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Interrelation between disorder of melatonin-forming function of epiphysis and dyslipidemia in patients with chronic kidney disease of V stage treated by hemodialysis

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The results of a number of studies have proved the relationship between the functional state of the pineal gland and renal function. However, violations of the melatonin-forming function of the epiphysis (MFE) in patients with chronic kidney disease (CKD) undergoing hemodialysis (HD) and its relationship with dyslipidemia in this patient population is a poorly understood issue.
The objective: **to analyze disorders of MFE and blood lipid spectrum in patients with CKD of 5 stage treated with HD and to determine the relationship of epiphysis dysfunction with dyslipidemia.**
Materials and methods**. 130 people (50% of men) aged 58.5 were surveyed [43; 66] which are on permanent hemodialysis treatment. Control passed 20 healthy individuals. The determination of day and night level of melatonin (MT) in saliva was conducted, based on the level of which patients (treated with HD) were divided into two groups: group I – 110 patients with impaired MFE, group II – 20 patients with normal MFE. Clinical and laboratory researches were carried out for all patients: general and biochemical analyzes of blood with determination of cholesterol level and its fractions, measurements of office blood pressure (BP) were made.**
Results**. Significant prevalence of MFE disorders in patients with CKD of 5 stage treated with hemodialysis and its relationship with blood lipid spectrum were found. The level of total cholesterol (TC), triglycerides (TG) and low density lipoproteins (LDL) in patients with impaired MFE was higher by 26.4% (p<0.05), 16.7% (p<0.05) and 22 , 6% (p= 0.03) according to the outcome of the comparison group patients. The level of high-density lipoprotein (HDL) of the main group is lower by 11.8% compared to the group with preserved MFE. The data obtained indicate the relationship of MFE disorders with the duration of RRT treatment, the duration of arterial hypertension, the age of patients, and their effect on the lipid spectrum of patients with CKD of 5 stage treated with hemodialysis. Night feedback correlation of MT with TC level was established (r=-0.256; p<0.05). Correlation analysis confirms that a decrease in MT at night is combined with an increase of TG level (r=-0.272; p<0.05) in the blood of patients. The feedback correlation of night (r=-0.347; p=0.03) and daytime level (r=-0.198; p<0.05) of MT with LDL level and positive relationships between MT in daytime (r=0.27; p=0.03) and the night period (r=0.331; p=0.02) with HDL levels.**
Conclusion**. For patients with CKD of 5 stage undergoing hemodialysis, there is a frequent violation of MFE (84.6%) and significant disorders of lipid metabolism (58%). Analysis of the lipid metabolism study revealed more profound abnormalities in the form of an increased concentration of TC and all its fractions in patients with impaired MFE, which may indicate a connection between epiphysis dysfunction and lipid metabolism in patients with RRT. In patients with hemodialysis, melatonin-forming dysfunction and disorders of lipid metabolism are age-dependent and are determined by the duration of RRT, the duration of hypertension, the level of hemoglobin.**
We have identified a relationship between the deterioration of lipid metabolism on the background of deeper disturbance of MFE by daytime and nighttime MT.
Key words: *chronic kidney disease, hemodialysis, melatonin, melatonin-forming function of the epiphysis, dyslipidemia, total cholesterol, triglycerides, low-density lipoproteins, high-density lipoproteins, coefficient of atherogenicity.*

Взаємозв'язок порушення мелатонінутворювальної функції епіфізу та дисліпідемії у хворих на хронічну хворобу нирок V стадії, що лікуються гемодіалізом

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Результати низки наукових досліджень довели наявність взаємозв'язку між функціональним станом епіфізу та функцією нирок. Проте порушення мелатонінутворювальної функції епіфізу (МФЕ) у хворих на хронічну хворобу нирок (ХХН), що лікуються гемодіалізом (ГД), та її зв'язок з дисліпідемією у даної когорти пацієнтів є маловивченим питанням.
Мета дослідження: аналіз порушень МФЕ та ліпідного спектра крові у хворих на ХХН V стадії, що лікуються ГД, та визначення взаємозв'язку дисфункції епіфізу з дисліпідемією.
Матеріали та методи. Обстежено 130 осіб (50% чоловіки) віком 58,5 [43; 66] року, що перебувають на постійному лікуванні ГД. До контрольної групи увійшли 20 здорових осіб. Проведено визначення денного та нічного рівня мелатоніну (МТ) у слині, на підставі чого хворих, що лікуються ГД, розподілили на дві групи: група I – 110 хворих з порушеною МФЕ, група II – 20 пацієнтів з нормальною МФЕ. Усім хворим проведені клініко-лабораторні дослідження: загальний та біохімічний аналізи крові з визначенням рівня холестерину та його фракцій, проведено вимірювання офісного артеріального тиску (АТ).
Результати. Виявлено значну поширеність порушення МФЕ у хворих на ХХН V стадії, що лікуються ГД, та її взаємозв'язок з ліпідним спектром крові. Рівень загального холестерину (ЗХ), тригліцеридів (ТГ) та ліпопротеїдів низької щільності (ЛПНЩ) у пацієнтів з порушеною МФЕ вищий на 26,4% (p<0,05), 16,7% (p<0,05) та 22,6% (p=0,03) відповідно щодо пацієнтів групи порівняння. Рівень ліпопротеїдів високої щільності (ЛПВЩ) основної групи нижчий на 11,8% за аналогічний показник групи зі збереженою МФЕ. Отримані дані свідчать про взаємозв'язок порушення МФЕ з тривалістю нирково-замісної терапії (НЗТ), стажем артеріальної гіпертензії, віком хворих та їхнього впливу на ліпідний спектр крові хворих на ХХН V стадії, що лікуються ГД. Встановлено зворотній кореляційний зв'язок нічного рівня МТ з рівнем ЗХ (r=-0,256; p<0,05). Кореляційний аналіз підтверджує, що зниження нічного рівня МТ поєднується з підвищенням рівня ТГ (r=-0,272; p<0,05) у крові хворих. Встановлений зворотній кореляційний зв'язок нічного (r=-0,347; p=0,03) та денного рівня (r=-0,198; p<0,05) МТ з рівнем ЛПНЩ та позитивні зв'язки між рівнем МТ у денний (r=0,27; p=0,03) та нічний період (r=0,331; p=0,02) з рівнями ЛПВЩ.
Заключення. Для хворих на хронічну хворобу нирок V стадії, що лікуються гемодіалізом, притаманне часте порушення мелатонінутворювальної функції епіфізу (МФЕ) (84,6%) та значні порушення ліпідного обміну (58%). Аналіз результатів дослідження ліпідного метаболізму продемонстрував більш глибокі його порушення у вигляді підвищеної концентрації загального холестерину та

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всіх його фракцій у пацієнтів з порушеною МФЕ, що може свідчити про зв'язок дисфункції епіфізу з ліпідним обміном у пацієнтів на нирково-замісній терапії (НЗТ). У хворих на гемодіалізі мелатонінутворювальна дисфункція та порушення ліпідного обміну мають вік-залежний характер та детермінуються тривалістю НЗТ, стажем артеріальної гіпертензії, рівнем гемоглобіну.
Було визначено взаємозв'язок погіршення ліпідного обміну на тлі більш глибокого порушення МФЕ за денним та нічним рівнем мелатоніну.
Ключові слова: *хронічна хвороба нирок, гемодіаліз, мелатонін, мелатонінутворювальна функція епіфізу, дисліпідемія, загальний холестерин, тригліцериди, ліпопротеїди низької щільності, ліпопротеїди високої щільності, коефіцієнт атерогенності.*

Взаимосвязь нарушения мелатонинобразовательной функции эпифиза и дислипидемии у больных хронической болезнью почек V стадии, которые лечатся гемодиализом

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Результаты ряда исследований доказали наличие взаимосвязи между функциональным состоянием эпифиза и функцией почек. Однако нарушения мелатонинобразовательной функции эпифиза (МФЭ) у больных хронической болезнью почек (ХБП), находящихся на гемодиализе (ГД), и ее связь с дислипидемией в данной популяции пациентов является малоизученным вопросом.
Цель исследования: анализ нарушения МФЭ и липидный спектр крови у больных ХБП V стадии, которые лечатся ГД, и определение взаимосвязи дисфункции эпифиза с дислипидемией.
Материалы и методы. Обследованы 130 человек (50% из них – мужчины) в возрасте 58,5 [43; 66] года, которые находятся на постоянном лечении ГД. В группу контроля вошли 20 здоровых лиц. Проведено определение дневного и ночного уровня мелатонина (МТ) в слюне, на основании чего, больных на ГД разделили на две группы: группа I – 110 больных с нарушенной МФЭ, группа II – 20 пациентов с нормальной МФЭ. Всем больным проведены клинико-лабораторные исследования: общий и биохимический анализы крови с определением уровня холестерина и его фракций, проведено измерение офисного артериального давления (АД).
Результаты. Обнаружена значительная распространенность нарушения МФЭ у больных ХБП V стадии, которые лечатся ГД, и ее взаимосвязь с липидным спектром крови. Уровень общего холестерина (ОХ), триглицеридов (ТГ) и липопротеидов низкой плотности (ЛПНП) у пациентов с нарушенной МФЭ выше на 26,4% ($p<0,05$), 16,7% ($p<0,05$) и 22,6% ($p=0,03$) соответственно по сравнению с пациентами группы сравнения. Уровень липопротеидов высокой плотности (ЛПВП) основной группы ниже на 11,8% аналогичного показателя группы с сохраненной МФЭ. Полученные данные свидетельствуют о взаимосвязи нарушения МФЭ с продолжительностью лечения почечно-заместительной терапии (ПЗТ), стажем артериальной гипертензии, возрастом больных и их влияние на липидный спектр крови больных ХБП V стадии, которые лечатся ГД. Установлена обратная корреляционная связь ночного уровня МТ с уровнем ОХ ($r=-0,256$; $p<0,05$). Корреляционный анализ подтверждает, что снижение ночного уровня МТ сочетается с ростом уровня ТГ ($r=-0,272$; $p<0,05$) в крови больных. Установлена обратная корреляционная связь ночного ($r=-0,347$; $p=0,03$) и дневного уровня ($r=-0,198$; $p<0,05$) МТ с уровнем ЛПНП и положительные связи между уровнем МТ в дневное ($r=0,27$; $p=0,03$) и ночное время ($r=0,331$; $p=0,02$) с уровнями ЛПВП.
Заключение. Для больных хронической болезнью почек V стадии, находящихся на лечении гемодиализом, присуще частое нарушение мелатонинобразовательной функции эпифиза (МФЭ) (84,6%) и значительные нарушения липидного обмена (58%). Анализ результатов исследования липидного метаболизма продемонстрировал более глубокие его нарушения в виде повышенной концентрации общего холестерина и всех его фракций у пациентов с нарушенной МФЭ, что может свидетельствовать о связи дисфункции эпифиза с липидным обменом у больных на почечно-заместительной терапии (ПЗТ). У больных на гемодиализе мелатонинобразовательная дисфункция и нарушения липидного обмена носят возраст-зависимый характер и детерминируются длительностью ПЗТ, стажем артериальной гипертензии, уровнем гемоглобина.
Была определена взаимосвязь ухудшения липидного обмена на фоне более глубокого нарушения МФЭ по дневному и ночному уровню мелатонина.
Ключевые слова: *хроническая болезнь почек, гемодиализ, мелатонин, мелатонинобразовательная функция эпифиза, дислипидемия, общий холестерин, триглицериды, липопротеиды низкой плотности, липопротеиды высокой плотности, коэффициент атерогенности.*

CKD is one of the main problems of modern nephrology, because every year there is a clear tendency for the growth of people with this pathology. The high level of care delivery and the improvement of renal replacement therapy (RRT) do not provide a complete correction of the hemodynamic and metabolic processes associated with renal function loss [14].

The main reason of death for patients with CKD is cardiovascular disease (CVD), which accounts for more than 48% of the overall fatality rate. The presence of dyslipidemia is a key factor in the development and progression of CKD and CVD. Thus, in the analysis of blood lipid spectrum, dyslipidemic manifestations are observed in 35–70% of patients with CKD [6]. As is known in patients with RRT, atherosclerosis is the main cause of CVD and cerebrovascular disease, which is detected in 64% of cases. In CKD with an increase in uremia, atherosclerotic process in the coronary vessels leads to damage of the vessels of the brain and weakens the compensatory capacity of cerebral circulation, provoking the progression of cerebral ischemia [11].

The spectrum of dyslipidemia in patients with CKD includes all classes of lipoproteins and shows significant variations depending on the stage of the disease. Thus, triglycerides (TG) of plasma begin to increase in the early stages of CKD and reach the highest concentration in patients on dialysis [3, 5]. The accumulation of TG is due to the low catabolic rate, which is explained by a decrease in the activity of two lipases - lipoprotein lipase (LPL) and hepatic triglyceride lipase. The decrease of lipase activity in patients with RRT is due to the decrease in the enzyme pool, which is induced by frequent heparinization of patients with hemodialysis and secondary hyperparathyroidism [4].

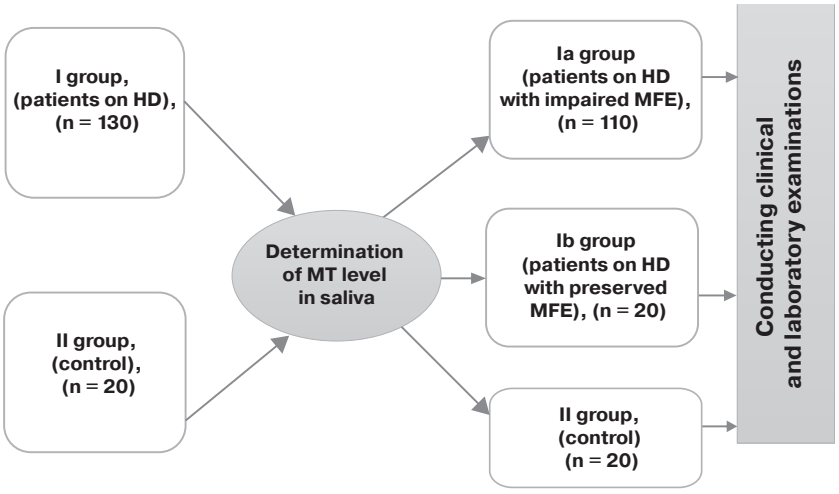
It is believed that the greatest damage to the renal glomeruli is due to the high content of total cholesterol (CH) in the serum. In experimental animal studies, the hypercholesterol diet leads to the appearance of lipid deposits in the glomerulus, monocytic infiltration, hypercellularity of mesangium, and an increase in mesangial matrix. Hypercholesterolemia leads to the development of proteinuria, uremia, glomerulosclerosis and an increase in intracellular pressure. Clinical studies have shown that hyperlipidemia in any nephropathy accelerates the progression of renal failure [2].

Quite often, patients with CKD have a decrease in high density lipoproteins (HDL). This is facilitated by the low concentration and activity of lecithin-cholesterol-acyltransferase, which leads to impaired synthesis, transport of HDL and their rapid cleavage. Hypoalbuminemia, which is often observed in terminal renal failure, also helps to reduce the content of HDLs that have prooxidant and anti-inflammatory properties [16].

Low density lipoproteins (LDLs) are formed during lipolysis and have high proatrogenic properties [18]. Mesangial cells have receptors for LDL, through which their binding and oxidize occurs, resulting in the formation of cytokines that stimulate mesangial proliferation and glomerulosclerosis [1].

Hypolipidemic therapy in patients with CKD is one of the most important elements of a nephroprotective strategy that not only prevents but significantly slows the progression of nephrosclerosis. The need for correction of lipid disorders in patients with CKD is evident already in the early stages [17]. However, in our time only 16% of patients with CKD receive hypolipidemic drugs and only in 50% of them, the level of total cholesterol is reduced to normal values [14].

In recent years, many studies have identified the role of pineal hormone (melatonin) in the regulation of lipid metabolism in organs and tissues [5]. It is proved that the development of stress response is accompanied by changes in all types of metabolism in the body, and melatonin (MT) is one of the leading components of the body's antistress system. Multiple reception of MT in chronic stress has been shown to prevent the development of lipid disorders [6]. Studies on rats have shown that modeling of acute stress leads to disruption of plasma content: TC by 54.4% ($p<0.001$), TG – by 38.0% ($p<0.01$), LDL – by 61.9% ($p<0.001$).



Pic. 1. The research design

Experimental studies have demonstrated the regulatory effect of MT on lipid metabolism due to its action on lipoprotein lipase activity, decreased lipolysis, increased LDL receptor activity, inhibiting the absorption of cholesterol from the intestine, and conversion of cholesterol to bile acids [9, 15].

The role of MT in the correction of dyslipidemia in many countries is no longer discussed, its action is mediated through antioxidant potentials and protection against the negative effects of proinflammatory cytokines [10, 13]. However, the melatonin-forming function of the epiphysis (MFE) and its association with the blood lipid spectrum in hemodialysis patients remains a poorly understood and important issue of nephrology, which needs further investigation.

The objective: to analyze MFE and blood lipid spectrum in patients with CKD of 5 stage treated with hemodialysis and to determine the relationship of epiphysis dysfunction with dyslipidemia.

MATERIALS AND METHODS

The results of clinical evaluation of MFE and blood lipid spectrum of 130 patients (men – 65, women – 65) with CKD of 5 stage who were undergoing hemodialysis treatment at the municipal non-profit enterprise named «Kyiv City Center of Nephrology and Dialysis» were analyzed. The average duration of RRT treatment was 11 [6; 13] years. All hemodialysis sessions were performed on an arterio – venous fistula.

20 healthy individuals (males –10, females – 10) were also included to the study and they were considered as a control group.

Exclusion criteria: refusal of patient to participate in the study, acute history of cerebral circulation, chronic heart failure III–IV functional class(according NYHA classification), acute infectious processes of any etiology diagnosed during the last 3 months, hemoglobin level <70 g/l, history of kidney transplantation, liver cirrhosis of any etiology, oncological diseases, parathyroid

Table 1

Clinical and demographic characteristics of patients on HD

Indicators	Patient, n=130
Age, years	58,5 [43; 66]
BMI, kg/m^2	21,3 [20,1; 22,3]
Waist volume, cm	88 [79; 92]
Office average SBP, mm Hg	150 [140; 160]
Office average DBP, mm Hg	90 [80; 92]
Hemoglobin, g/l	85 [77; 92]
Ferritin, ng/ml	311,4 [172,6; 505,4]
Saturation of transferrin, %	32 [22,8; 36,3]
TC, mmol/L	4,31 [2,93; 5,62]
TG, mmol/l	1,52 [1,24; 1,77]
CRP, g/l	17 [8; 23]
Uric acid, mkmol/l	399 [372; 428]
Albumin, g/l	35 [32; 37]
iPTH, pg/ml	530 [313; 614]
P, mmol/l	1,88 [1,55; 2,03]
Ca^{2+}, mmol/l	2,12 [1,98; 2,25]

Notes: BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, P – phosphorus, Ca2+ – calcium, iPTH – intact parathormone.

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Table 2

Indicators of blood lipid spectrum of the examined groups

Indicator	I group, n=130	II group, n=20	P_{1-2}
TC	4,31 [2,93; 5,62]	4,25 [3,85; 4,65]	0,9
TG	1,52 [1,24; 1,77]	1,16 [0,89; 1,25]	<0,001
LDL	1,61 [1,25; 2,25]	2,39 [2,15; 2,58]	<0,001
HDL	0,92 [0,8; 1,45]	1,17 [0,99; 1,31]	0,04
CA	3,14 [1,61; 5,57]	2,71 [2,13; 3,39]	0,04

Table 3

Clinical-demographic characteristics of patients on HD

Indicators	Ib group, n=110	Ia group, n=20	p
Sex m, abs. (%)	57 (52%)	8 (40%)	0,04
Age, years	59 [43; 67]	54 [48,5; 61,5]	0,13
Duration of treatment on HD, years	11,5 [6; 14]	7,5 [4,5; 11]	0,01
Duration of hypertension	14,5 [8; 17]	10 [6; 14]	0,04
BMI, kg/m^2	21,43 [20,3; 22,8]	20 [19,84; 21,21]	0,01
Waist volume, cm	89 [80; 93]	80 [77,5; 90]	0,04
Office average SBP, mm Hg	158 [142; 162]	134 [130; 137]	<0,001
Office average DBP, mm Hg	90 [80; 96]	80 [70; 87]	<0,001
Hemoglobin, g/l	85 [76; 92]	85,5 [80,5; 94]	0,3
Saturation of transferrin, %	32 [22,6; 36,3]	32,35 [27,94; 36,05]	0,9
CRP, g/l	18 [12; 24]	5,5 [4,5; 8]	<0,001
Albumin, g/l	34 [32; 37]	36 [35; 37]	0,006
iPTH, pg/ml	550 [325; 621]	510 [243; 581]	0,26
P, mmol/l	1,88 [1,57; 2,03]	1,78 [1,46; 2,11]	0,46
Ca^{2+}, mmol/l	2,12 [1,98; 2,23]	2,17 [2,04; 2,29]	0,4

adenoma, alcohol dependence, endocrinological diseases, rheumatological diseases.

Patient safety rules, patient rights, moral and ethical standards were respected in accordance with the GSP guidelines (1996), the Council of Europe Convention on Human Rights and Biomedicine, Declaration of Helsinki of the World Health Association about Ethical Principles for medical research involving human subjects (1964–2000), according to the order of the MoH of Ukraine № 281, № 523, and the code of ethics of the scientist of Ukraine (2009) during the work. All patients provided informed written consent to participate in the study. The research protocol was approved by the Commission for Bioethical Expertise and Ethics of Scientific Research at the O.O. Bogomolets National medical university.

For all patients were researched a level of creatinine to calculate glomerular filtration rates, serum levels of total calcium, phosphorus, hemoglobin, albumin, total protein, parathyroid hormone (PTH), total iron, ferritin, transferrin, % TSAT, the level of sodium, potassium, C-reactive protein (CRP) and day and night levels of MT.

Blood lipid spectrum (total cholesterol (TC), triglycerides (TG), high-density lipoproteins (HDL), low-density lipoproteins (LDL), coefficient of atherogenicity (CA)) were determined on a Vitalab Flexor Junior analyzer.

The concentration of MT was determined by enzyme immunoassay using the Human MS (Melatonin Sulfate) ELISA Kit, Elabscience. Sampling was carried out during the day and night, preferably in spring and summer, with a minimum illumination of 30 lx. Non-stimulated saliva was used, which was collected into an 1 ml Epindorf capsule, which was immediately frozen and stored at –20 °C. The research design is presented in pic. 1.

Office blood pressure (BP) measurements were performed before, during and after the HD session with the analysis of systolic BP (SBP), diastolic BP (DBP), pulse BP (PBP). The average blood pressure ≤135/85 mm Hg was taken as the target blood pressure level in the morning and evening for 6 non-dialysis days in a two-week period.

All patients with CKD received standard antihypertensive therapy. Patients from the main group and the control group were not treated with lipid-lowering drugs before and during the examination.

Demographic data and clinical characteristics of patients included in the study on HD are shown in Table 1.

Among patients with CKD of 5 stage, the prevalence of middle-aged patients (44–60 years) was 39%, the proportion of elderly patients (60–75 years) was 32%, the lowest number was of young patients (25–44 years) – 29%.

Statistical results were processed using Microsoft Office Excel 2010 and IBM Statistics Spss 22. Continuous data are represented by median and quarter-to-quarter swing (Me [Q25–Q75]), categorical – expressed as a percentage (%). Student's test was used to compare normally distributed data, and non-parametric Mann–Whitney (U-test) was used for inconsistency of the law of normal distribution. Correlation was determined by Pearson's (r) and Spearman's methods depending on the distribution of indicators.

RESULTS OF THE STUDY AND THEIR DISCUSSION

More significant MFE abnormalities in patients on HD are revealed according to analyzing the incidence of MFE disorders in patients with CKD of 5 stage treated with hemodialysis (HD) and practically healthy individuals. In patients with RRT, the level of MT at day and night is lower than in the control group (1.9 [1.5; 2.9] pg/ml, respectively, against 3.85 [3.55; 4.15] pg/ml

Table 4

Indicators of the lipid spectrum of blood of patients of CKD of 5 stage on HD (main group and comparison group)

Indicator	Ib group, n=20	Ia group, n=110	P_{1-2}
TC	3,37 [2,37; 5,26]	4,4 [3,1; 5,7]	< 0,05
TG	1,3 [1,2; 1,4]	1,56 [1,25; 1,78]	< 0,05
LDL	1,27 [1,14; 1,82]	1,64 [1,27; 2,26]	0,03
HDL	1,02 [0,94; 1,52]	0,9 [0,79; 1,44]	0,03
CA	2,04 [1,38; 3,17]	3,49 [1,72; 5,77]	0,01

Table 5

Lipid profile of the blood depending on the nosological form

Indicator	Hypertensive nephropathy, n=38	Glomerulonephritis, n=37	Tubulointerstitial nephritis, n=9	Gouty nephropathy, n=16	Polycystic disease, n=5	Urolithiasis, n=5
TC	4,81 [3,61;5,8] *	4,26 [3,28;5,62] *	5,52 [3,21; 6,28] *	2,89 [2,66; 3,9]	5,7 [5,6; 5,78]	3,38 [2,86; 5,75]
TG	1,62 [1,34;1,93] #	1,45 [1,19;1,63]	0,85 [0,76;1,23]	1,33 [1,21; 1,72]	1,62 [1,52; 1,64]	1,49 [1,17; 2,41]
HDL	0,85 [0,76;1,23]	0,89 [0,82; 1,58]	0,94 [0,91;1,62]	0,84 [0,58; 1,19]	0,91 [0,9; 0,92]	0,97 [0,75; 1,72]
LDL	1,93 [1,38;2,61] *	1,62 [1,25;2,15]	1,86 [1,41;2,24]	1,28 [1,25; 1,63]	1,86 [1,67; 2,18]	1,31 [1,27; 2,27]
CA	4,95 [1,81; 6,2]	2,88 [1,46; 5,49]	3,16 [2,14;5,96]	3,26 [1,44; 4,02]	5,35 [5,2; 5,56]	3,77 [0,57; 4,93]

Notes: * – p<0,05 compared with patients with gouty nephropathy;
– p<0,05 compared with patients with glomerulonephritis

and 20.1 [18.2; 37.5] pg/ml against 126.85 [102.15; 135.85] pg/ml, both p<0.001).

The level of MT in the daytime is lower by 50.6% (p<0.001), in the night period by 84.2% (p<0.001) in patients on HD compared with the control group, which is consistent with the results of other clinical studies in which the relationship of renal dysfunction with MFE has been demonstrated [7].

The study of the lipid spectrum of the blood of our examinees revealed differences between the control group and the patients on RRT in the levels of TC, TG, HDL and CA. Patients on HD had significantly higher TG by 23.7% (p<0.001) and CA by 13.7% (p=0.04) and lower HDL by 21.4% (p=0.04) (table 2).

During the study of MFE disorders in patients with CKD of 5 stage, 84.6% of patients were detected, which allowed to divide them into two groups. Ia group (main) – patients with CKD of 5 stage on HD with impaired MFE (n=110) and IB group – patients with CKD of 5 stage on HD with normal MFE (n=20).

It was found that the patients of the main group compared with the patients of the comparison group had significantly lower levels of MT in saliva, according to the daily profile of MT, which is more pronounced in the night period (by 82.4%) than in the daytime (by 41.9%). In patients of Ia group , the daily MT level was 1.8 [1.5; 2.5] pg / ml against the obtained values of the group Ib – 3.1 [2,6; 3.5] pg/ml (p<0.001). Night level of MT in patients of Ia group was determined at 19.5 [17.8; 29.7] pg/ml against 111.0 [97.3; 130] pg/ml (p<0.001) the result of the comparison group.

Patients with impaired MFE compared with patients in the comparison group had significantly higher BMI by 7% (p<0.01) and waist volume by 10.1% (p=0.04). Patients with impaired epiphyseal function have a longer duration of treatment on HD by 34.8% (p<0.01), a higher level of SBP by 15.2% (p<0.001) and DBP by 11% (p<0.001). In results of laboratory studies, patients in the main group compared to group II had increased level of CRP by 69% (p<0.001) and a lower albumin level by 6% (p<0.01), which is shown in Table 3. The latter may indicate association between impaired protein metabolism and epiphysis dysfunction.

In the two groups there are no significant differences according to the comparative analysis of the values of calcium, phosphorus, parathormone, saturation of transferrin.

Analysis of the lipid metabolism study revealed the presence of an elevated concentration of TC and all its fractions in patients of CKD of 5 stage on HD. However, these disorders were more profound in patients with impaired MFE, which may indicate a connection between epiphyseal dysfunction and lipid metabolism in patients with RRT. The level of TC in the patients of the main group was on 26.4% (p<0.05) higher than that of the patients in the comparison group. The TG and LDL rates of patients with impaired MFE were higher than those of II group by 16.7% (p<0.05) and 22.6% (p=0.03), respectively. The HDL level of the main group is lower by 11.8% compared to the group with preserved MFE. CA of Ia group on 41.5% higher than the comparison group and it's shown in Table 4.

Among the main nosological causes that led to the development of terminal renal failure in the studied patients were dominated by glomerulonephritis and hypertensive nephropathy (40% each nosology), a smaller proportion were patients with gouty nephropathy (15%) and tubulointerstitial nephritis (10%), the least patients were determined with urolithiasis (7%) and polycystic kidney disease (6%).

Analysis of the blood lipid spectrum of patients with CKD of 5 stage treated on HD by etiologic factor showed the highest level of TC in patients with polycystic disease, which exceeded the reference values by 42.5%. The highest TG level was determined in patients with hypertensive nephropathy and polycystic

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Table 6

Lipid spectrum of blood of the main group by sex

Indicator	Men, n=57	Women, n=53	p
TC	4,6 [3,01; 5,6]	3,76 [3,21; 5,78]	0,9
TG	1,56 [1,3; 1,81]	1,53 [1,22; 1,77]	0,7
LDL	1,65 [1,35; 2,34]	1,61 [1,26; 2,18]	0,3
HDL	0,9 [0,8; 1,43]	0,91 [0,78; 1,44]	0,8
CA	4 [1,92; 5,63]	3,16 [1,71; 6,18]	0,9

Table 7

Lipid spectrum of blood of patients with CKD of 5 stage on HD depending on age

Indicator	Young age, n=34	Middle age, n=36	Old age, n=40
TC	4,13 [3,29; 5,32]	4,6 [3,06; 5,86]	4,26 [2,85; 5,7]
TG	1,53 [1,26; 1,75]	1,59 [1,22; 1,98]	1,56 [1,25; 1,89]
LDL	1,44 [1,22; 2,05]	1,73 [1,29; 2,26]	1,72 [1,3; 2,47] *
HDL	1,1 [0,82; 1,75]	0,9 [0,81; 0,97]	0,86 [0,72; 1,19] *
CA	2,3 [1,22; 5,3]	4,09 [2,4; 5,84]	3,5 [2,1; 6,19]

Note: * – p<0,05 compared to young patients.

Table 8

Disorders of lipid metabolism depending on the duration of treatment of RRT

Indicator	1–5 years, n=24	5–10 years, n=20	10–15 years, n=66
TC	3,65 [2,86; 5,55]	3,32 [2,86; 5,12]	4,88 [3,38; 5,8] *
TG	1,47 [1,16; 1,7]	1,35 [1,2; 1,58]	1,58 [1,35; 1,93]
LDL	1,27 [1,16; 1,72]	1,54 [1,32; 2,17]	1,88 [1,37; 2,45] *
HDL	0,93 [0,84; 1,59]	1,13 [0,9; 1,79]	0,84 [0,75; 0,97] #
CA	2,62 [1,31; 4,33]	1,99 [0,74; 4,45]	4,92 [2,43; 6,24] * #

Notes: * – p<0,05 compared with patients of I group (1–5 years); # – p<0,05 compared with patients of II group (10–15 years).

disease, that was above the recommended values by 8%. The level of LDL was highest in patients with hypertensive nephropathy and 37.9% higher than the allowable level. HDL was the lowest in patients with hypertensive and gouty nephropathy, that below the reference values by 16% and 15%, respectively (Table 5). The results show that the most pronounced disorders of the blood lipid spectrum are inherent in patients with hypertensive nephropathy.

The analysis of MFE disorders by gender revealed lower daytime levels and a tendency for women's MT of nighttime to decrease by 11% (p=0.03) and 4% (p=0.06), respectively. The level of daytime MT in women was 1.7 [1.4; 2.1] pg/ml; in men – 1.9 [1.5; 2.9] pg/ml. Nightly MT in women was 19.3 [17.3; 21.3] pg/ml against 20.1 [18.4; 32,8] pg/ml result of men. Indicators of TC and all its fractions exceeded the reference values in most patients with RRT, but no significant differences in blood lipid spectrum between men and women were identified (check it in Table 6). From the foregoing, we can conclude that the reduction of nocturnal levels of melatonin in the body, compared with daytime indicators, affects on the lipid metabolism.

The next stage of the study is the analysis of MFE disorders in patients of the main group depending on age. It was found that elderly patients, compared with the group of young patients, have significantly lower rates of MT, both at night by 35% and at daytime by 31.1% (both p<0.01). The level of daytime MT in elderly patients was 16.2% (p<0.01). It's lower than the average index of patients of middle age, and the index of nightly MT by 7%, respectively (p=0.07). Comparative analysis of MT levels in middle-aged patients and young patients showed lower levels of MT in middle-aged patients by 30.1% and 17.8 %% in the daytime (both p<0.05), what is shown in Table 7. This indicates that the worsening of the MFE progresses with age and the most severe disorders are present in elderly patients.

Analysis of the blood lipid spectrum of patients with RRT, depending on age, showed the most profound abnormalities in elderly and middle-aged patients, demonstrating the relationship of lipid spectrum disturbance with the age of the examined subjects and the circadian rhythm of MT.

For further analysis of disorders of MFE and lipid spectrum of blood, depending on the duration of hemodialysis treatment, patients with CKD of 5 stage, divided into 3 groups:

- I group (n=24) – treatment on HD for 1 to 5 years,
- II group (n=20) – treatment on HD for 5 to 10 years,
- III group (n=66) – treatment on HD for more than 10 years.

The level of daytime MT in I group was 3.15 [2.8; 3,45] pg/ml, II group – 2,1 [1,8; 2,65] pg/ml, III group – 1,55 [1,3; 1.8] pg/ml. The level of nocturnal MT in I group was 33.35 [30.6; 38,2] pg/ml, II group – 28,75 [19,15; 36,2] pg/ml, III group – 18,4 [17,2; 19.5] pg / ml. It should be noted that in patients of III group, the level of daytime MT in saliva is lower than its level in I group by 50.8% (p<0.05), in II group by 26.2% (p<0.05). The level of nocturnal MT is lower than in the I group by 45.7% (p<0.05) and 36% (p<0.05) – II group. Comparative analysis of the results of MT levels between I and II groups showed significantly higher levels of hormone in I group, both day and night, by 33.3% (p<0.05) and 13.8% (p<0.05) in accordance. The results suggest that an increase of duration of HD is associated with an increase of MFE disruption.

Table 9

Disruption of lipid metabolism depending on the duration of hypertension

Indicator	I group (1–5 years), n=10	II group (5–10 years), n=27	III group (10–15 years), n=32	IV group (>15 years), n=41
TC	4,8 [3,14; 5,78]	3,29 [2,78; 4,46]	4,49 [2,77; 5,56]	5,1 [3,67; 5,9] #$
TG	1,17 [0,82; 1,49]	1,44 [1,25; 1,76]	1,51 [1,23; 2,09] *	1,58 [1,53; 1,92] *
LDL	1,62 [1,06; 1,86]	1,34 [1,22; 1,64]	1,78 [1,35; 2,17] #	1,78 [1,35; 2,17] #
HDL	0,89 [0,84; 1,53]	1,29 [0,84; 1,8]	0,91 [0,76; 1,67]	0,91 [0,76; 1,67] #
CA	3,95 [2,62; 5,3]	1,92 [0,97; 4,07]	3,33 [1,69; 5,31]	3,33 [1,69; 5,31] #$

Notes: * – p<0,05 compared with patients of I group (1–5 years); # – p<0,05 compared with patients of II group (10–15 years);
$ – p<0,05 compared with patients of III group (>15 years).

Table 10

Disruption of lipid metabolism depending on the level of daytime MT in saliva

Indicator	I group (2,6–3,9 pg/ml), n=26	II group (1,3–2,6 pg/ml), n=68	III group (<1,3 pg/ml), n=16
TC	3,65 [2,93; 5,48]	4,9 [3,35; 5,79] *	3,49 [2,83; 4,56] #
TG	1,48 [1,25; 1,63]	1,57 [1,26; 1,93]	1,56 [1,22; 1,78]
LDL	1,39 [1,17; 1,62]	1,92 [1,37; 2,45] *	1,38 [1,26; 1,96] #
HDL	1,34 [0,84; 1,61]	0,85 [0,76; 1,1] *	0,96 [0,74; 1,27]
CA	2,11 [1,19; 4]	4,8 [2,31; 6,22] *	3,06 [1,42; 5,17]

Notes: * – p<0,05 compared with patients of group I (1,3–2,6 pg/ml); # – p<0,05 compared with patients of group II (1,3–2,6 pg/ml).

Table 11

Disorders of lipid metabolism depending on the nighttime MT level in saliva

Indicator	I group (39–49,1 pg/ml), n=9	II group (26–39 pg/ml), n=27	III group (12,6–25 pg/ml), n=74
TC	3,28 [3,01; 4,17]	4,26 [2,93; 5,62]	4,63 [3,34; 5,7]
TG	1,38 [1,31; 1,64]	1,46 [1,16; 1,63]	1,57 [1,26; 1,93]
LDL	1,16 [1,06; 1,4]	1,61 [1,26; 2,13] *	1,78 [1,31; 2,42] *
HDL	1,5 [1,29; 1,6]	0,91 [0,83; 1,58]	0,86 [0,76; 1,28] *
CA	1,46 [0,97; 2,2]	3,5 [1,41; 5,3]	3,9 [2,06; 6,18] *

Notes: * – p<0,05 compared with patients of group I (39–49,1 pg/ml).

Comparative analysis of the blood lipid spectrum of patients with RRT showed the highest level of TC in patients with the biggest duration of RRT and exceeded the same index of I group by 25.2% and by 32% of II group. The TG level of patients with the biggest duration of RRT exceeded the values of II group by 14.6% and of I group by 7%. LDL of III group by 32.4% higher than I group and on 18.1% of II group. The result of HDL of patients undergoing hemodialysis treatment for more than 10 years, was lower by 34.5% than the data of II group and by 10.7% of I group, as shown in table 8.

The data obtained indicate the relationship of MFE disorders with the duration of RRT treatment and their effect on the blood lipid spectrum of patients with CKD of 5 stage treated with hemodialysis.

For the analysis of lipid metabolism of blood patients were divided into four groups according on the duration of hypertension:

- I group (n=10) – duration of hypertension for 1–5 years;
- II group (n=27) – duration of hypertension for 5–10 years;
- III group (n=32) – duration of hypertension for 10–15 years;
- IV group (n=41) – duration of hypertension more than 15 years.

Data analysis showed the relationship between the severity of the blood lipid metabolism and the duration of hypertension. Thus, in patients of IV group, the level of TC exceeded by 35.5% the result of II group, by 12% the data of III group and by 6.3% the value of I group. The result of TG of IV group was on 26% higher than I group, on 8.9% than II group result and on 4.4% than III group. The highest LDL indicator was observed in patients of IV group, and exceeded the similar indicator of II group by 24.7% and by 9% the result of I group, which is shown in table 9.

Analysis of MFE disorders in hemodialysis patients with CKD of 5 stage allowed to determine the minimum and maximum values of daytime and nighttime levels of MT in saliva, which allowed patients to be divided into groups according to the levels of MT and performed analysis of lipid spectrum of blood of patients.

Patients were divided into 3 groups according to the daily level of MT:

- I group (n=26) – daily MT level from 2.6 to 3.9 pg/ml;
- II group (n=68) – daily MT level from 1.3 to 2.6 pg/ml;
- III group (n=16) – daily MT <1.3 pg/ml.

Analysis of the level of TC showed the highest level in patients of II group , which by 40.4% exceeded the value of III group and by 25.5% of I group. The TG level of patients in III group was 5.1% higher than the result of I group. The highest LDL value was observed in patients of group II, and exceeded the level of group III by 39.1% and by 27.6% of group I. The lowest level of HDL was determined in patients of group II, its level is lower by 11.5% for the result of group III and by 36.6% of group I, which is shown in table 10.

Patients were also divided into 3 groups according to night level of MT:

- Group I (n=9) – the level of night MT 39–49.1 pg/ml;

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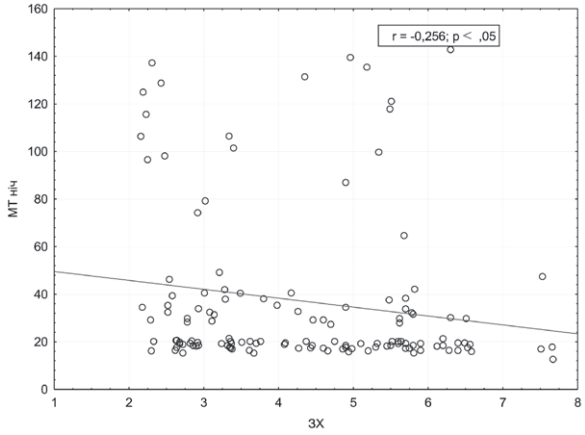
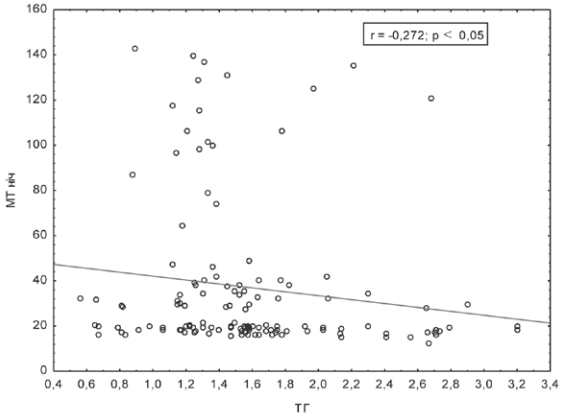
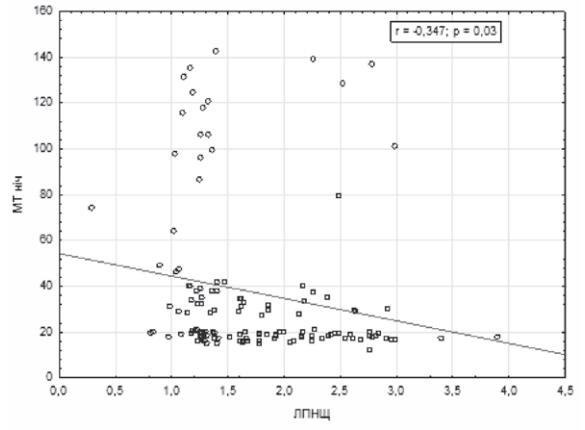


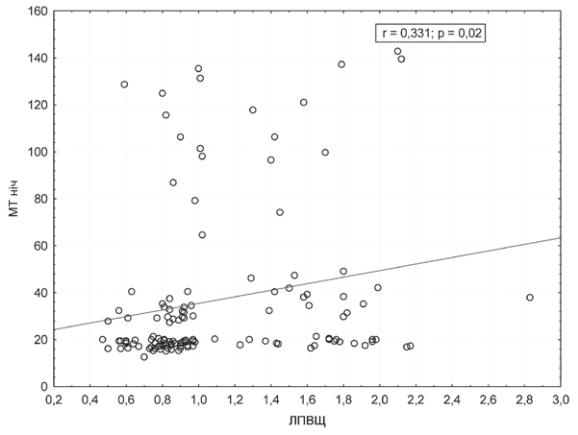
Pic. 2. Correlation between nighttime melatonin level and TC level



Pic. 3. Correlation between nighttime melatonin level and TG level



Pic. 4. Correlation between nighttime melatonin level and LDL level



Pic. 5. Correlation between nighttime melatonin level and HDL level

• Group II (n=27) – the level of night MT 26–39 pg/ml;
• Group III (n=74) – the level of night MT 12.6–25 pg/ml.

In the analysis of the level of TC, depending on the night level of MT, the deepest disturbances were observed in patients with the lowest level of night MT in saliva, so its level is higher by 41.2% than the data of group I and is higher by 8.7% than the value of group II. The result of group II is on 29.9% higher than the value of group I.

The highest TG level was also observed in patients of group III, exceeding group I by 13.8%, group II by 7.5%.

The highest level of LDL was determined again in patients with the lowest level of nocturnal MT in saliva and exceeded values of group I by 53.4% and by 10.6% of group II. LDL results were on 38.8% higher than data of group I .

The lowest level of HDL was observed in patients of group III, which is on 42.7% less than the results of group I and on 5.5% of group II. HDL in Group II is on 39.3% lower than Group I, as shown in Table 11. Analysis of HDL level with anti-atherogenic properties shows the greatest decrease in patients with the most severe disorders of MFE, which may indicate a higher risk of development and progression of atherosclerosis and cardiovascular disease.

The results show that the correlation between MT and lipid metabolism in patients with CKD of 5 stage treated with hemodialysis.

We conducted a correlation analysis in order to further determine the relationship of lipid metabolism disorders in patients with CKD of 5 stage with MFE violation.

The correlation of the night level of MT with the level of TC (r=-0.256; p<0.05) is shown, which is presented in Pic. 2. Correlation analysis confirms that a decrease of MT at night is combined with an increase of TG level (r=-0.272; p<0.05) in the blood of patients, which may indicate the formation of hypercholesterolemia and hypertriglyceridemia in the case of a decrease of MT synthesis and demonstrated in Pic. 3. The data obtained are confirmed by studies on rats demonstrating an increase of TG and TC levels after pinealectomy [13].

However, negative correlations between TG and hemoglobin level (r=-0.20; p<0.05) and a positive relationship with the duration of hypertension (r=0.24; p<0.05) and the duration of RRT (r=0.19; p<0.05) were revealed. It is evidence of an increase in the degree of dyslipidemia with increasing duration of underlying pathology and hemodialysis treatment.

The correlation of night (r=-0,347; p=0,03) and daytime level (r=-0,198; p<0,05) of MT with the LDL level is presented on pic. 4.

Positive correlations were established between the MT level in the daytime (r=0.27; p=0.03) and the night period (r=0.331; p=0.02) with HDL levels, as shown in Pic. 5.

The interconnection between HDL and MFE may be explained by the presence of an important component of HDL, the enzyme paraoxonase, which inhibits LDL oxidation. The activity of this enzyme in patients with CKD may decrease and contribute to the processes of LDL oxidation. MT is known to

prevent the latter, so a decrease in melatonin synthesis may be associated with a decrease of HDL level, which is also observed in our work [13, 18]. Negative correlation of HDL with body mass index of patients (r=-0.25; p<0.05), SBP (r=-0.3; p<0.05) and DBP (r=-0,31; p<0.05).

Assessing the relationship of dyslipidemia with MT levels in the body, it can be assumed that normalization of MT levels may influence the improvement of the blood lipid spectrum of patients undergoing treatment for HD and require more detailed study and separate analysis.

CONCLUSIONS

For patients with CKD of 5 stage on hemodialysis, there is a frequent violation of MFE (84.6%) and significant disorders of lipid metabolism, which is manifested by an increase in atherogenic concentrations (up to 58%) and a decrease in antiatherogenic (up to 62%) fractions. Analysis of the lipid metabolism study revealed more profound abnormalities in the form of an increased concentration of TC and all its fractions in patients with impaired MFE, which may indicate a connection between epiphyseal dysfunction and lipid metabolism in patients with RRT.

Violation of MFE and blood lipid spectrum is determined by the nosological factor and is most clearly observed in patients with hypertensive nephropathy. In patients receiving hemodialysis therapy, melatonin-forming dysfunction and disorders of lipid metabolism are age-dependent and most pronounced in the elderly. Dyslipidemia in patients with CKD of 5 stage is determined by the duration of RRT, the duration of arterial hypertension, hemoglobin level, and the depth of MFE disorders by day and night.

Prospects for further research. Changes in the lipid spectrum of blood in patients with CKD of 5 stage on hemodilysis on the background of melatonin administration are the subject of further research and will be presented in subsequent reports.

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

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