higher than triglycerides compared with the group of non-DN (2.72 ± 1.53) mmol/L and (1.55 ± 1.14) mmol/L, respectively. An interesting regularity was that patients with non-DN had a tendency to drop their BP in the morning, and thus the morning rise in systolic BP (SBP) and diastolic BP (DBP) in this group of patients was negative (−4.88 ± 21.35) mm Hg and (−70.88 ± 14.35) mm Hg, respectively. In patients with DN, these parameters exceed the norm and make up for SBP (66.02 ± 21.48) mm Hg and for DBP (57.13 ± 12.75) mm Hg. The mean daily diastolic pressure in the group of patients with DN was significantly higher than in the group of non-DN ([124.50 ± 33.78] and [111.50 ± 11.5] mm Hg, $P < 0.05$), the SBP variability was significantly lower than in the group with non-DN (13.67 ± 2.99) mm Hg and (16.35 ± 3.69) mm Hg, respectively. Severe disturbances in the circadian rhythm of arterial pressure with low BP variability, high rates, and rates of morning ascent of SBP and DBP were characteristic of the group of DN. **Conclusions:** In patients with DN with comparable values of glomerular filtration rate, higher albumin to creatinine ratio, lipid profile disorders were significantly more frequent than in the group of patients with the non-diabetic renal disease. The mean daily diastolic pressure in the group of patients with DN was significantly higher than in the group of non-DN ([124.50 ± 33.78] and [111.50 ± 11.5] mm Hg, $P < 0.05$), the SBP variability was significantly lower than in the group with non-DN (13.67 ± 2.99) mm Hg and (16.35 ± 3.69) mm Hg, respectively.

Key words: 24 h ambulatory blood pressure, blood pressure variability, diabetic nephropathy, glycemic control, glycated hemoglobin, hypertension

INTRODUCTION

The increase of blood pressure (BP) in diabetic of the 2nd type is associated, in most cases, with the presence of diabetic nephropathy (DN), and the basis of hypertension is damage to the renal parenchyma, accompanied by the formation of nodular or diffusive

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glomerulosclerosis.[1] 80% of patients with DN have a rise of BP even in the early stage of nephropathy, which is a significant cause of cardiovascular mortality in this group of patients.[2] The reason of damage to the glomerulus of the patients with the 2nd type of diabetes is progressive microangiopathy, which leads to a disturbance of autoregulation of the intrarenal pressure by the kidney, and, as a result of this, the development of microalbuminuria and increased pressure in the glomerulus. The increase in arterial pressure of these patients is secondary compared with microalbuminuria and with increased intra-glomerular pressure, and it occurs under the influence of two mechanisms:

1. Increase in the amount of metabolic sodium and the volume of extracellular fluid
2. Increased sensitivity of resistant vessels to noradrenaline and angiotensin II.[1]

According to the data of the diabetes control and complications trial research group (DCCT, 2004), the role of metabolic disorders, mainly hyperglycemia, in the pathogenesis of DN has been convincingly proved.[2] Such concept as "without diabetes, there are no diabetic complications" is the basis in understanding the nature of complications of diabetes, includes nephropathy. However, in a number of researches we can see that in the process of the development of DN, the direct dependence of the progression of nephropathy from the level of compensation of carbohydrate metabolism is lost.[3] It seems that the pathological process in the kidney gains its independent value.[4] At the same time, a growing number of research results show the importance of dyslipidemia in the genesis of diabetic kidney damage already at the early stages of the development of diabetes. The system of accounting for standard risk factors is used when forming a risk group, whose role has been convincingly proven in different studies such as sex, age, body mass index, serum urine nitrogen, the values of the albumin/urine creatinine index, and BP indicators. However, there is still no explanation for the differences in the clinical features of kidney damage between a group of patients with diabetic and non-DN or differences between subgroups with different levels of glycated hemoglobin (HbA1c).[5] The adoption of a screening program for DN in the framework of the Saint Vincent Declaration is a significant breakthrough in the diagnosis of the preclinical stage of nephropathy. According to this program, the main laboratory criterion for early DN stage is microalbuminuria, and according to the latest recommendations the albumin/creatinine ratio in urine.[6] An urgent task in diabetology remains the evaluation of the functional state of the structures of the medullary substance of the kidney, and the determination of their concentration ability.[7] This is due to the fact that standard methods of assessing of kidney function, which is used in non DNs, are not informative in diabetes. It is determined that the basis for the prevention and treatment of DN is the achievement and maintenance of stable metabolic compensation of violations not only of carbohydrate but also of lipid metabolism.[8] Subsequent studies of the population as a whole[9] and hypertensive cohorts[10] have generally confirmed, that increased night BP was an independent predictor of a high level of cardiovascular complications, especially in patients with DN.[11,12] It is considered that arterial pressure physiologically is regulated by various complex factors (e.g., environmental stimulation, genetic factors, autonomic nervous system, increased activity of the renin-angiotensin-aldosterone system, endothelial dysfunction, aging, prolonged smoking, excessive alcohol ingestion, obesity, caloric overload, emotions, and inflammation).[5,8,13] However, the correlation between these factors and their effect on hypertension and BP variability is not studied sufficiently nowadays.[14]

The indicants of BP variability were recognized as independent predictors of cardiovascular cases, which are independent of indicants of mean arterial pressure.[14] It was proved that the indices of the variability of arterial pressure depend on the activity of the sympathetic nervous system and changes in arterial extensibility.[10] Therefore, the hyperactivity of the sympathetic nervous system, the violation of baroreflex sensitivity, and arterial stiffness inherent to diabetes mellitus - all these factors contribute to the increase in the variability of arterial BP (ABP), thereby aggravating the damage of target organs,[14] and increase the incidence and severity of cardiovascular cases.[9]

However, nowadays the peculiarities of the ABP variability in patients with DN have been studied extremely little. In this research, we have analyzed 24-h BP monitoring (BPM) of patients with diabetic and non DNs to clarify the peculiarities of pressure profiles in these patient groups and identifying factors that can potentially affect the BP variability of patients with DN.

The objective

The objective is, on the one hand, to estimate in a comparative aspect the relationship between the daily ABP rhythm, and, on the other hand, the renal function of patients with III Stage of diabetic and non-diabetic etiology.

Research tasks

1. To study the peculiarities of the daily profile of arterial pressure of patients with III Stage of chronic kidney disease (CKD) of diabetic and non-diabetic etiology.
2. To determine the factors those most strongly affect the indicators of the daily profile of BP of patients with III Stage of CKD of diabetic and non-diabetic etiology.

MATERIALS AND METHODS OF RESEARCH

This study includes patients aged ≥18 years, with essential hypertension of 1–2°, diagnosed in a hospital based on

criteria of hypertension according to the recommendations of the Ukrainian Cardiology Association (2012) and the clinical recommendations of the European Society of Hypertension (2013)[9] and CKD of diabetic and non-diabetic etiology of III Stage (according to the NKF K/DOQI classification, 2012, and the classification of the Ukrainian Association of Nephrologists [2013]).[15] The functional state of the kidneys was assessed by the glomerular filtration rate according to the formula CKD-epidemiology, as well as the ratio of albumin to creatinine in urine. 60 patients were examined: 30 patients with DN and 30 CKD patients with non-diabetic etiology (24 patients with chronic glomerulonephritis and 6 patients with chronic pyelonephritis). The median age of patients was approximately 48.6 ± 5.1 years. The 24-h BPM was carried out on the apparatus BAT41-2 with an oscillometric method for 24 h with a measurement interval of 15/30 min day/night. All patients were instructed about the need to fill individual diaries, to record the time of falling asleep, the morning rise and other activities. Hence, the values of "daily" and "night" indicators of BP and pulse of patients were recorded in accordance with the time of wakefulness and sleep noted in their diaries. If patients had more than 20% of the errors in the measurement of BP or the absence of measurement values of ABP for more than 2 h in a row, then they should have daily BPM over the next 24 h. Values of systolic BP (SBP) >240 or <70 mm Hg and diastolic BP (DBP) >150 or <40 mm Hg. st. were removed from the profile as technical artifacts.

Exclusion criteria were: Patients who undergo dialysis or patients after kidney transplantation, patients with clinically significant heart disease (heart failure III-IV Stage according to NYHA, GB III, and myocardial infarction), stroke, stenosis of the renal arteries, hepatic dysfunction, pheochromocytoma, thyrotoxicosis, and hyperaldosteronism.

All patients with DN received standard therapy in the form of a combination of metformin and glimepiride/glibenclamide, while dieting and the scheme of physical activity.

According to the recommendations of the Ukrainian Association of Cardiologists Treatment of arterial hypertension included α- and β-blockers, angiotensin-converting enzyme or sartans, calcium channel blockers, and diuretics. Clinical examination of patients included collection of complaints, anamnesis, objective examination data, and biochemical and instrumental survey methods.

According to the level of HbA1c, patients with DN were divided into two subgroups: 1 Group (HbA1c <7%) and 2 Group (HbA1c ≥7%). The data, which characterized the clinical and laboratory indicators of patients with CKD III Stage of diabetic and non-diabetic etiology are presented in Table 1.

Statistical processing of data was carried out with the help of the software package Statistica 6.0 for Windows. The values of the indicators were: Median (Me), 25% - was the lowest quartile and 75% - was the upper quartile (IU [25% and 75%]). Statistical differences were determined at a significance level of $P < 0.05$. The Mann–Whitney U-test was used for unrelated samples, and the Wilcoxon criterion for linked samples was used to compare the indices in this two groups.

RESULTS AND DISCUSSION

In the results of the study made in the group of DN patients, there was found the certain majority of patients with "non-dipper" (25 patients) and "night-peaker" (3 patients) day rhythms comparing to the group of non-DN patients (21 and 0 correspondently). In the same group, the level of albumins in relation to creatinine in urine was accurately 185.3% higher than in the group of non-DN patients. Furthermore, in the group of DN patients there was found the accurate increase of triglycerides level comparing to the group of non-DN (2.72 ± 1.53 mmol/l or 1.55 ± 1.14 mmol/l correspondently). Estimating the indexes of daily BPM there draws attention the fact, that accurate differences first of all related to exponents of diastolic pressure - in such a way the level of average daily DBP in the DN patients group was certainly 11.7% higher than in the non-DN group. There was an interesting dependency that in patients with a non-DN there was found the tendency to the drop of BP in the morning instead of its rise as it should be within the norm, so the rate of SBP and DBP morning rise in this patient's group was negative. However, for the DN patients these exponents are above the norm and make (66.02 ± 21.48) mm Hg for SBP and (57.13 ± 12.75) mm Hg for DBP; nevertheless, this exponent will not be informative enough for the patients with a monotonous daily BP profile. Joint studying of the rate of morning rise and speed of morning rise (SMR) of BP gives the more full characteristics. As the SMR is an integral exponent and depends only on the rate and time of BP increase, it is not influenced by neither daily rhythm nor absolute values of BP which are not always maximum in the morning. Exponent of the speed of morning increase of SBP and DBP in diabetic and non-DN patients had the significant differences, exponents for SBP were accurately 121.1% higher in the DN group, and 173.4% more for DBP in the non-DN group. This phenomenon has the great clinical meaning, as in the period from 6:00 to 12:00 there is noted a leap of BP, increase of vascular tone which coincide with neurohumoral changes. At this time, there is also noted the only period during the day when there is defined the increase of thrombocyte aggregation, hypercoagulability, and reduction of fibrinolytic activity. In the morning, there is noted the physiological activation of sympathoadrenal and renin-angiotensin-aldosterone systems, increase of sympathetic and a decrease of parasympathetic activity. In such a way, the significant increase of BP in the morning in conjunction with neurohumoral changes may be the trigger of the range of well-known processes non-favorable regarding the cardiovascular complications. In such a way, the high rate and speed of BP increase in the early morning time are the independent risk factor for the left ventricular myocardial hypertrophy.

Table 1: Clinico-laboratorial findings in patients with III Stage CKD of diabetic and non-diabetic etiology

Index	Diabetic nephropathy	Non-diabetic nephropathy
Number of patients	30	30
Age	61.58±6.14	58.68±12.75
Sex (men/women)	38/22	30/21
Smokers	22 (36.8%)	16 (31.4)
Duration of diabetes (months)	114	-
Height-and-weight index (kg/m^2)	28.24±2.15	23.44±3.23
Hemoglobin (g/l)	105.92±11.16	107.02±27.84
Hematocrit	0.43±0.04	0.42±0.08
Fasting glucose (mmol/l)	11.44±1.73	5.01±0.6*
HbA1c (%)	8.76±0.78	5.55±1.45*
BUN (mmol/l)	4.97±0.77	5.51±1.05
Creatinine (mmol/l)	198.75±12.08	237.30±14.05
Albumins/creatinine of urine	4.08±6.15	1.43±2.94*
GRF (ml/[min*1.73 m^3])	31.96±3.55	22.53±3.05
Total cholesterol (mmol/l)	4.485±2.09	4.47±1.17
Triglycerides (mmol/l)	2.72±1.53	1.55±1.14*
Calcium (mmol/l)	2.45±0.11	2.09±0.13
Phosphorus (mmol/l)	1.13±0.17	1.23±0.54
SBP 24 h., mm Hg	140.83±10.83	139.12±18.90
Maximum day DBP, mm Hg	124.50±33.78	111.5000±11.5*
RMR in SBP, mm Hg	66.02±21.48	−54.88±21.35*
RMR in DBP, mm Hg	57.13±12.75	−70.8750±14.35*
SMR in SBP, mm Hg	54.83±2.48	24.8±2.36*
SMR in DBP, mm Hg	10.83±2.69	29.61±8.24*
Variability of SBP per 24 h, mm Hg	12.23±3.66	10.74±5.26*
Variability of DBP per 24 h, mm Hg	8.02±1.93	8.30±2.40
Day variability of SBP, mm Hg	20.71±6.34	20.5±5.26
Day variability of DBP, mm Hg	15.81±2.69	18.37±2.4
Night variability of SBP, mm Hg	13.67±2.99	16.35±3.69*
Night variability of DBP, mm Hg	12.25±2.41	14.38±3.09
Number of non-dipper patients	25 (83%)	21 (70%)*
Number of night-peaker patients	3 (10%)	0*

*Possibility of deviation in indexes comparing to the group of diabetic nephropathy patients ($P < 0.05$). HbA1c: Glycated hemoglobin, BUN: Blood urea nitrogen, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, RMR: Rate of morning rise, CKD: Chronic kidney disease, SMR: Speed of morning rise

Besides, in the DN patients group, the exponents of night variability of SBP were accurately 19.6% lower than in the non-DN patient's group.

CONCLUSIONS

In the DN patients, there was found the tendency to increase of DBP. It is shown that alongside with the comparable reduction of the kidneys operant behavior the DN hypertension differs from the DN hypertension for the higher exponents of pressure load, frequency, and severity of disorder of daily BP rhythm with the lower values of variability and higher rate and speed of morning BP rise.

With the equal exponents of GRF is glomerulus filtration rate in DN patients, the level of urinary albumins/creatinine is significantly higher than in the non-diabetic kidney damage patients group.

DN patients have the more obvious disorders of triglycerides level in the lipid pattern than in the non-diabetic kidney damage group with the equal GRF values.

Prospective of the further research

There is expected to analyze the influence of the DPP-IV (sitagliptin) drug on the kidneys and liver function, lipid panel, and albumins/creatinine correlation of urine in patients with CKD of the III Stage of diabetic etiology.

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