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FACULTY OF MEDICINE

DEPARTMENT OF NEPHROLOGY, HEMATOLOGY, AND GASTROENTEROLOGY

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CURRENT ASPECTS IN THE TREATMENT OF RENAL ANAEMIA IN PATIENTS WITH CHRONIC KIDNEY DISEASE

ABSTRACT

Of a dissertation for the award of the educational and scientific degree "Doctor", Professional field 7.1 MEDICINE

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The dissertation work contains 173 pages, of which: Introduction – 2 pages; Literature review – 50; Conclusions from the literature review – 2 pages; Aim and objectives – 1 page; Material and methods – 4 pages; Pesults and discussion – 68, Conclusions – 1; Contributions – 2, bibliography – 27. It is illustrated with 36 tables and 58 figures. The bibliography includes 331 sources, of which 9 are Cyrillic and 322 are Latin. The dissertation was discussed at an extended departmental council meeting of the Department of Nephrology, Hematology, and Gastroenterology of the Medical University - Pleven and was directed for public defense before a scientific jury. The scientific jury comprises members appointed by Order No3373/26.11.2024 of the Rector of Medical University - Pleven:

The dissertation defense will be held on February 20, 2025, at 1:30 p.m. in the Conference Hall of the Faculty of Pharmacy at MU-Pleven.

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CONTENTS:

ABBREVIATIONS

AACI -Age Adjustment Charlson's Comorbidity Index
AVF- arteriovenous fistula
BMI -Body mass index
CAI- Catheter-Associated Infection
CKD- chronic kidney disease
DCC - Diagnostic Consultation Center
DTD -Dialysis Treatment Department
eGFR - Glomerular filtration rate
EPO - Erythropoietin
ERI - Erythropoietin resistance index
ESAs - Erythropoiesis stimulating agents
ESRD - End-stage renal disease
ID- Iron deficiency
Hb - Hemoglobin
HD- Hemodialysis
HDF - Hemodiafiltration
PRCA -Pure red blood cell aplasia
PTC - Permanent tunneled catheter
PTH - Parathyroid hormone
QoL - Quality of life
KDOQI- Kidney Disease Outcomes Quality Initiative.
LAESA - Long-acting Erythropoiesis stimulating agents
NKDIGO - National Kidney Disease Improving Global Outcomes
ORG - Obesity-Related Glomerulopathy
RA - Renal anemia
RKF - Residual kidney function
ShESA - Short-acting Erythropoiesis stimulating agents
VDRAs -Vitamin D receptor activators

INTRODUCTION

Anemia is a cardinal syndrome in people with chronic kidney disease (CKD). It has a serious impact on cardiovascular risk, mental stress and quality of life (QoL). Worldwide, the frequency of patients with CKD is constantly increasing - respectively, the number of patients with renal anemia (RA) is also increasing. As the prevalence of RA increases, the associated morbidity and, accordingly, costs for people and the health system are also increasing. This requires the search for different ways and approaches to identify high-risk patients and the search and discovery of additional and new factors influencing the course and treatment of the anemia syndrome. There are many uncertainties regarding the resistance of patients to anti-anemia treatment. The number of overweight people in the world is increasing alarmingly, which raises numerous problems both in the diagnosis and in the individual approach to the treatment of RA in these patients. The patient's response to treatment is also different in the different stages of CKD, as well as differences by gender. In recent years, the average age of the population has increased, respectively of patients with CKD and patients undergoing renal replacement therapy, which has its own characteristics and risks. All this gives grounds for conducting a comprehensive study of current aspects in the treatment of RA and to try to resolve some of the numerous ambiguities in the individual approach to each patient.

CKD affects about 10% of elderly people worldwide, but according to experts in Bulgaria this percentage is higher - about 12.7%. In areas such as resistance to RA treatment, obesity as a factor in worsening CKD and RA, the specificity of care for patients with Permanent Tunneled Catheter (PTC), as well as the relationship between RA and Secondary Hyperparathyroidism (SHP), new factors and dependencies are constantly being discovered. The answers to questions such as: Which Erythropoietin Stimulating Agents (ESAs) are preferable - short- or long-acting? Are there any dangers in converting from one type of ESA to another? Are there gender differences? Is monitoring by a nephrologist and treatment with ESAs in the predialysis period important? All this provoked interest in the development of the present work. The systematic analysis of the modern literature on this interdisciplinary problem highlights both a number of undeniable achievements in diagnostics and treatment, as well as a large number of unresolved issues. This gives grounds to conduct the present comprehensive study in an attempt to resolve some of the numerous unresolved problems.

AIM

To clarify current aspects in the treatment of renal anemia in patients with chronic kidney disease.

OBJECTIVES

1. To determine the significance of the Erythropoietin Resistance Index in the treatment of renal anemia with Erythropoiesis-Stimulating Agents (ESAs) and to characterize the relationship between renal anemia, obesity, and the degree of renal function impairment

2. To determine the impact of infection in patients with a permanent tunneled catheter as vascular access for hemodialysis on Renal Anemia (RA).

3. To determine the relationship between RA treatment and secondary hyperparathyroidism.

4. To assess the conversion from short-acting to long-acting ESAs, and vice versa, in patients on dialysis and those not on dialysis treatment.

5. To characterize the trend for response to ESAs in dialysis patients depending on whether they received ESAs or not before starting dialysis treatment. Individual and holistic approach to the treatment of RA in patients with CKD on dialysis treatment and in the pre-dialysis period.

MATERIALS AND METHODS

1. Study design. The study is a single-center, longitudinal, ambispective study. Data on RA of 2963 patients with CKD stage 5D, on hemodialysis (HD), and in the predialysis stage were analyzed. All patients were over 18 years of age.

2. Place and time of the study: The study was conducted in the Dialysis Treatment Department (DTD) of the University Hospital "St. Anna" Sofia. Data were used on patients from the DTD of the University Hospital "St. Anna" Sofia, the Diagnostic and Consulting Center "St. Anna" Sofia, and single patients from Montana Hospital, covering 20 years from 01.01.2004 to 30.09.2024.

3. Study administration: A questionnaire was prepared and approved by the Ethics Committee of the Medical University - Pleven. The work with documentary data was carried out by the principal investigator and was supervised by the Scientific Director.

4. Methods used: 4.1. Documentary method. A detailed analysis of data from medical documentation included in the HD patient's file was carried out - epikrisis of hospitalizations, laboratory test results, results of imaging studies - radiographs, computed tomography, echocardiography, coronary angiography, etc. Demographic data were collected on age, gender, body mass index (BMI), and the main renal disease - the cause of end-stage renal disease (ESRD). Data on new events related to the relevant concomitant diseases that occurred during the follow-up were also collected. The available information on the use of iron medications, phosphorus-binding medications (phosphate scavengers), calcimimetics, antibiotics, probiotics, anticoagulants, antiplatelet agents, folic acid, vitamin D receptor activators (VDRAs), and erythropoietin-stimulating agents (ESAs), known as inclusion in the study, as well as new ones that occurred during the study period, was analyzed. Similarly, data were collected on the presence of changes in the patient's condition. The duration of dialysis treatment was defined as the number of months. The collaboration of patients was assessed based on an analysis of data on taken/refused medications provided by the ODL. Data on vascular access for HD and medication intake were collected. Data on the therapy performed were processed. The NKDIGO recommendations from 2009, updated in 2017, were adopted as assessment criteria. Patients were followed until the end of the study period, until kidney transplantation, or until death. The causes of death in the study population were

4. 2. Laboratory tests. Blood samples from patients were taken using standard techniques at the beginning of the hemodialysis session and were performed in the Clinical and Microbiological Laboratory of the University Hospital "St. Anna" AD Sofia and the Bodymed laboratory (only 2010-2012 for PTH). For patients not on HD - from the attached documentation. Automated and standardized methods of processing biological samples were used. The laboratory parameters studied were: Hemoglobin (Hb), Hematocrit (Hct), total serum and/or ionized calcium, serum phosphate, serum albumin, serum creatinine, intact parathyroid hormone (PTH), blood culture.

4. 3. Statistical methods. The data from the study were processed with the Excel 365 statistical software packages. The following statistical methods were applied in the analysis of the results: Statistical methods - methods for prospective follow-up. Data Analysis - t-test: Data Analysis – t-Test: Two-Sample Assuming Unequal Variances (Two samples assuming unequal variances. The significance of the results, conclusions, and inferences are determined at a significance level of $p<0.05$. Descriptive and deductive statistics, Variance,

and parametric analysis. Descriptive statistics: point estimates of the mean values to find parameters.

4. 4. The following methods were also used: 1. Questionnaire - All patients were interviewed using a standardized questionnaire to provide the following data: gender, age, weight, monitoring during the pre-dialysis period, and ESA administration.

2. Calculation of the Erythropoietin resistance index (ERI) by the formula: weekly ESA dose/body weight in kg divided by Hb in g/dL.

3. Calculation of BMI by the formula BMI=W/h2 (weight in kg/height in m).

4. Measurement of eGFR by formula-MDRD and EPI.

5. Application of the Charlson Index for calculating comorbidity.

RESULTS AND DISCUSSION

<u>on Task 1.</u> To determine the significance of the Erythropoietin Resistance Index in treating renal anemia with Erythropoiesis-Stimulating Agents (ESAs) and to characterize the relationship between renal anemia, obesity, and the degree of renal function impairment.

There is variability in response to treatment of renal anemia (RA); in 5–10% and even up to 34% of patients, resistance to ESA therapy occurs. Resistance to ESA is associated with inflammation, infections, oxidative stress, iron deficiency (ID), obesity, secondary hyperparathyroidism (SHPT), etc. Some dialysis patients require high doses of ESA, which increases the risk of death. Erythropoietin Resistance Index (ERI) is an accurate indicator for measuring the degree of resistance to ESA. It is calculated by dividing the weekly dose of ESA by weight in kg by Hb in g/dl. ERI≤10 is considered normal. The response to ESA may vary between different patients and according to different circumstances, over time within a given individual. The etiological mechanisms associated with the development of ESA-resistant anemia are known, as well as the risks associated with the use of high doses of ESA to achieve target hemoglobin levels. ERI is used to assess the dose-response effect of ESA treatment. ERI is also directly related to comorbidity (age-adjusted Charlson's index), age, female gender, and low BMI, without any connection with the etiology of chronic kidney disease. Patients with previous heart failure, acute infection, or malignant neoplasm have significantly higher ERI compared to other patients. Thus, calculating ERI (a quick and easy way to calculate) and establishing high values is reliable evidence of the presence of resistance and saves expensive tests: hepcidin, ferroportin, markers of iron status adequacy.

In the DTD, ERI is calculated every quarter. This helps a lot for accurate correction and dosing of ESA, saving money from expensive blood tests. Three retrospective follow-ups were conducted, with Hb level and ERI - in 2008-2009 and 2013-2015. Patients from the corresponding years were selected.

The study from 2013-2015. explains the need for the application of ERI and finds a correlation between ESA resistance (between ERI) and the risk of death, and a correlation between ESA resistance and body weight (between ERI and BMI) in HD patients. The study is retrospective. The results of 58 patients (34 men and 24 women), with a mean age of 59.56 ± 1.9 years on HD, were analyzed. They were followed for a period of 23 months (2013-2015). According to the ERI calculations, patients were grouped into 3 groups: Group 1: ERI below 5; Group 2: ERI 5 -10; Group 3: ERI above 10. Patients were followed by age, gender, ERI, and mortality.

Results: Table 1 presents the mortality rate in the monitored patients depending on the ERI value. In both men and women, ERI is associated with mortality. The highest mortality rate is in patients with ERI above 10. Mortality is higher in men for each ERI group. Our results are consistent with the results of other authors. A higher degree of ESA resistance in HD patients is associated with increased mortality. Patients with the highest ERI have a significantly higher mortality rate.

Table 1. Number and relative proportion of deceased patients according to ERI.

2013	Number of cases	Number of cases	Deaths	Deaths
	men	women	men	women
total	34	24	9/26,5%/	3/12,5%/
ERI up to 5	6	2	2 /33%/	0
ERI 5to 10	8	6	3 /38%/	1 /16%/
ERI 10 to 15	7	9	4/57%/	2 /22%/

The association of ERI with BMI in all patients and separately by gender is presented in Figure 1. The highest ERI is in patients with body weight below physiological - BMI below 18.

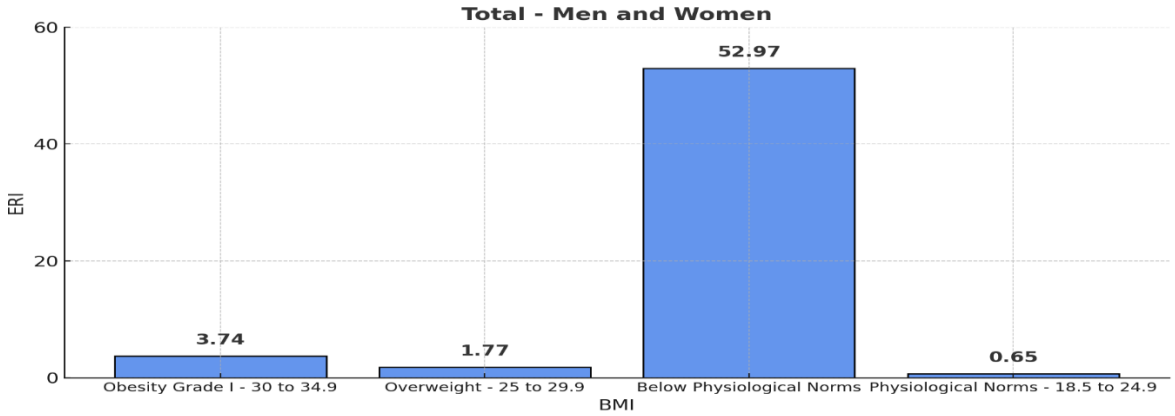

Figure 1. The highest ERI is in patients with body weight below physiological

The follow-up from 01.02. 2008-01.02. 2009 studies the entire pathology of patients in the ODL and clarifies the degree of anemia control, dose, and response to ESA using ERI. It is determined whether there is a relationship between comorbidity and anemia treatment (Assessment of the relationship between Age Adjustment Charlson's comorbidity Index (AACI) and Hb level, doses of ECA and ERI. A total of 58 patients from the DTD at the University Hospital "St. Anna" Sofia were included in the follow-up. Of them, 18 were women; 40 were men with a duration of HD treatment from 6 months to 15 years as of 28.02.2009. Of them, 31 were with arteriovenous fistula (AVF), and 27 - with Permanent tunneled catheter (PTK). The clinical files and documentation were reviewed, as well as outpatient consultations with specialists from different fields of medicine. Scoring and indexing of each patient according to the Charlson index were performed.

The patients were grouped into 2 groups: with ERI above 10 and ERI below 10. During the period, Epo alpha, Epo beta, and Darbepoetin were used.

Results: Table 2 and Figure 2 show the etiology of kidney disease leading to end-stage renal disease (ESRD) and HD.

Table 2. Etiology of kidney disease leading to ESRD and HD

Diagnosis	Number of patients	Relative share (%)
Chronic tubulointerstitial nephritis(CTIN)	30	52%
Diabetes mellitus	13	22%
Glomerulonephritis	8	14%
Polycystic kidney disease	4	7%
Gout	2	3%
Hypertensive nephrosclerosis	1	2%

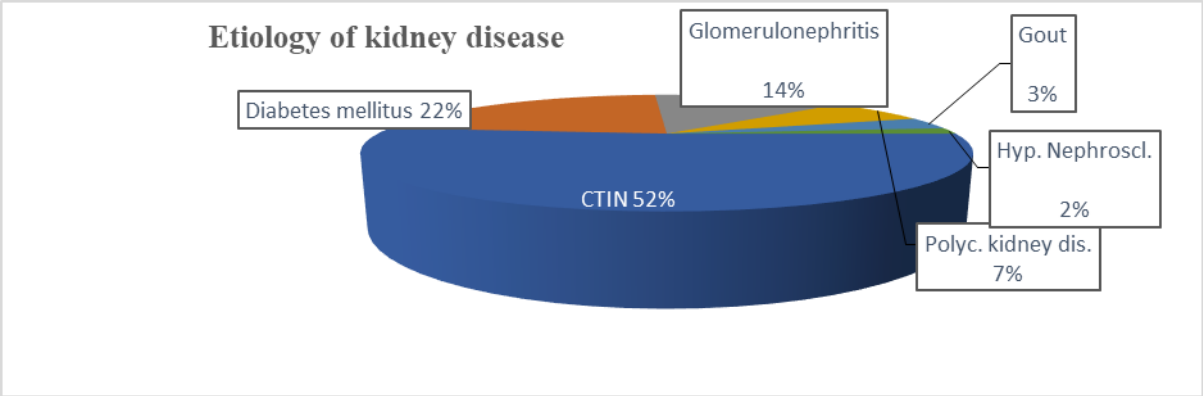

Figure 2. The etiology of kidney disease leads to ESRD and HD (Relative share -%).

The average Hb level of all patients is 97g/l. 47 patients, this is 81%—have Hb below 110g/l. Five of them are resistant to ESA treatment—they receive ESA from 306-480IU/kg/week.

The average Hb level in women is 96g/l. Of the women, 8 have A-B fistula and average Hb level 102g/l. Of these, 3 women have ERI below 10, and 5 women have ERI above 10. Of the women, 10 have PTC and an average Hb level of 90.8g/l. With ERI below 10, there are 4 patients, and with ERI above 10, there are 6 patients. In men - 40 in number, the average Hb is 98.3g/l. 23 patients had AVF and mean Hb level 99.8g/l. 16 patients had ERI below 10, and 7 had ERI above 10. Men with PTC were 17 in number and the mean Hb level was 96.8g/l. 12 men had ERI below 10, and 6 men had ERI above 10.

The weekly dose of ESA was from 17.24 to 480IU/kg/week. The calculated ERI was from 0.23 to 44.64. Table 3 shows the AACI and the mean Hb levels.

Table 3. Charlson index - Age-adjusted Charlson's index (AACI)and mean Hb levels.

Age-adjusted Charlson's index (AACI)	Number of patients	Mean Hb levels g/l
2	10	105,6
3	6	88
4	7	96,1
5	13	99,3
6	8	96,3
7	10	98,4
8	3	93,3

p=0,001908

The intensity of Charlson's index is related to the severity of anemia and the level of control of the anemic syndrome, as well as the response to treatment with ESA (p=0.001908). The comorbidity index is high in HD patients. The average Hb level in patients with a high Charlson's index is lower. There is a statistically significant difference between Charlson's index and Hb level (p=0.001908). The response to ESA is inadequate.

During the study, the Hb level and ERI were monitored for a period of 1 year in HD patients; The reasons for the presence of low Hb and high ERI, respectively the reasons for the use of very high doses of ESA; The reasons for the presence of high Hb in patients without ESA were studied.

A total of 58 patients with HD at the University Hospital "St. Anna" AD Sofia were included in the follow-up. Of them, 18 were women; men - 40. Of these, 30 had AVF, and 28 had PTK. The following results were obtained: Average Hb level for all patients was 97 g/l. Women - 96 g/l. Men - 98 g/l. The dose of ECA/kg/week was from 17.24IU/kg/week to 480 IU/kg/week. Calculated ERI was from 0.23 to 44.64. Patients with ERI below 10 predominated. These are 30 patients = 51.72%. There were 24 patients with ERI above 10. In 4 patients, Hb was above 11 permanently for more than 1 year and did not receive ECA. In 5 patients, Hb was below 11g/l and they received high doses of ECA - more than 300IU/kg/week. One of the patients for the period after September 2008. maintains a stable hemoglobin level above 11 g/dl and is free of ESA. Of all 18 women followed, 8 have AVF and have an average Hb level of 10.2 g/l. 3 patients have an ERI below 10, the remaining 5 have an ERI above 10. Of all 18 women followed, 10 have PTC and an average Hb level of 90.8 g/l.

Discussion: In two patients, myelofibrosis and suppressed erythropoiesis as a result of immunosuppressants administered during the period with a transplanted kidney - over 2 years and for the treatment of chronic rejection of a transplanted kidney are discussed. There was no suspicion of Pure red blood cell aplasia (PRCA). No studies were conducted to detect antibodies against EPO. The reasons for the high Hb in patients without ESA remain unclear. It is assumed that for unknown reasons these patients have preserved erythropoiesis, including extrarenal.

The results obtained are in accordance with those published in the literature. Women with PTC have lower Hb levels than women with AVF, with higher ERI and with a higher weekly dose of ECA/kg of weight. The same is the characteristic for men with PTC, compared to men with AVF. The reasons for this are Catheter-Associated Infection (CAI), systemic infections, iron deficiency, and VHPT.

Three more follow-ups were conducted in different periods and in different populations with CKD:

• Follow-up of patients with CKD in the pre-dialysis period (patients with and without ESAs were included).

• Follow-up of patients with CKD in the pre-dialysis period (patients without ESAs, and without Cytostatics were included).

• Follow-up of patients with CKD on HD.

Monitoring of patients with CKD in the predialysis period (patients with and without ESA are included): It is monitored in the database of the Nephrology consulting room of the Diagnostic and Consultative Center (DCC) St. Anna, Sofia, whether the patients who have undergone kidney disease are obese; What is the degree of obesity; Is there a relationship between obesity and the degree of renal function impairment; Is there a relationship between obesity and RA; Is there a relationship (differences) in the two sexes - obesity - degree of CKD - renal function - anemia. Patients with CKD from the DCC St. Anna, Sofia, were studied for the period 01.01.2012 - 31.12. 2012. 272 predialysis patients were monitored - 145 men and 127 women, with an average age of 66.7±0.77 years. The youngest patient was 24 years old, and the oldest was 88 years old. Patients with and without ESA treatment were included. Age, height, weight, serum creatinine, and hemoglobin were monitored. BMI and eGFR were calculated using the MDRD formula. Retrospective analysis methods were used. BMI and eGFR are calculated using standard formulas. eGFR- according to MDRD. BMI=W/h2

There was only 1 patient with a BMI below physiological values (below 18.5 kg/m2) and he was on ESA treatment. There were 28 men and 25 women with physiological values (Normal BMI =18.5-24.9 kg/m2). 12 men and 15 women were treated with ESA. There were 93 men and 72 women with overweight and BMI (25-29.9 kg/m2). Of these, 33 men and 13 women are on treatment with ESA. Obesity I stage. BMI (30-34.9) has 21 men and 20 women. Of these, 7 men and 11 women are on treatment with ESA. Obesity II stage. BMI (35-39.9) have 2 men and 10 women. Of these, 1 man and 6 women are on treatment with ESA. The results show that the largest proportion of the monitored patients are overweight - BMI (25-29.9kg/m2). 64.13% of all men and 56.69% of all women are overweight. This is also the group with the largest number of patients on treatment with ESA. It is obvious that patients with CKD and overweight have more pronounced anemia, requiring treatment with ESA.

The results obtained show:

1. In all patients monitored for 1 year /1.1.2012-31.12.2012/ in the different weight and gender categories of patients there are patients with both normal renal function and impaired function to varying degrees.

2. With BMI below and with physiological values only 29 (20%) of all monitored men and 25 women (19.63%).

3. With BMI above physiological values - above 24.9 (i.e. with overweight and obesity) 80% of men and 80.31% of women.

4. The average serum creatinine value for all groups of patients of both sexes is above the reference value.

5. The average value of eGFR is below 45 for all groups. In all monitored predialysis patients, eGFR is reduced, and in women with a BMI over 30, eGFR decreases significantly and proportionally with increasing BMI.

6. The average Hb level for all groups is below 121g/L.

7. In men from the predialysis stage with a BMI over 30, there is anemia - the average Hb level is 120g/L and lower with increasing BMI.

8. The largest proportion of the monitored patients are overweight - BMI (25-29.9kg/m2). 64.13% of all men and 56.69% of all women are overweight. This is also the group with the largest number of patients on ESA treatment. Patients with CKD and overweight - BMI (25-29.9kg/m2) have more pronounced anemia, requiring treatment with ESA. This is explained by the pathophysiology of the relationship between obesity and kidney disease.

Retrospective follow-up of patients with CKD stage 3-5 -not on HD, without ESA and without Cytostatics) The degree of obesity of patients with CKD is monitored; a relationship between obesity and renal function impairment is sought; a relationship between obesity, CKD and anemia is found and related to gender.

These are patients with CKD stage 3-5 not on HD and were carried out for 6 months from 01.01.2013 to 30.06.2013 with patients from the DCC St. Anna "St. Anna" EOOD Sofia. 315 patients were monitored. Of them, 123 men and 192 women of average age-60.33±3.06 min-18y. max-96; men -63.39±1.33 min-25 max-96; women-57.27±1.24 min-18 max-87. The results are grouped by gender and according to BMI. Demographic, clinical, and paraclinical parameters (age, gender, height, weight, serum creatinine, Hb level) were monitored. Patients had different degrees of CKD. The methods of retrospective analysis were used. BMI and eGFR were calculated according to standard formulas. eGFR-according to MDRD.

It was found that: A large percentage of the monitored male patients were overweight and obese. Women with a BMI below 24.9 were 142 (73.95%), and men -29 (23.57%). 94 (74.79%) of men and 52 (27.08%) of women are overweight and obese; In both sexes, with increasing BMI, glomerular filtration decreases. The results obtained show a relationship between the degree of obesity and the degree of renal function impairment. The results confirm the results published in the medical literature. A relationship between BMI and the average Hb level is found in women with obesity stage II. There are no similar data in world literature so far. This is the first time such a relationship by gender has been reported.

In the follow-up of HD patients, the degree of obesity is monitored; a relationship between obesity and the level of serum creatinine and a relationship between obesity and anemia are sought. 65 dialysis patients were followed - 41 men and 24 women. The results are grouped by gender and according to BMI. With BMI below physiological values - below 18.5 kg/m², there are two men (4.87%) and 3 (12.5%) women. In 1 man and 1 woman, treatment with ESA is applied. With physiological values of 18.5-24.9 kg/m², there are 27 (65.83%) men and 12 (50%) women. Of these, 26 men and 12 women use ESA. With overweight and BMI of 25-29.9 kg/m are 8 men and 7 women. Of these, 6 men and 7 women use ESA. Obesity I St. has a BMI of 30-34.9, and it has 4 men and 2 women. Of these, 3 men and 2 women use ESA. With overweight and obesity are 13 (31.70%) of men and 9 (37.5%) of women on HD.

No correlation was found between BMI and serum creatinine level (p=0.09156).

The follow-up included patients with and without treatment with ESA. The obtained results for the correlation between CKD and obesity confirm the results of other authors. In all followed-up pre-dialysis patients, eGFR is reduced, and in women with a BMI over 30, eGFR decreases significantly and proportionally with increasing BMI. In men from the pre-dialysis stage (I follow-up from 2012, not HD patients with/without ESA) with a BMI over 30, anemia is present - the average Hb level is 120 g/l and lower with increasing BMI. In the follow-up from 2013, where patients with ESA were not included, anemia was found only in women with obesity 2 cm. For the first time, such a dependence is found for female gender, obesity, and RA.

On Task 2. To determine the impact of infection on renal anemia in patients with a permanent tunnel catheter as a permanent vascular access for HD.

Permanent tunneled catheters are increasingly used for permanent vascular access for HD and their increasing frequency of use is associated with infectious complications. CAI is

most often due to Gram-positive or Gram-negative microorganisms and in a small percentage can be polymicrobial. Prevention of CAI, as well as treatment of CAI, can be a difficult problem and lead to the need for removal of the PTC. In the ODL of the University Hospital "St. Anna" Sofia PTCs have been used since 1998. In 2006, the number of patients with PTCs who undergo HD in the department was 11 and represented 12.8% of all patients. The number of patients with vascular access for HD PTCs is gradually increasing. The following table shows the number and relative share of patients with PTK during the period 2006-2021.

Table No. 4. Tracking the number and relative share of patients with PTK for the period 2006-2021.

Total PTC	Year	Total PTC (%)
26	July 2006	26 (34,22%)
26	July 2008	26 (31,3%)
61	July 2014	61 (81,33%)
47	July 2017	47 (77,04%)
37	July 2019	37 (78,72%)
40	July 2021	40 (83,63%)

Local anesthesia and strict antiseptics are used for catheterizations. Patients with PTC are cared for by staff with sufficient experience in PTC care, following the KDOQI rules.

Patients with KAI are treated persistently with intravenous antibiotics and an “antibiotic lock” after each HD session.

1. All catheter manipulations are performed by specialized and experienced personnel.

2. At each dialysis session, the outside of the PTC is examined, and the dressing is changed.

3. During all procedures, the patient and the personnel serving him wear surgical masks.

26 patients /11 women and 15 men/ on HD in the DTD of the University Hospital “St. Anna” AD Sofia were followed for 2 years. This is 34.22% of all HD patients in the department.

The results of microbiological examination of blood taken from the PTC of hemodialysis patients with chills during a dialysis session in the DTD of the University Hospital "St.

Anna" Sofia for the period 01.01.2004-31.01.2006 are reflected in Figure 3 (blue color-number; purple color -in %):

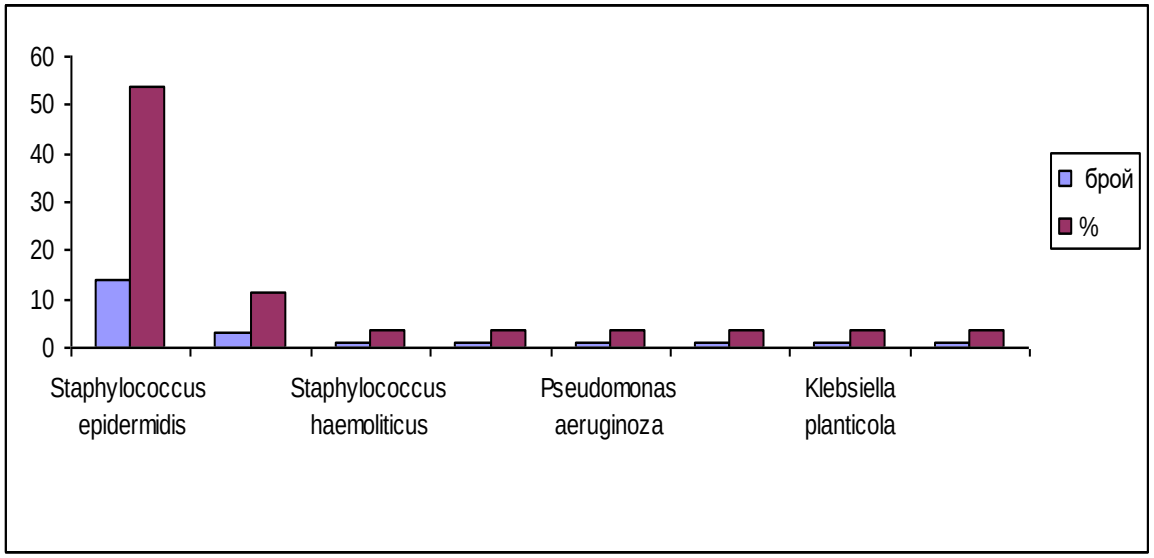

Figure 3. Results of microbiological examination of blood taken from the PTC of hemodialysis patients with chills during a dialysis session.

Staphylococcus aureus carriage in the nose of patients on HD is very common - about 25%. Therefore, it is recommended that the patient and staff wear a surgical face mask - this reduces the spread of infected secretions and reduces contamination of the PTC. In addition, it is recommended to place Mupirocin in the nostrils of patients.

In another follow-up from 2008, the results of the treatment of anemia syndrome in patients on HD and vascular access to the PTC are presented. At a distance of 1 year - every quarter, paraclinical biochemical indicators and a complete blood count, as well as the number of hospitalizations, were monitored in graphs and tables. 26 patients (15 men and 11 women) with ESRD - HD treatment with vascular access for hemodialysis PTC were monitored (Table 5). This represents 31.3% of all HD patients as of 20.1.2008. All are undergoing bicarbonate hemodialysis with a low flux membrane on the dialyzer. Of these, 61% have chronic pyelonephritis; 31% have diabetes mellitus; 4% - glomerulonephritis, 4% - others.

Table №5. Distribution of patients with PTC by number, sex, age, and number of hospitalizations.

Sex	**Number**	**Age(year)**	**Age (year)**	**Hospitalizations (number)**
men	15	25-82	60.66 ± 15.2	2

women	11	36-81	65 ± 15.69	1

All patients receive treatment with EPO alpha or beta intravenously, in a dose depending on the supplies under Regulation 34. At the same time - substitution with intravenous iron - 100 or 200 mg per month, according to the results of serum iron, BSA, and Ferritin. PTK Gam Cath -Gambro or medCOMP are sized according to the patient's habit. In the present follow-up, 26 patients presented for 1 year, who underwent chronic hemodialysis in the DTD of UMBAL "St. Anna" AD Sofia. Table 6 shows the percentage of diseases of patients with PTK.

Table №6. Distribution of patients with PTC by nosological units.

Main disease	**Men number (%)**	**Women number (%)**
Cr. Tubulointerst. nephritis	10 (67)	6(55)
Diabetes mellitus	4 (27)	4(36)
Others	1 (6)	1(9)

Results and discussion: The following parameters were monitored: Complete blood count – Hb, hematocrit (Ht), erythrocytes, leukocytes, platelets, MCV, MCH, MCHC, and biochemistry – urea, creatinine. The results were monitored for 1 year.

In 3 out of 11 women, Hb from 100 to 128 was maintained for 1 year - i.e. these are 27.27% of women with stable Hb and one hospitalization of one patient who is not in this group with stable Hb levels. Five of the men, which is 33.3%, had Hb from 100 to 128 for 1 year and were not hospitalized. One patient had 2 hospitalizations, but he is also outside the group of stable Hb levels. This percentage is much higher than the 6.5% stable Hb levels published in the literature.

Treatment of the anemic syndrome and maintenance of stable clinical and paraclinical indicators in HD patients with PTC is possible only if comprehensive care is observed for:

1. Prevention of infections - Catheter-associated infections, systemic infections, and inflammatory diseases.

2. Prevention of malnutrition.

3. Management of manifestations of secondary hyperparathyroidism.

4. Absence of iron deficiency.

5. Correction and treatment of arterial hypertension and proteinuria.

6. Sufficient /appropriate/ dosage of Erythropoietin.

By observing this complex of measures in HD patients with PTC in the department, good results were achieved in terms of a stable Hb level for 1 year - 100-128 g/l.

During the one-year observation of HD patients with PTC, surprisingly good results were obtained for 8 (30.76%) of all 26 patients, who maintained stable Hb from 100 to 128 g/l. They also had stable clinical and paraclinical indicators - complete blood count, and residual nitrogen products in serum. These patients had no hospitalizations and no deterioration in their condition. Three women (27.27) % of women with PTC had stable Hb. Five of the men, which is 33.3%, also had stable Hb. A total of 8 (30.76%) of patients with PTC maintained stable Hb for the 1-year follow-up period. This is much higher than the 6.5% stable Hb levels for HD patients published in the literature, regardless of access to HD.

Six years later - as of 30.03.2014 The same problem was discussed and 61 patients with vascular access for HD PTK were followed. The increase in the number of this type of patient is explained by the increased overall morbidity, as well as the increase in the number of elderly and diabetic patients in need of HD treatment. This type of patient has numerous cardiovascular diseases, problematic vessels, and the inability to construct an AVF that provides a good flow rate for dialysis. This is the explanation for the increase in the number of such patients worldwide

If as of 20.01.2008 the number of patients with PTK was 26 and this is 31.3%, then six years later the patients are 61 and their relative share is 81.33% of HD patients in the dialysis structure of UMHAL "St. Anna" Sofia. - this is an increase of more than 2 and a half times. In 2021 the percentage of patients with PTK is 83.62. The data are presented in Table №7 and 8. The data on the low number of hospitalizations is evidence of the good work of the department.

Table №7. Tracking the number of patients with PTK, age, and hospitalizations - comparison over the years - 2008 and 2014.

Sex	**Years-Number**	**Years-Age min-max**	**Average age**	**Hospitalizations 2008г.**

men	2008- 15	2008- 25-85	60,66± 15,27	2
	2014-34	2014- 25-83	63,38± 12,43	2
women	2008- 11	2008-36-81	65,24 ± 15,69	1
	2014- 27	2014-21-80	66,12± 14,26	5

Of the total 61 patients with PTC in 2014, 30 had a stable Hb level of 100-132g/l. This represents 49.18%. The data are presented in Table №8.

Table №8. Monitoring of stable Hb levels 100-132g/l of patients with PTC-30.76% in 2008, and 49.18% - in 2014.

year	**Number (%) of patients with stable Hb levels- 2008**	**year**	**Number (%) of patients with stable Hb levels-2024**
2008	8 (30,76%)	**2014**	30(49,18%)
men	5	**men**	18
women	3	**women**	12

What the comparative data show: In 2008, 3 women and 5 men - a total of 8 patients - maintained stable Hb levels between 100-128 g/l. This is 30,76% of patients with PTC. In 2014, 30 patients had stable Hb levels of 100-132 g/l. This is 49,18% of patients with PTC (although the average age of patients is increasing). For comparison: the stable hemoglobin levels of dialysis patients worldwide are 6,5%. In 2008, there was 1 hospitalization per woman and 2 hospitalizations per man. These two patients are outside the group of patients with stable Hb levels. In 2014, there were 5 hospitalizations of women (with the same patient being hospitalized twice) and 2 hospitalizations of men. These patients are outside the group of patients with stable Hb. All patients undergo bicarbonate dialysis with a Helixon membrane with an area individually tailored to the needs, clinical condition and paraclinical indicators of the patient. Over the years, the number of patients with PTC has been constantly increasing

(Table №9), while the number of patients with atrial-venous fistula (AVF) has been decreasing.

Table №9. Tracking the number and relative share of patients with PTC and AVF by year.

Total number of patients total number of patients	Year	Total number of patients with PTK (%)	Total number of patients with AVF (%)
76	July 2006	26(34,22%)	50(66,78%)
83	July 2008	26 (31,3%)	58(68,7%)
75	July 2014	61(81,33%)	14(18,67%)
61	July 2017	47(77,04%)	14(22,96%)
47	July 2019	37(78,73%)	10(21,27%)
49	July 2021	40(83,62%)	9(16,38%)

For the period 2014-2021 Hb levels and weekly doses of ESA of patients with PTK and AVF were monitored and compared. The following figures present average Hb levels of patients with PTK and Hb levels of patients with AVF over the years. The average weekly doses of ESA for the groups of patients with PTK and AVF by year were also monitored.- Figure 4 - blue coloring - data for patients with AVF, orange coloring - for patients with PTC.

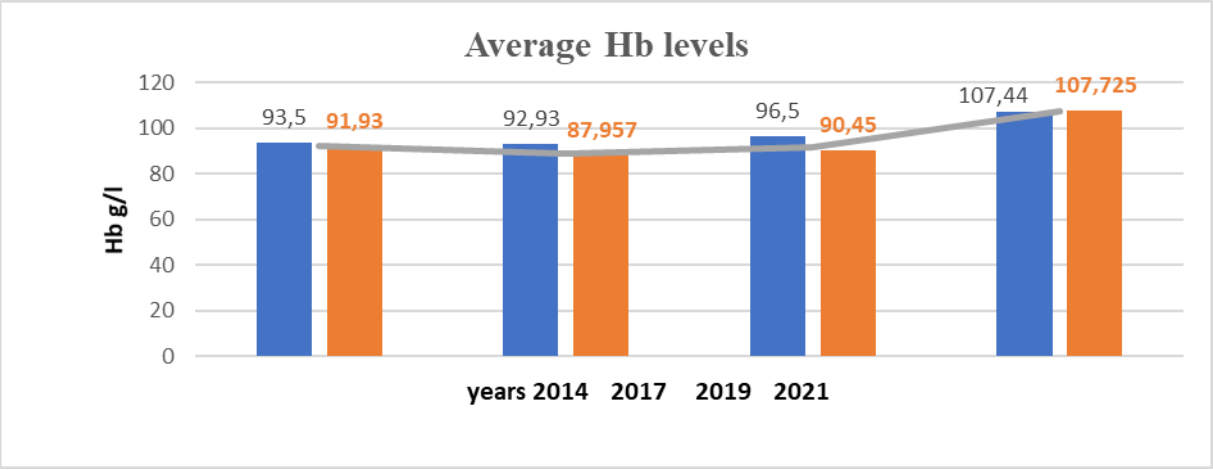

Figure 4. Comparison of mean Hb levels of patients with PTK and AVF.

Results and discussion: Over 15 years, the frequency of using PTC as vascular access for HD in the department has been constantly increasing. These growth rates correspond to modern

world trends, although not such extreme percentages. The average Hb levels of the two groups of patients have a negligible statistically insignificant difference, although a slightly higher Hb is noted in patients with AVF. No statistically significant difference was found for the average weekly dose of ESA ($p>0.05$). Despite the polymorbidity of this type of patient, the increased risk of infections, with a lot of work, effort, and resources, stable hemoglobin levels are achieved, meeting the standards for the treatment of dialysis patients. The fact is the uniqueness of monitoring the anemia syndrome in patients with PTC and the high percentage of stable Hb levels in patients on HD with PTC. There are no publications on this topic- There are no publications on this topic - comparing the average weekly dose of ESA between HD patients with different vascular access.

Our experience shows that the most common flow disorders in PTC occur with:

• Incorrect manipulation with it - ineffective flushing at the end of the dialysis session and allowing blood to enter the catheter.

• Infection of the PTC, which requires combining Nadroparin calcium with an antibiotic.

• Incorrect positioning of the catheter.

• Gradual obliteration over time.

• Filling the catheter with saline solution due to lack of financial resources.

To solve the problem of catheter thrombosis, initially, both arms of the catheter were filled with Heparin, and since January 2005. Nadroparin Calcium is used as an anticoagulant according to the following methodology: In recent years, instead of Fraxiparine Forte, we have been successfully using TauroLock U25000 (Taurolidine with 4% citrate and 25000IU urokinase), and after subsequent HD sessions - TauroLockHep 500IU (Taurolidine with 4% citrate and 500IU Heparin/ml). As a prophylaxis of PTK thrombosis, patients take nattokinase - Nataspin H - 2 times 1 capsule for the first 10 days, and then 1 capsule daily. Usually, both arms of the PTK after an HD session are washed with 40ml of physiological saline and then filled with 10,000 U of Heparin. Other systemic anticoagulants and or antiplatelet agents that are used are acetylsalicylic acid, acenocoumarol (prescribed by a cardiologist for atrial fibrillation, heart surgeries - valve prosthesis, stenting), in isolated cases - dipyridamole.

<u>on Task 3.</u> To study the relationship between the treatment of secondary hyperparathyroidism and renal anemia.

Chronic kidney disease leads to severe disorders in mineral metabolism - impaired levels of serum calcium and serum phosphorus. The imbalance of these electrolytes causes impaired mineral metabolism, increased production of PTH, hyperplasia of the parathyroid glands,

VHPT and the development of bone disease. To clarify the relationship between RA and VHPT, several follow-ups of dialysis and pre-dialysis patients were conducted. The effect of treatment with Paricalcitol, Cinacalcet, and combinations of medications was analyzed.

First follow-up. 52 patients treated with Paricalcitol in different stages of CKD were followed for 21 months - 2010-2012. The patients were grouped into two groups - Group One - pre-dialysis patients and Group Two - HD patients. All patients were administered 1 microgram of the drug. The first group included a total of 39 patients - 22 men and 17 women with a mean age of 58.18 years ± 8.18. The second group included 13 HD patients - 9 men and 4 women - with a mean age of 49 years ± 3.9. The following parameters were followed at the beginning - at the start of the drug administration and the end of the follow-up: Intact PTH, Serum creatinine, Hemoglobin, Total serum calcium, Serum phosphorus, and Calcium-phosphorus product. The data obtained are shown in the following tables:

Table 10. Results of pre-dialysis patients.

Parameters	**Mean value at the beginning of the medication**	**Mean value at the end of the observation**	**P VALUE**
Intact PTH (Pg/ml)	197,55±21,63	173,42±29,11	p=0,0355
Serum creatinine (µmol/l)	221,88±16,43	200,21±15,09	p=0,1
Hemoglobin (g/l)	113,32±2,74	118,64±2,00	p=0,02
Total serum calcium (mmol/l)	2,25±0,02	2,22±0,02	p=0,1
Serum phosphorus (mmol/l)	1,26±0,04	1,24±0,05	p=0,47
Calcium-phosphorus multiplication (mmol/l)	2,82±0,10	2,78±0,12	p=0,27

After processing the data, a statistically significant difference was found for the Hb level after the treatment, p=0.02, and for intact PTH, p=0.0355. This shows that our results are identical to the results of other authors After the treatment, a decrease in intact PTH (iPTH) and

an increase in Hb was recorded. This proves the successful effect in the treatment of RA in patients with VHPT. The effect on the level of iPTH was particularly pronounced in patients who started treatment with Paricalcitol at iPTH 80-140pg/ml (Reference value 15-68.3 pg/ml). In dialysis patients, the following were monitored: Intact PTH, Weekly dose of ESA, Hb, Total serum calcium, Serum phosphorus, and Calcium-phosphorus multiplication. The data obtained are shown in Table 11.

Table 11. Results of dialysis patients.

Parameters	**Mean value at the beginning of the medication**	**Mean value at the end of the observation**	**P VALUE**
Intact PTH (Pg/ml)	594,02±65,05	402,93±132,11	p=0,009
Serum creatinine (µmol/l)	112±1,06	110±3,9	p=0,0960
Hemoglobin (g/l)	6461,53±447,73	6076,92±858,3	p=0,0161
Total serum calcium (mmol/l)	2,25±0,05	2,1±0,04	p=0,12
Serum phosphorus (mmol/l)	2,44±0,27	2,08±0,23	p=0,4
Calcium-phosphorus multiplication (mmol/l)	5,42±0,47	4,6369±0,5	p=0,4

From the results obtained, a statistically significant difference p=0.0161 for the average weekly dose of ESA and for iTH p=0.009 after the end of the observation is evident. Adequate treatment with Paricalcidole leads to a decrease in the level of iPTH. After treatment with the drug, an improvement in RA and a decrease in the dose of ESA are found (although there is no significant difference in the Hb level at the beginning and end of the observation - Hb is maintained stable). No significant, statistically significant differences are found for Hb, total calcium, serum phosphorus and calcium-phosphorus product.

The following figures show the results for each dialysis patient: in blue - Hb at the beginning of the follow-up; in orange - at the end of the follow-up

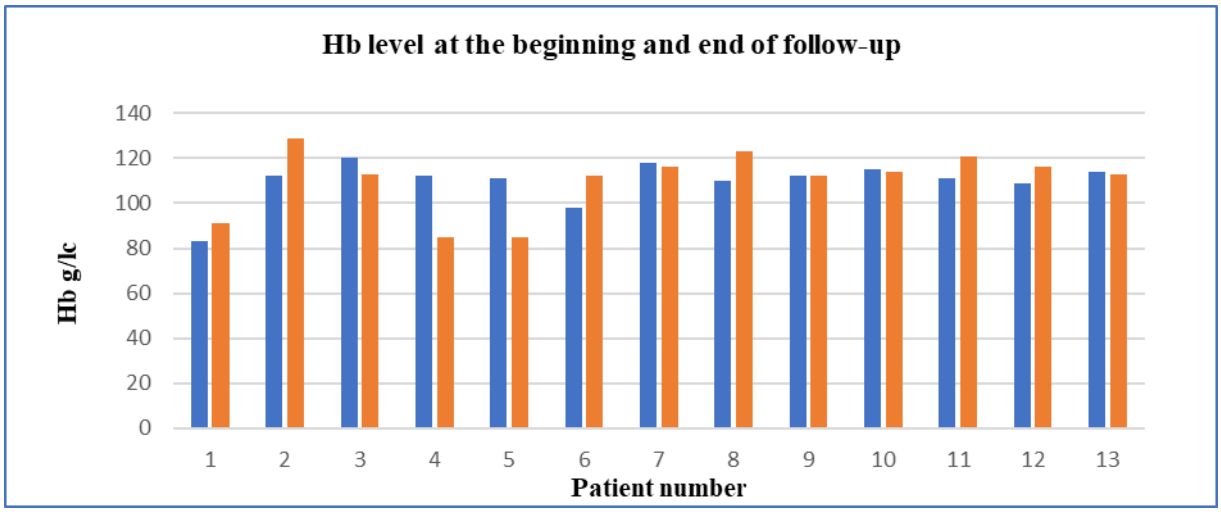

Figure 5. Comparison of mean Hb levels of patients.

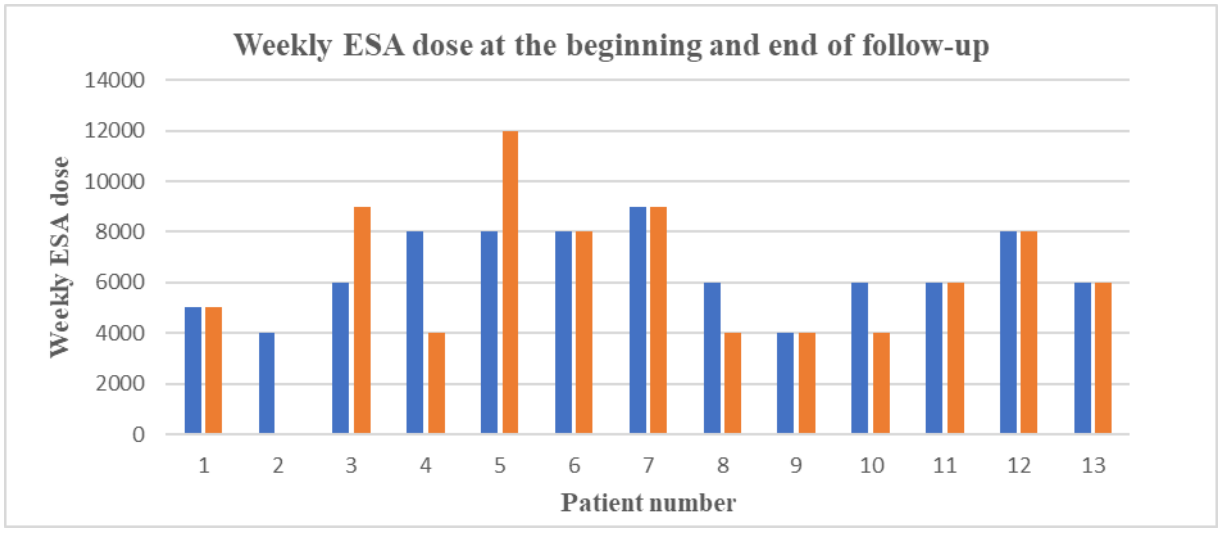

Figure 6. Comparison of weekly ESA dose at the beginning and end of follow-up.

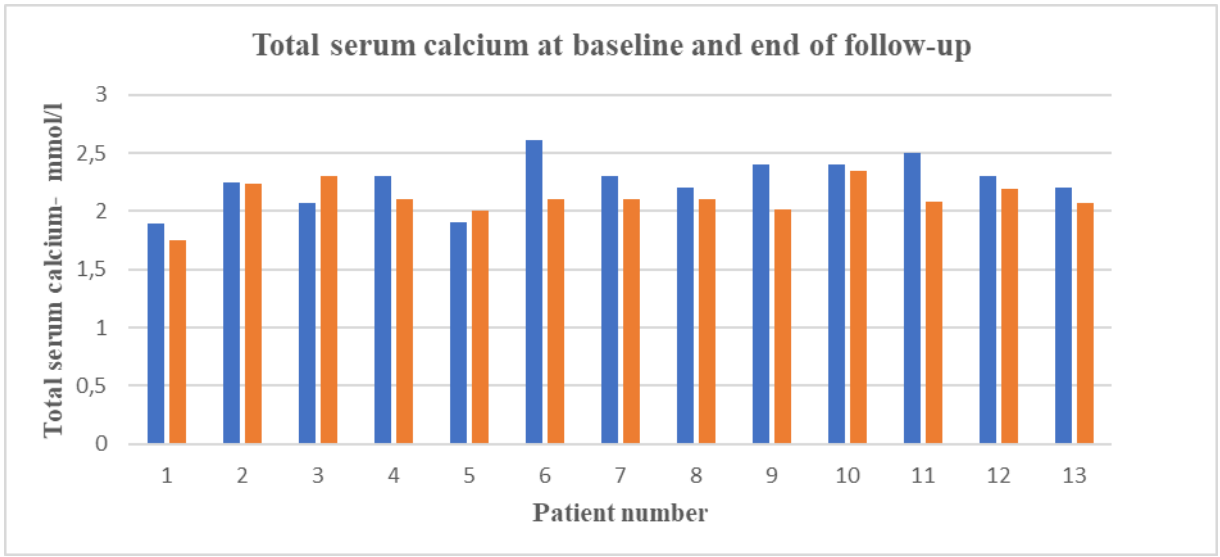

Figure 7. Comparison of Total serum calcium at baseline and end of follow-up.

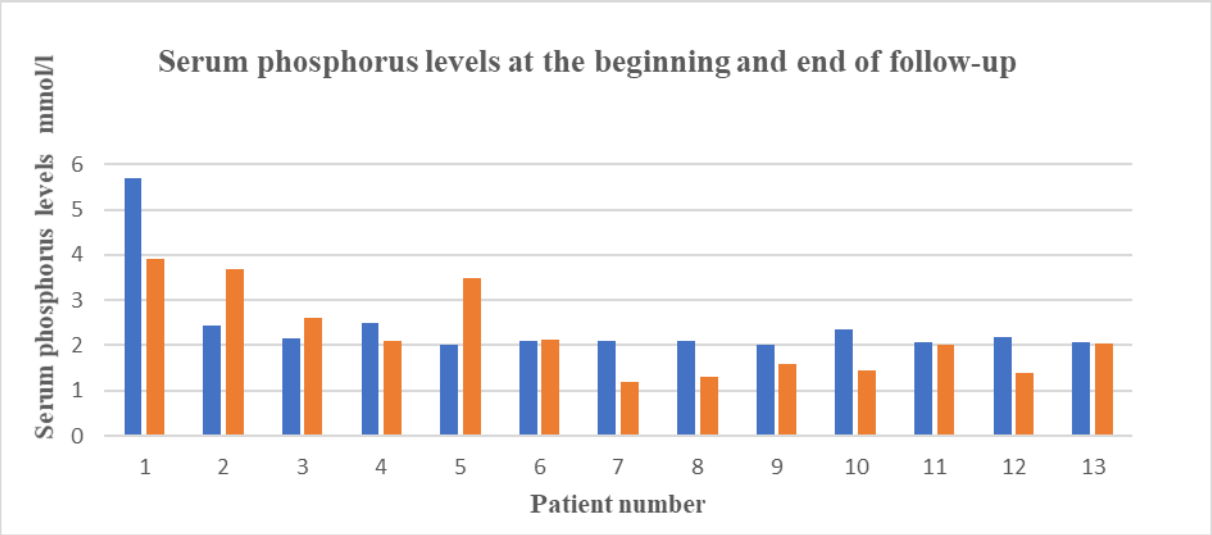

Figure 8. Comparison of Serum phosphorus levels at the beginning and end of follow-up.

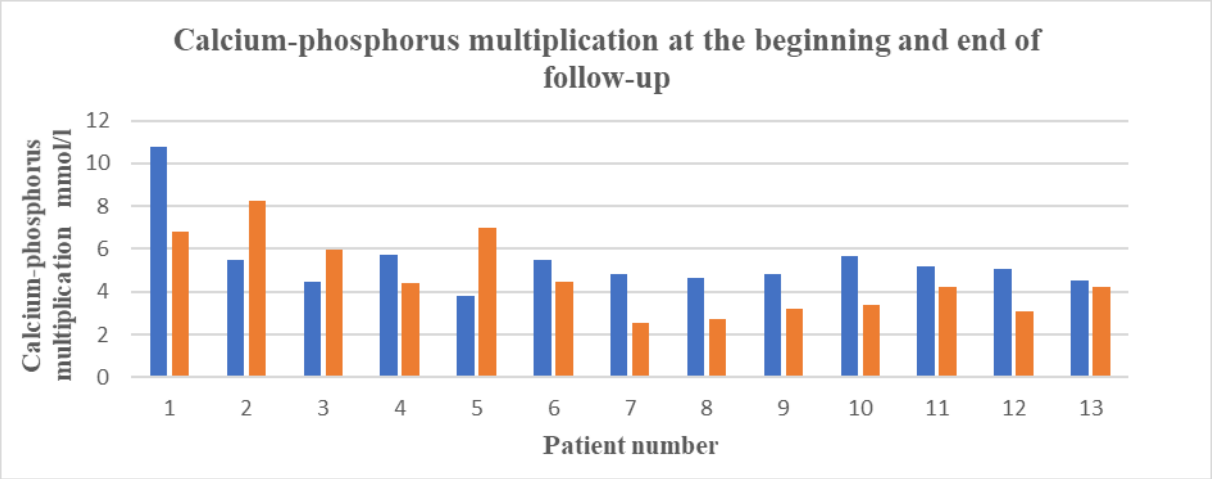

Figure 9. Comparison of Calcium-phosphorus multiplication at the beginning and end of follow-up.

During the treatment of VHPT, an optimized approach to the complex management of CKD was followed, which included a hygienic dietary regimen, HD, ESA, calcimimetics, phosphorus binders, BDRAs, Vitamin D, vitamins, and minerals, with the goal of improving the patients' quality of life.

Second follow-up: 58 HD patients were examined for serum levels of Ca, phosphorus, and iPTH. All patients had pronounced hyperphosphatemia. 20 patients with a level of iPTH above 300 pg/ml - 12 men and 8 women - were selected. Treatment with cinacalcet was started for all, with a serum Ca level above 2.2 mmol/l. The patients were followed for the period from

26.6.2010 to 30.10.2010 - 4 months. The tests of Ca and P are performed every 14 days in the laboratory of the University Hospital "St. Anna" Sofia.

The tests for iPTH were performed in the Bodymed laboratory.

Blood collection technique for PTH: Before starting the HD procedure, blood is taken in a vacuum container. It is placed on ice for about 30 minutes. It is centrifuged at 3500 rpm/5 min. The separated serum is pipetted into a micro “Eppendorf” tube and stored in a freezer until delivery to a courier from the laboratory and transported to the laboratory in a refrigerated bag.

Treatment with Cinacalcet was applied to 20 patients on HD. 2 patients dropped out of the group due to: Vomiting and headache after taking the first 2 tablets - 1 patient; Hypersensitivity to medications - 1 patient.

All patients started with a dose of 30 mg/day of the medication.

During the control tests of PTH, a decrease was found in 14 patients.

According to the results obtained, a dose adjustment was made:

In 5 patients, the dose was reduced to 30 mg/day due to a decrease in the level of iPTH; In patients with a higher level of iPTH than the initial one, the dose was increased to 60 mg/day; In 1 patient, the amorphous nodules decreased in size or disappeared.

The results of the use of Cinacalcet show:

A tendency towards normalization of the level of serum phosphorus and normalization of iPTH; Improvement of the subjective complaints of the patients; The use of the drug in HD patients is effective and highly effective; Careful selection of patients and their cooperation are key to the success of the treatment. The effect of the drug at high levels of serum Ca is particularly pronounced and in a positive aspect.

After the short, 4-month observation of dialysis patients, a longer observation was carried out for a year and a half.

Third follow-up: As of 30. 10. 2010. In the Department of Hypertension of the University Hospital "St. Anna" AD Sofia, 60 patients were treated with HD. Of these, 24 were women and 36 were men. PTH was also tested in 46 patients. 20 patients were selected - 14 men and 6 women with PTH over 700 pmol/ml and treatment with Cinacalcet 30 mg/day was started. As of April 30, 2012, 11 patients from this group continue to be treated with good effect. The duration of the observation is 1 year and 6 months = 18 months. Initially, calcium and phosphorus are tested weekly, then monthly, and, if necessary, substitution with Calcium Carbonate tablets is applied. Reasons for the patients who dropped out are: In 2 patients, treatment was discontinued after one week of treatment due to severe gastroenterocolitis

syndrome; After 1 year of treatment, 2 patients dropped out due to poor collaboration; After 10 months of treatment, 1 patient was transferred to another dialysis facility; 4 patients died.

Patients with VHPT, suitable according to the clinic and paraclinic, were treated with active vit. D3. These were from 12 to 30 patients in different periods of time depending on the serum levels of calcium and phosphorus. Of these, 1 patient received active vit. D3 + Paricalcitol. 5 patients were treated with Paricalcitol. 10 patients were treated with phosphorus scavengers /Renagel/ due to hyperphosphatemia. 7 patients received phosphorus scavengers for periods of 6-9 months + Cinacalcet. 59 patients were treated with ESA. 15 patients were followed for 2 and a half years. 11 patients were treated with Cinacalcet and 4 - with Paricalcitol. The results are shown for two periods - 1 year before starting treatment and 1 and a half years of treatment with Cinacalcet or Paricalcitol. The average age of the patients is 45.13 years ± 3.25 Min. - 21 years. Max. - 68 years. The duration of HD treatment is 5.26 ± 0.91 years. Min. - 1 year. Max. - 14 years. Of them 4 are women, 11 - men.

The group treated with Cinacalcet consists of 11 patients - 2 women and 9 men.

The group treated with Paricalcitol consists of 4 patients - 2 women and 2 men

Hb levels of the patients before and after starting treatment with Cinacalcet/Paricalcitol are shown in the following figures.

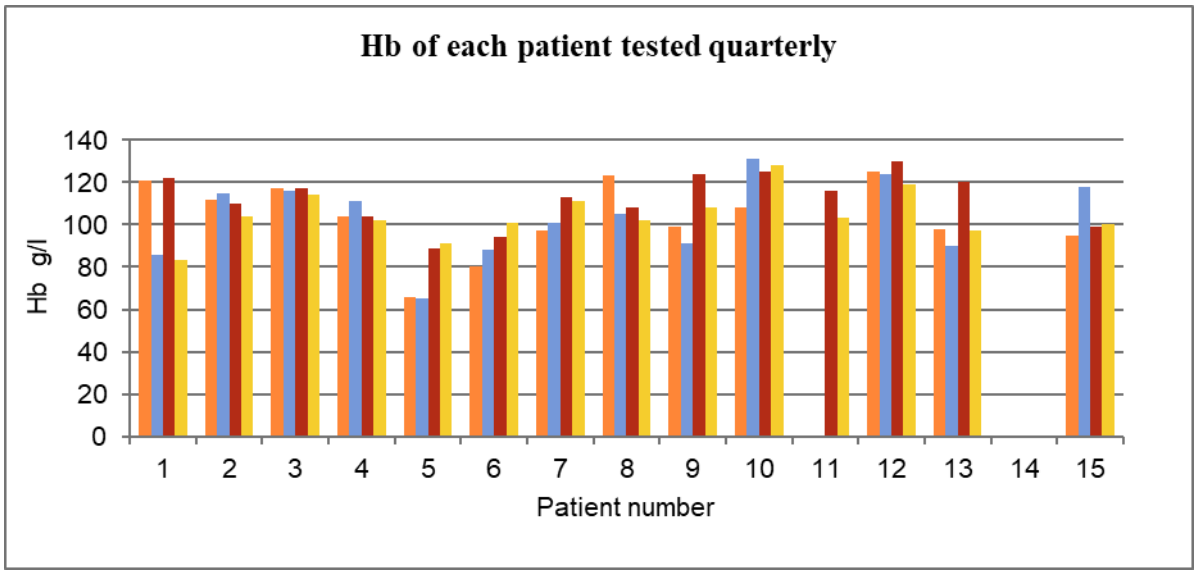

Figure 10. Hb level/ by quarter/ before starting treatment with Cinacalcet or/and Paricalcitol

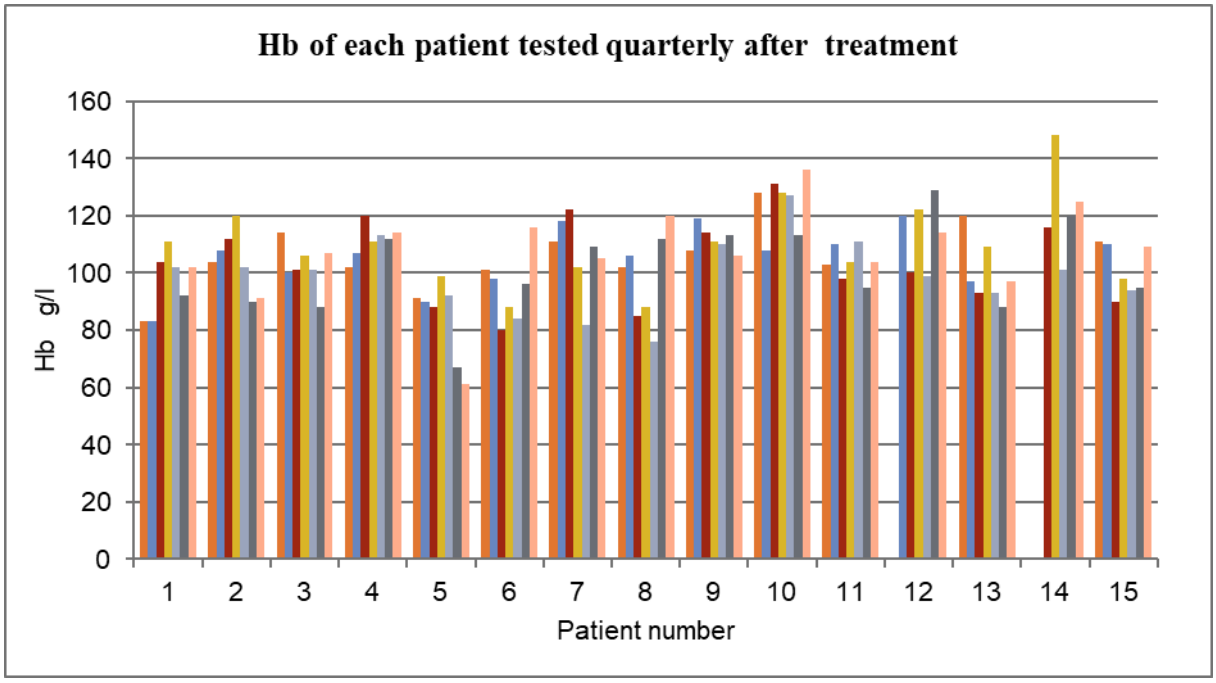

Figure 11. Hb level/ by quarter/ individually for each patient after treatment with Cinacalcet or/and Paricalcitol.

The average Hb level of the entire group for 1 year. before starting treatment with Cinacalcet/Paricalcitol is Hb 105±96 g/l min 63.7 max 124. For 1 year and a half after treatment with Cinacalcet/Paricalcitol, the average Hb level is 106±48 g/l min. 61.3; max. 148. The weekly doses of ESA before and after starting treatment with Cinacalcet or/and Paricalcitol are reflected in the following figures:

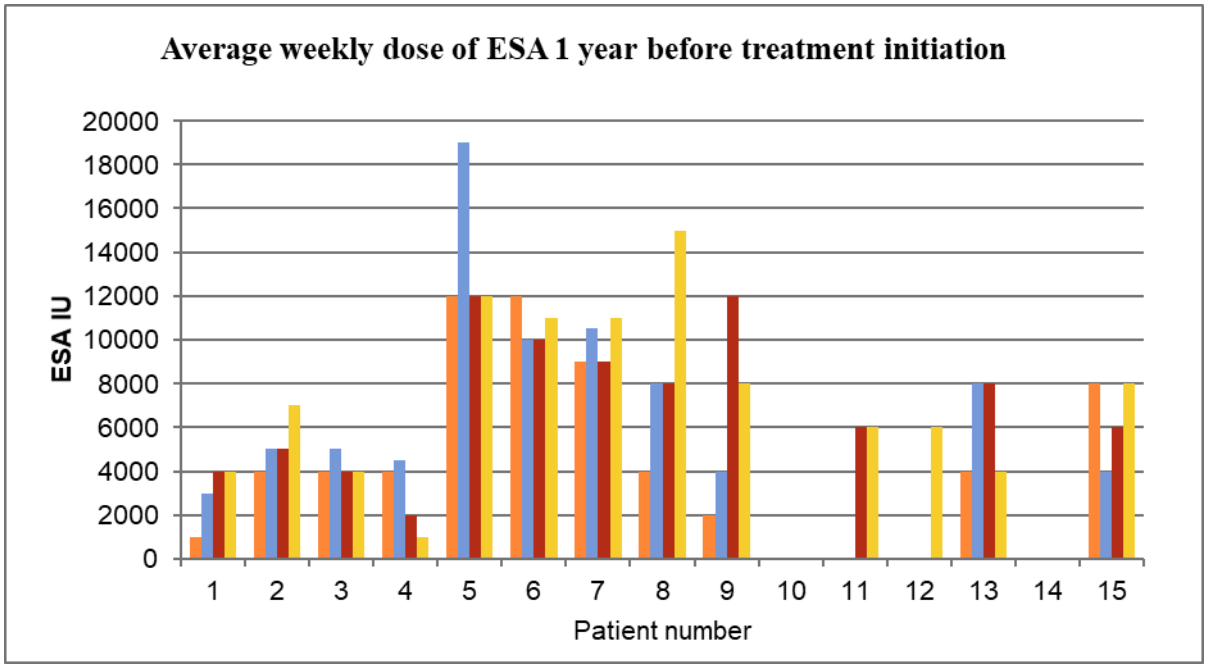

Figure 12. Average weekly dose of ESA = 5857.143 IU before starting treatment with Cinacalcet or/and Paricalcitol

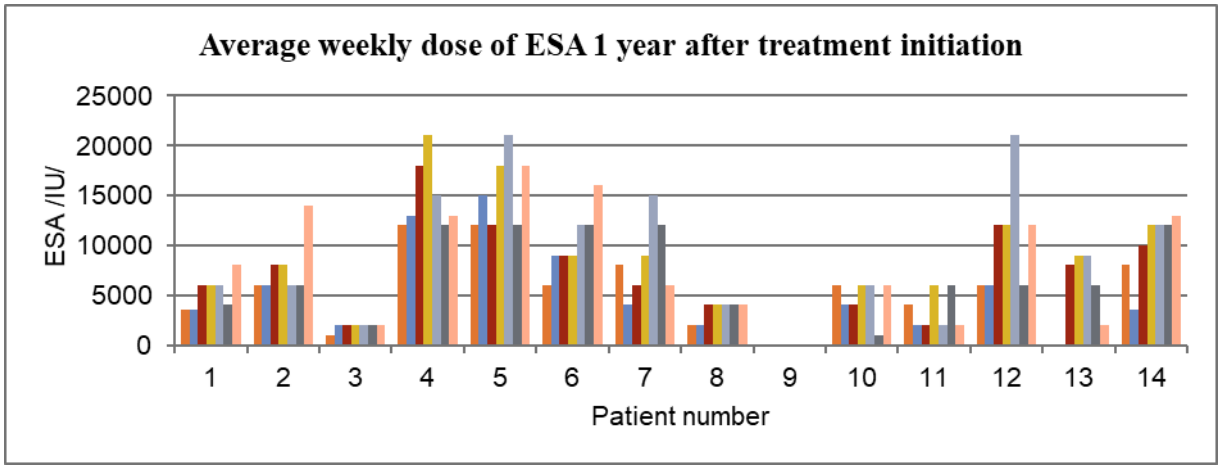

Figure 13. Average weekly dose of ECA = 6157.142 IU after treatment with Cinacalcet or / and Paricalcitol

A slight increase in the dose of ESA was reported after administration of the medications, but the difference was statistically insignificant - p = 0.08.

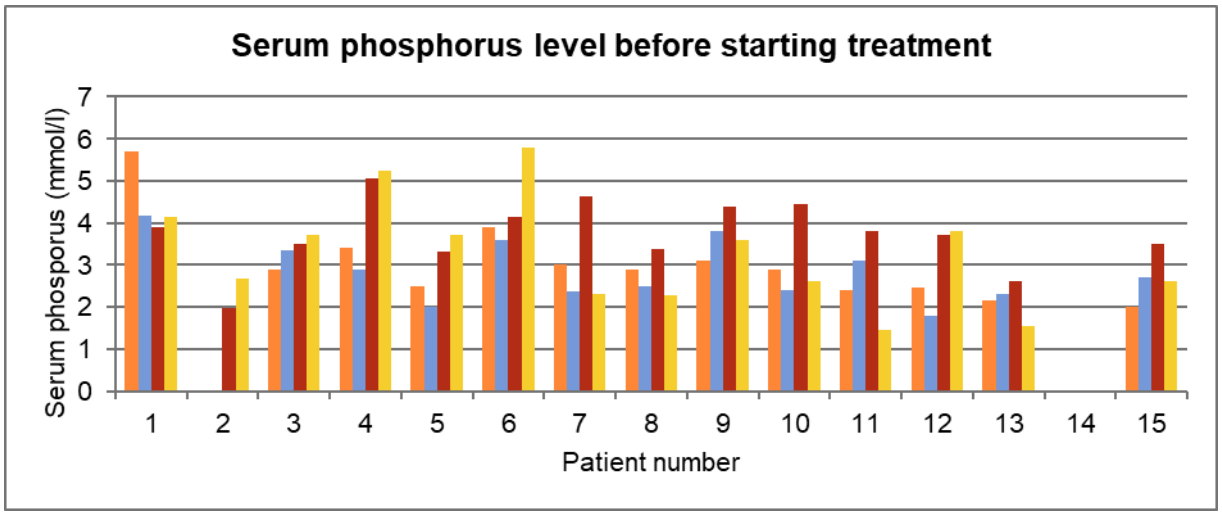

Figure 14. Average serum phosphorus level = 3.10 mmol/l before starting treatment with CINACALCET or/and PARICALCITOL

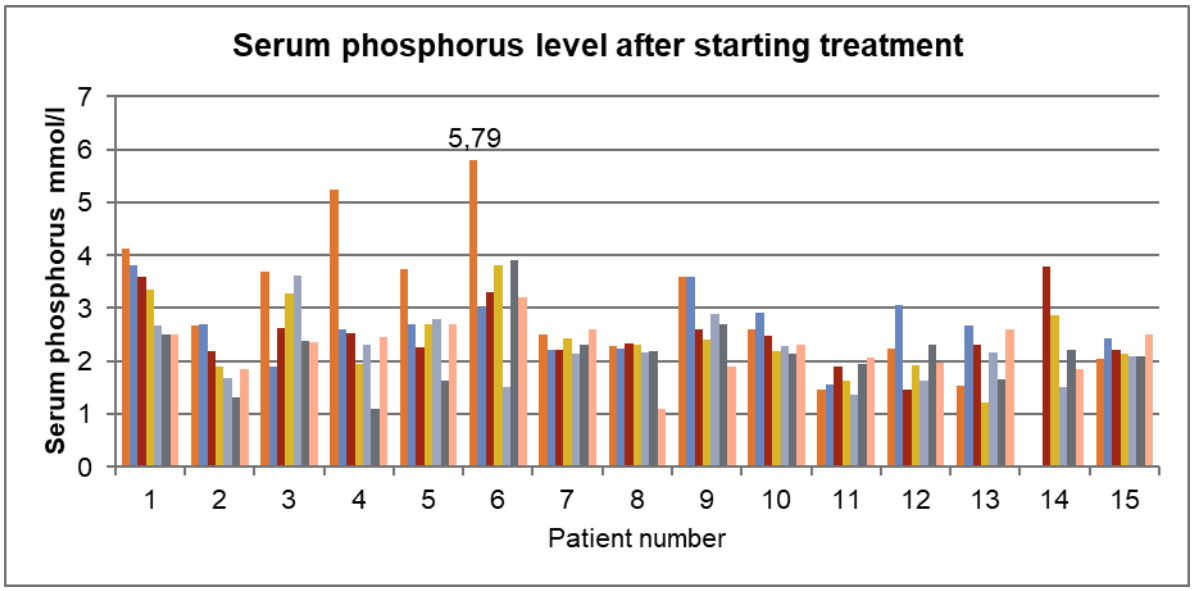

Figure 15. Average serum phosphorus level = 2.41 mmol -l after treatment with Cinacalcet or/and Paricalcitol

A decrease in serum phosphorus level was reported after 18 months of treatment with Cinacalcet or/and Paricalcitol

The eighteen-month observation of the patients confirmed the results of treatment with Cinacalcet from the previously, conducted for 4 months observation. Combining medications leads to better management of calcium-phosphorus metabolism and quality of life - with an increase in Hb level. Only through strict paraclinical control, and good collaboration between patients and staff can the complex treatment of patients with CKD be optimized individually for each patient. This is done by administering one or more medications. The application of an optimized approach to the complex treatment of CKD with HD, ESA, Calcimimetics, VDRAs, Vit D3, phosphorus scavengers, HDR, vitamins and minerals achieves the goal of a better quality of life and good results in the treatment of renal anemia.

<u>On Task 4.</u> To assess the conversion from short-acting to long-acting ESAs, and vice versa, in patients on dialysis and those not on dialysis treatment.

The observation assesses the stability of Hb levels when using long-acting ESAs (LAESA) and finds out whether switching treatment from Short-acting ESAs (ShACEs) to LAESA and vice versa leads to abrupt changes in Hb levels and serum creatinine and whether this poses risks for the patient and difficulties for medical specialists. All patients are also on therapy with iron medication - oral or intravenous and do not have iron deficiency.

A total of 91 patients were followed up - for periods of 12 months (in 2010 and 2022-23). Of these: 71 patients had CKD and anemia in the pre-dialysis period /group 1A and 1B/ in 2010.

13 HD patients (group 2A and 2B) in 2010 and 7 HD patients (group 3 in 2022-2023.

The results of a 90-year-old patient for 10 years with a different sequence of treatment are also presented - from 2005 to 2015 with a long history of CKD and anemia before starting treatment with ESA. Hb levels and serum creatinine were examined at 3 months.

The results of the observation of 3 groups of patients with RA and CKD, treated with ShAESA and LAESA are presented. The initial therapy was of one or the other type in a different sequence of switching the type of ESA.

1. First group - in the predialysis stage with 2 subgroups: 1A. Patients treated with NeoRecormon switched to treatment with CERA. 1B. Patients treated with CERA → NeoRecormon → CERA.

2. Second group - in the dialysis stage with 2 subgroups: 2A. Patients treated with NeoRecormon → CERA → NeoRecormon. 2B. Patients treated with MIRCERA switched to treatment with NeoRecormon.

3. Third group - in the dialysis stage, treated with Binocrit and then with CERA

The treatment regimen for patients in group 1A is 6 months of treatment with KDESA-Neo Recormon in a dose according to the Hb level - for Hb below 90 g/l - the dose is 100 IU / kg, subcutaneously, two or three times a week, and for Hb 9-11 g/dl - 90 IU / kg and then in individual maintenance doses with the aim of constant Hb levels of 110-120 g/l. When switching treatment to LAESA in this group, CERA is dosed for 3 consecutive months 2 times a month at 0.6 μg/kg of weight and the next 3 months-1.2 μg/kg subcutaneously once a month.

In patients from group 1B, CERA is initially started in corrective doses of 0.6 μg/kg subcutaneously twice a month for 3 months. Then 6 months. treatment with KDESA is applied and then 3 months of CERA at a dose of 1.2 μg/kg.

In the second group of patients - in the dialysis stage, the treatment regimen in group 2A is - 6 months. treatment with ShAESA. and then months. Long-acting ESA(LAESA), then again 3 months. ShAESA, with the difference that the supplies under Regulation 34 in the DTD for the year are irregular and insufficient to reach target Hb levels of 110-120 g/l. Treatment with CERA was carried out with the kind assistance of Roche in the form of a donation to the Hemodialysis Department.

The therapeutic regimen of patients from group 2B is treatment in a corrective dose of CERA 0.6 μg/kg subcutaneously every 15 days for 3 months, followed by 9 months of treatment with ShAESA.

The therapeutic regimen of patients from group 3 is 6 months of treatment with Binoclit subcutaneously in doses that correspond to the Hb level, then 6 months of CERA at a dose of 1.2 μg/kg once a month.

1. First group - with 2 subgroups: 1A. Patients treated with NeoRecormon →CERA. 66 patients were observed, with an average age of 68.24 years. Of these - 35 men and 31 women. The Hb levels of the patients were monitored: before the inclusion of treatment with ESA; after 6 months of treatment with KDESA = start of treatment with DDESA, after 3 months of treatment with DDESA; after 6 months of treatment with DDESA. The serum creatinine level was also monitored. The results are presented in the following figures.

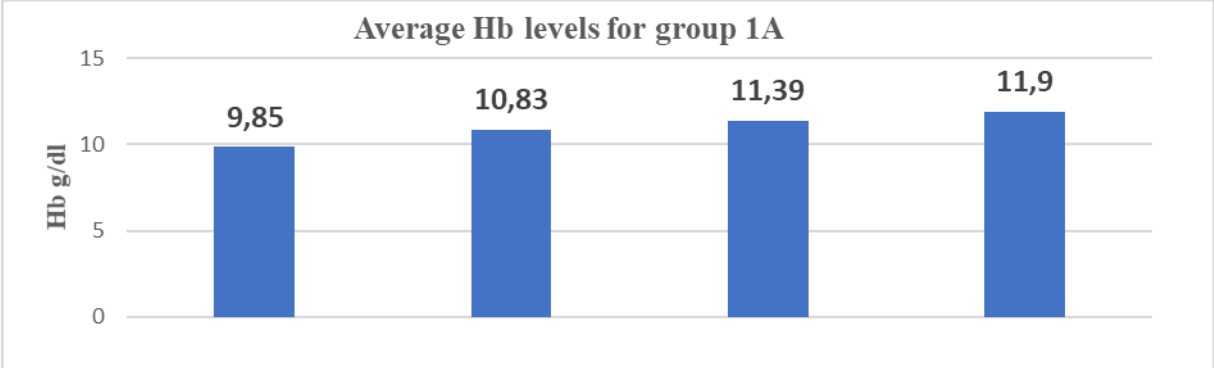

Figure. 16. Slow and smooth increase in Hb level of patients from group 1A of tracking.

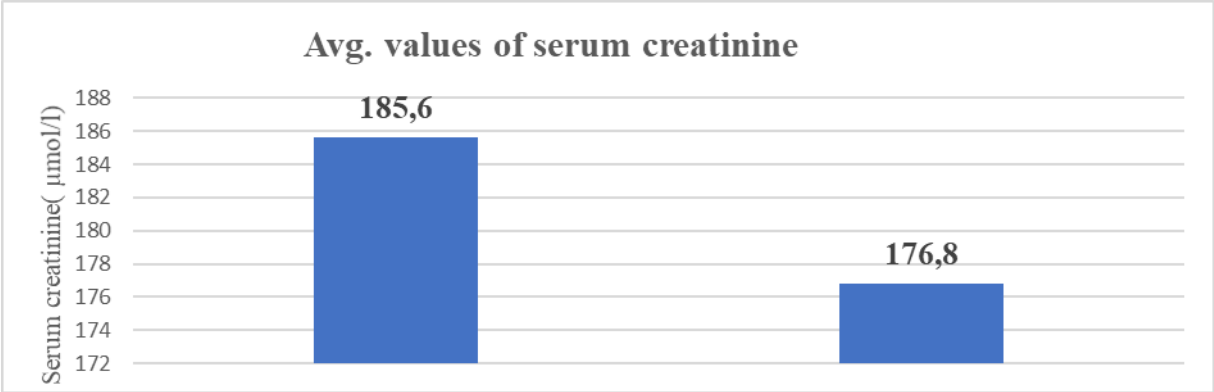

Figure 17. Average serum creatinine values of patients from group 1A from the beginning to the end of tracking.

The results of the Hb tests of patients from group 1A are in a very narrow range and remain constant with a smooth increase. Only in 1 patient (female) there is an increase in Hb to 13.9 g/dl in the 6th month after administration of LAESA at a dose of 100 µg/month. The next dose was administered after a 40-day interval and the following six months of treatment with a 25% lower dose was prescribed - i.e. 75 µg/month.

The results of the studies of patients from group 1B, who were treated in the sequence LAESA→ShAESA→ LAESA are shown in Figure 20. Five patients were observed with an average age of 68.8 years ± 4.2 years. With a duration of CKD from 1 to 5 years and a duration of anemia of 2.6 years ± 0.4. The starting Hb of the 1B group was 93.6 g/l ± 0.448. This was followed by 3 months of treatment with DDESA at a dose of 0.6 micrograms/kg

subcutaneously every 15 days, then 6 months of treatment with ShAESA, and then 3 months of treatment with LAESA again for 30 days subcutaneously at 1.2 µg/kg. At the end of the observed period, the average Hb level of the subgroup was 123 g/l ± 0.114. No significant difference was observed during follow-up of the ser. creatinine at the beginning and end of follow-up.

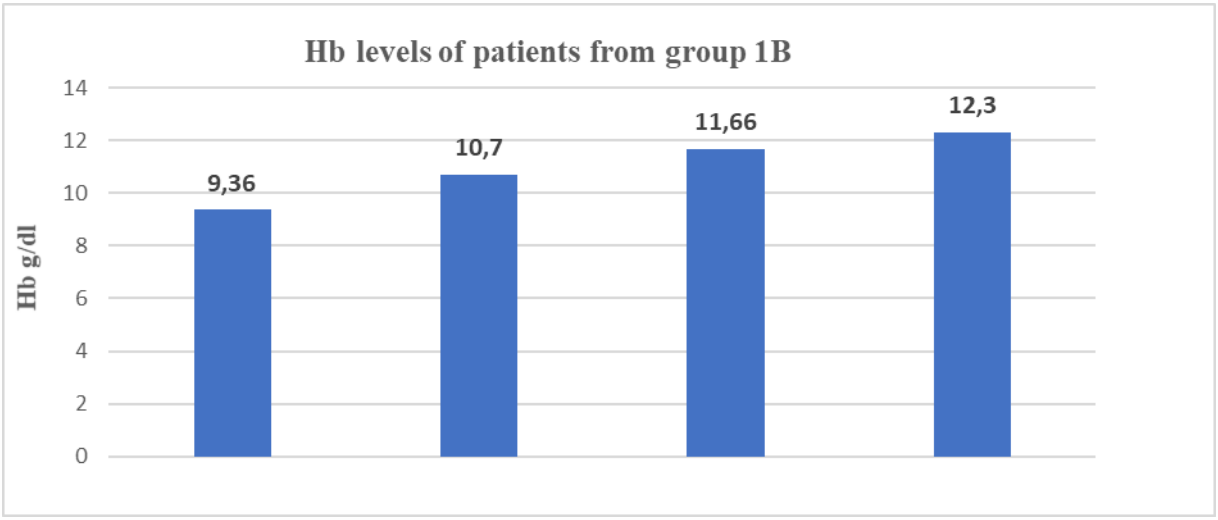

Figure 18. Results of the studies of patients from group 1B

Serum creatinine was also monitored at the beginning and end of the year and a very slight increase of 10 micromol/l was reported, and the number of patients monitored was only 5.

The results of the second group of patients with RA on HD were much different. 13 patients were monitored in 2 subgroups. In group 2A, 8 patients were monitored with a mean age of 52.75 years ± 20.26, and the mean duration of HD treatment was 3.56 years ± 1.97. The patients were treated with ShAESA-6 months, then with LAESA at a dose of 1.2 µg/kg. subcutaneously once a month for 3 months and then again with ShAESA for 3 months, according to the Hb level. The results are presented in Figures 21, 22.

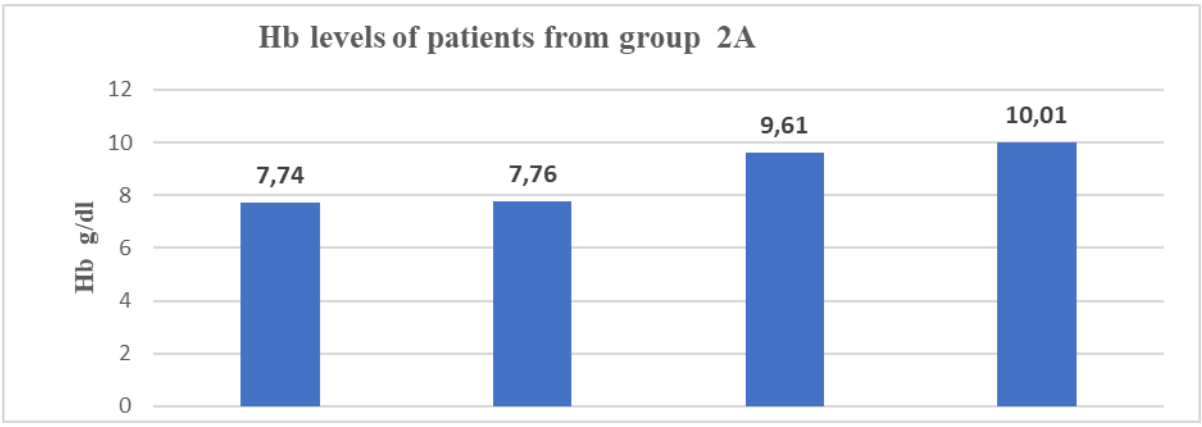

Figure 19. Results of Hb Levels in Group 2A Patients

An increase in the average hemoglobin (Hb) level was observed in patients from group 2A after 1 year of treatment with a modified treatment sequence.

Figure 20 below illustrates the average serum creatinine values over 1 year for patients in group 2A. A minimal increase of 14.5 µmol/L was reported during this period.

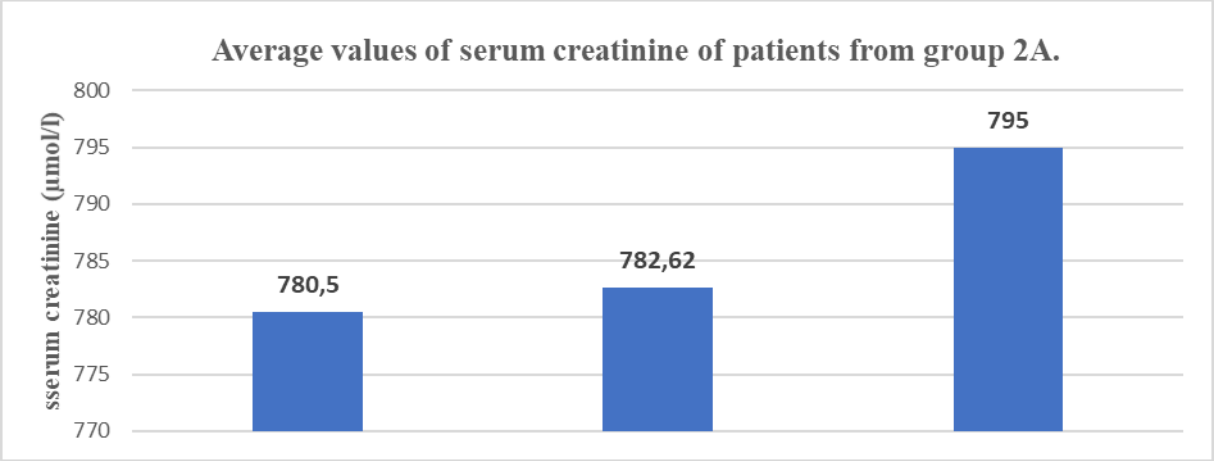

Figure 20. Average values of serum creatinine of patients from group 2A.

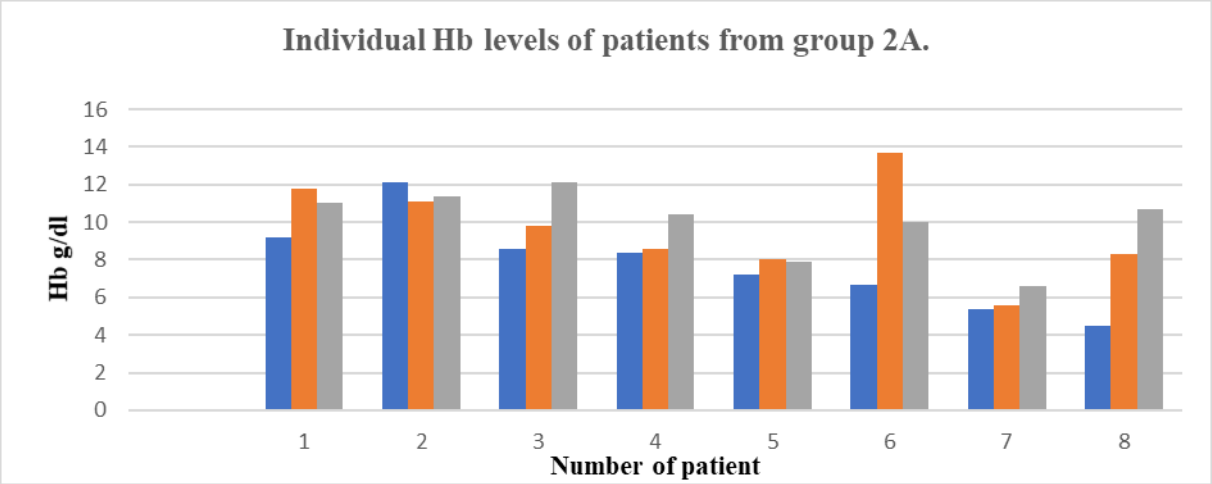

Figure 21. Individual Hb levels of patients from group 2A.

A distinct effect was observed in the treatment with LAESA. A low average Hb level was noted in the treatment with ShAESA during the first 6 months, but this can be explained by the insufficient quantities of the medication received under Regulation 34 in the Dialysis Department in 2010. Two patients 5 and 7 have long-standing chronic kidney disease, treated with pulse therapy with cytostatics and corticosteroids, then they were included in HD, and after a few years they were 2 years with a transplanted kidney and again on therapy with

cytostatics and corticosteroids, they experienced the reactions of chronic rejection of the transplant and were again included in HD. Both of them have severe hyperparathyroidism and hypertensive disease. In these patients, Hb levels before being included in treatment with LAESA were 61-72 g/l. Figure 22 shows the results of group 2B.

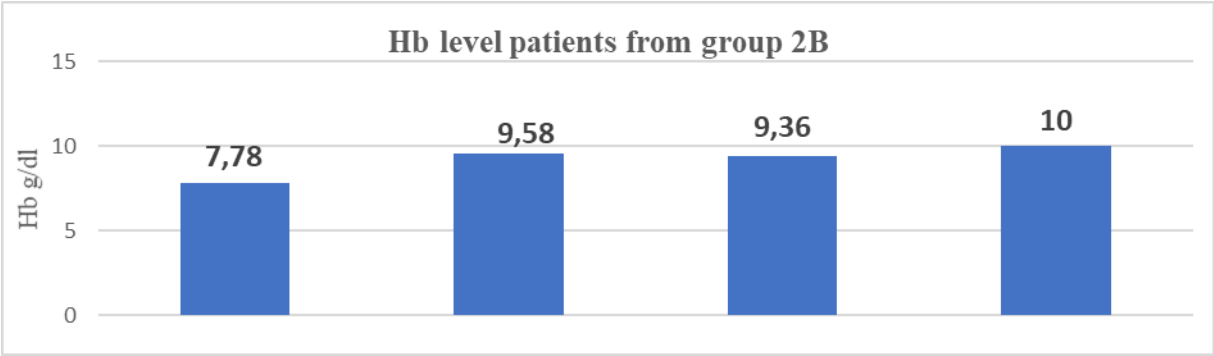

Figure 22. Results of patients from group 2B.

Figure 23 shows the Hb levels of each patient for the observed time. Exceptional stability is shown by the Hb of patient 5. This is a 74-year-old man who has been observed since the predialysis stage when he was treated with LAESA and Hb was 107 g/l. With worsening of renal function and the onset of HD, treatment with LAESA continues, and Hb remains 107. Later, the patient switches to treatment with ShAESA. Hb remains the same.

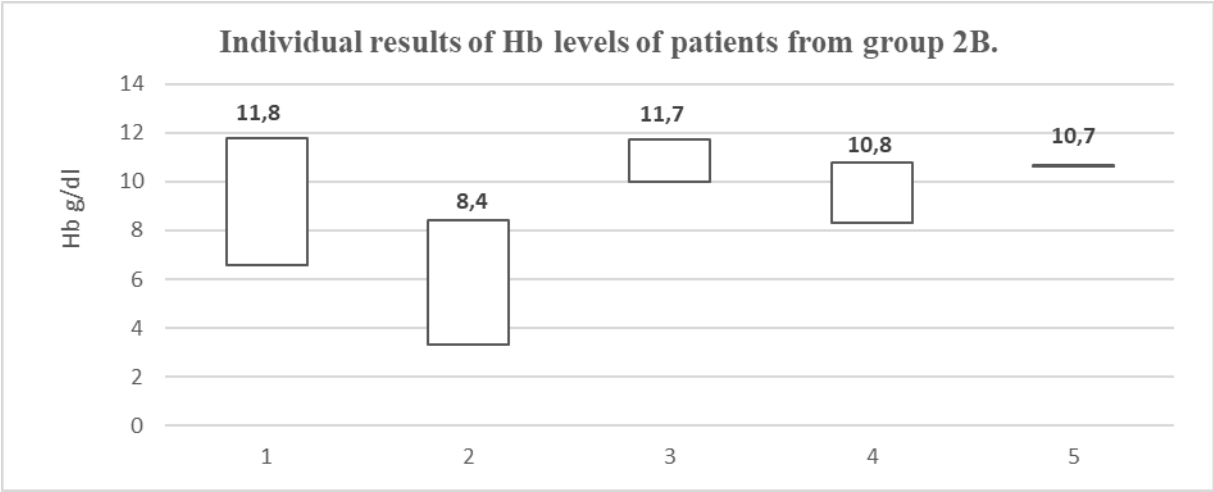

Figure 23. Individual results of Hb levels of patients from group 2B.

The third group included 7 patients with a mean age of 57.14 years ± 16.87 years - from 23 to 76 years. 6 men and 1 woman were followed up. The data from the obtained results are presented in Figure 26.

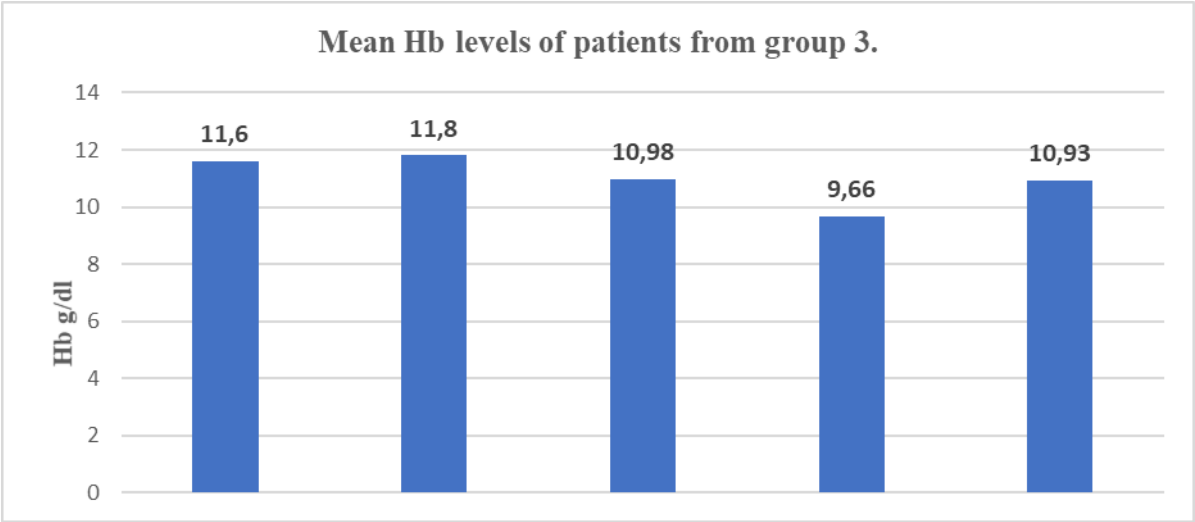

Figure 24. Mean Hb levels of patients from group 3.

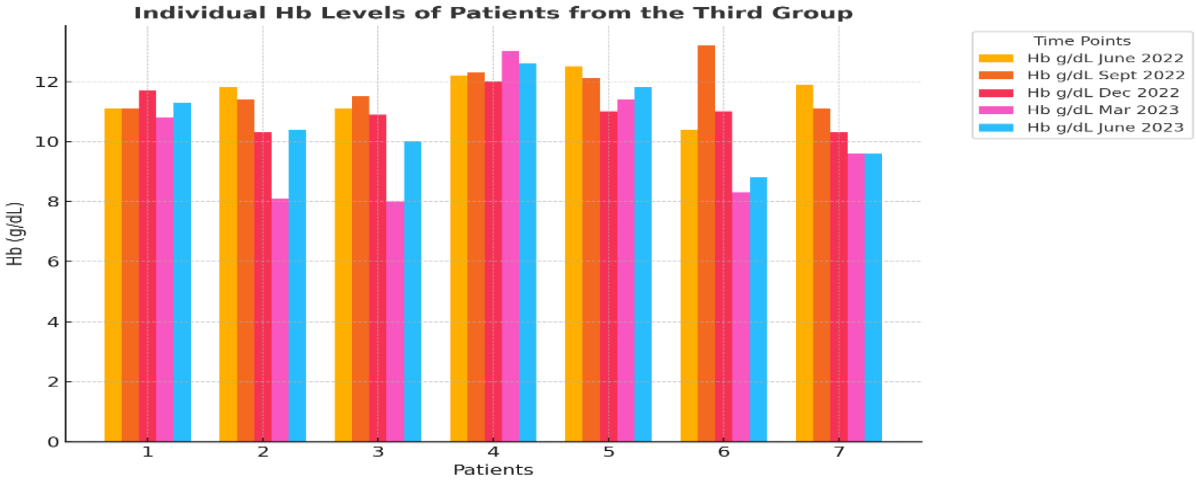

Figure 25. Individual Hb levels of patients from group 3.

When comparing the results for Hb levels after 6 months of treatment with Binocrit and 6 months with CERA, no statistically significant difference was observed ($p = 0.05126$). Regardless of the type of treatment—ShAESA or LAESA—the difference in Hb levels remains insignificant.

Moreover, regardless of the sequence of ESA treatment, Hb levels and serum creatinine values remain stable.

Why might the use of CERA be preferred over other ESAs?

For all patients with Anemia and CKD - on hemodialysis and in the predialysis period: CERA has a half-life of 139 hours and is administered every 15 or 30 days. With the introduction of CERA, a new era in the treatment of anemia begins; CERA offers real benefits in the treatment and ensures stable hemoglobin values with a single monthly administration; Hb values are effectively maintained stable, regardless of the route of administration of the drug (i.v. or s.c.); The safety profile is comparable to that of ESA with a short half-life; It is well

tolerated; The treatment is convenient for the patient; A high success rate is demonstrated in correction, target hemoglobin values are achieved. The Hb threshold of 13 g/dl is rarely exceeded; it provides a smooth and stable increase in hemoglobin levels. No cases of Pure Red Cell Aplasia have been reported.

The single monthly administration of ESA saves time for the staff and provides more time for the patient. With the lower number of injections per year (12 in number MIRCERA) compared to ShAESA - half-life EPO alfa or Epo beta - 2 times, or 3 times a week = 96 or 156, applications respectively per year or with Darbepoetin alfa 1 time a week = 52 applications per year, the risk of pricking the staff is minimized and, in addition, the patient is minimally traumatized. The fewer injections and pain with subcutaneous administration motivate patients to adhere to their treatment.

There are other real benefits – for example, the storage of CERA at room temperature for 31 days compared to other ECAs - Darbepoetin alfa - 7 days, Epo beta - 3 days, and fl. - 5 days. EPO alfa - 1 day.

<u>To Task 5.</u> To evaluate the response trend to ESA treatment in dialysis patients, depending on whether they received ESA prior to initiating dialysis. An individualized and comprehensive approach is essential in managing renal anemia in CKD patients, both during dialysis and in the pre-dialysis phase.

The answer to the following question remains unclear: Do patients treated with ESA before progressing to ESRD exhibit different hemoglobin levels and/or resistance to ESA after initiating renal replacement therapy compared to those not treated with ESA prior to dialysis?

The number of dialysis patients in Bulgaria is steadily increasing, currently exceeding 3,700. However, the proportion of CKD patients starting planned HD sessions, as well as those receiving ESA treatment during the pre-dialysis period under nephrological supervision, remains small. This underscores the need for comprehensive studies focusing on this patient population, which forms the basis of the current follow-up.

Over 12 years, the following were followed by gender: age, Hb levels, ERI, dosage of ESA in patients with intermittent HD in the DTD of UMBAL "St. Anna" Sofia - from 2009 to 2020. The patients were grouped into two groups - group A - patients who received ESA before being included in HD and group B - patients who did not receive ESA before being included in HD. 286 women and 489 men were followedA total of 775 patients were included in the study. A comparative analysis was performed between group A and group B based on gender. The female patients in group A were compared to the male patients in the same group, as well as the

women in group B to the men in the same group. The following parameters were analyzed: age, mean Hb level, mean weekly ESA dose, mean weekly ESA dose per kg of body weight, and ERI.All subjects were surveyed using a standardized questionnaire to provide the following data: gender, age, weight, predialysis observation, and ESA administration in the predialysis period. Hemoglobin is tested. ERI is calculated using the formula.

Figure 26 presents the data for patients who were observed by a nephrologist before starting HD and treatment with ESA before HD. Annually, at the beginning of January, a survey is conducted using a standardized questionnaire to provide the following data: gender, age, predialysis observation, and ESA administration in the predialysis period. Patients are examined - complete blood count and biochemistry, weekly dose per patient is monitored, as well as weekly dose per kg/weight, and ERI is calculated for each patient.

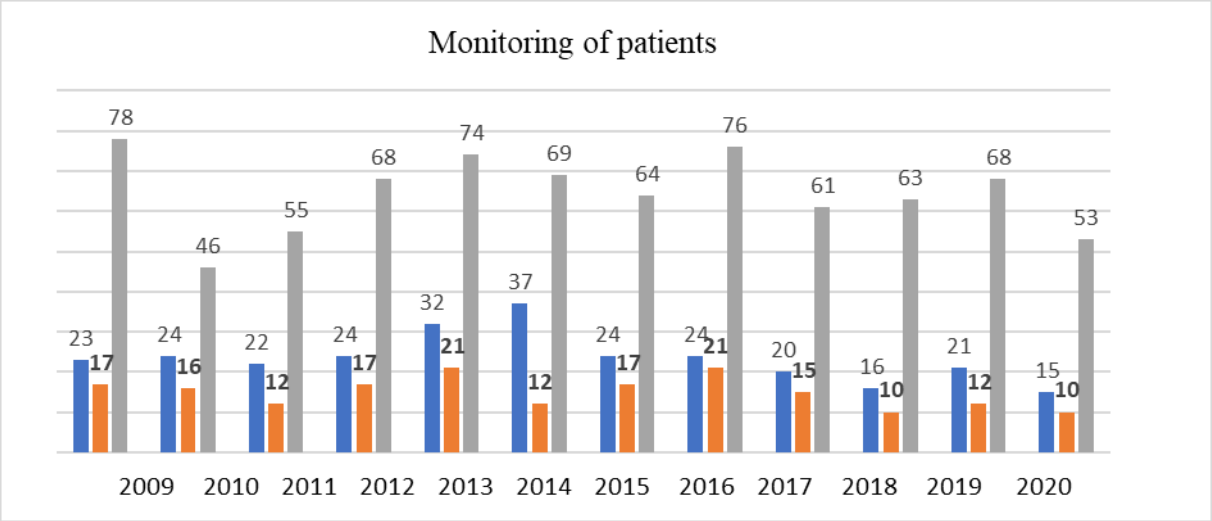

Figure 26 Monitoring of patients observed by a nephrologist (in blue color) and treated with ESAs (in orange color) and comparison with the total number of HD patients during the years 2009-2020.in the ODL of UMHAL "St. Anna" AD Sofia

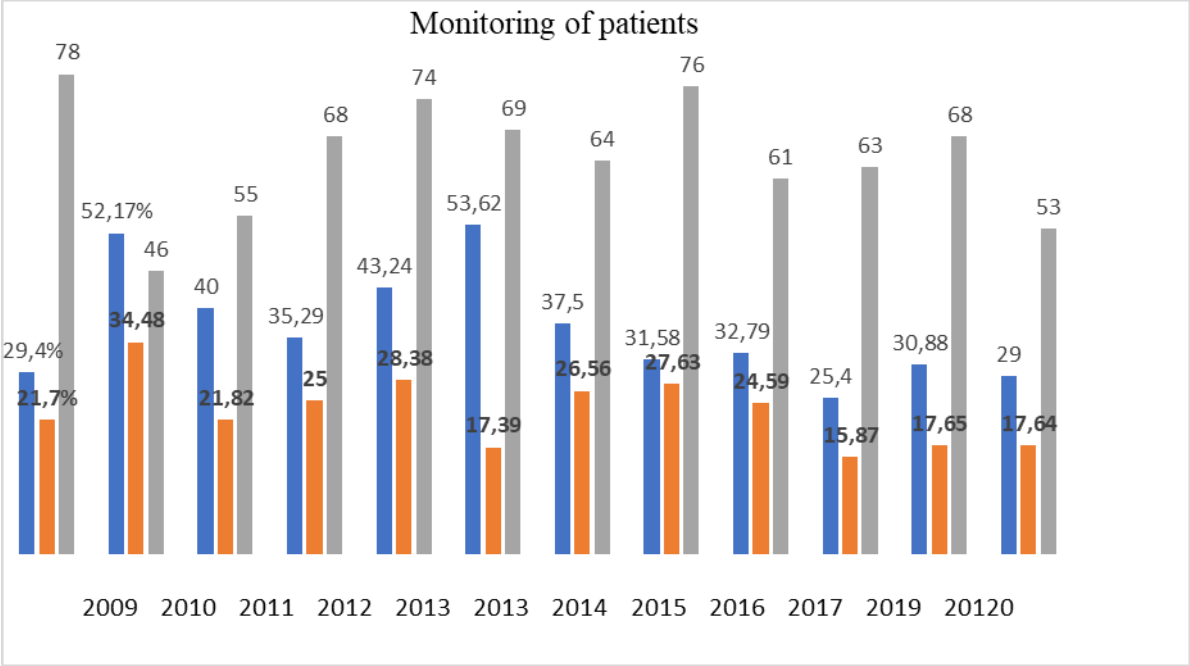

Figure 27.Monitoring of patients under nephrological care (represented in blue) and treated with ESAs (represented in orange), expressed as a percentage, and compared to the total number of DTD patients over the years 2009–2020.

The relative share is presented in percentages (%).The two groups of patients, with or without ESA before starting HD, are studied and compared by gender with the following parameters: Hb, ESA dose, and ERI. Group A consists of patients who received ESA before HD, while Group B consists of those who did not receive ESA before HD. A statistically significant difference is observed when comparing the Hb levels in women without ESA (Group B) before HD to those of men (Group B) without ESA before HD ($p = 0.047006$). Female patients are found to have significantly lower Hb levels, with a mean of 93.45 ± 0.25 g/L, compared to men, who have a mean of 99.5 ± 0.13 g/L. When comparing the mean Hb levels between men and women who received ESA (Group A), no statistically significant difference is found ($p = 0.833$). There is no data in the global literature comparing the results of these two patient groups (with ESA vs. without ESA prior to HD) in terms of Hb, mean weekly ESA dose, mean weekly ESA dose per kg of body weight, or ERI.

The following results were obtained from the calculations for the parameter "mean weekly ESA dose per kg of body weight": Women who did not receive ESA (Group B) have a significantly higher mean dose of ESA, with a value of 134.58 ± 6.835 IU/kg, compared to men, whose mean value is 109.18 ± 6.2061 IU/kg. A statistically significant difference between the sexes is observed ($p = 0.011646$).

A statistically significant difference is also noted in terms of resistance/ERI between women who did not receive ESA (Group B) prior to HD and men who did not receive ESA (Group B) prior to HD ($p = 0.0098$). Female patients are found to have significantly higher resistance, with a mean ERI value of 15.83 ± 1.1862, compared to men, whose mean ERI value is 12.00369 ± 0.55.

It is important to note that a much larger proportion of patients on periodic hemodialysis (HD) started such treatment on an emergency basis, with unknown chronic kidney disease (CKD) status. The highest number of observed patients was in 2014, at 53.62%, while the lowest was in 2018, at 25.4%. Similar statistics are observed for patients who received erythropoiesis-stimulating agents (ESA) during the pre-dialysis period. The highest number of patients who received ESA was in 2010, at 34.78%, and the lowest was in 2018, at 15.78%. Similar data is available for the United States for the period 2007–2016. While in the U.S. the percentage ranged from 27.3% in 2007, steadily increasing to 36.8% by 2016, at the Dialysis Unit of "St. Anna" University Hospital in Sofia, for the period 2009–2020, it ranged from 15.78% to 34.48%.

The two groups of patients, with or without ESA treatment prior to starting HD, are studied and compared by gender with the following parameters: hemoglobin (Hb) levels, ESA dose, and erythropoiesis resistance index (ERI). Group A includes patients who received ESA prior to HD, while Group B consists of those who did not. A statistically significant difference is observed when comparing Hb levels between women without ESA treatment (Group B) prior to HD and men (Group B) without ESA treatment ($p=0.047006$). Women were found to have significantly lower Hb levels, with a mean of 93.45 ± 0.25 g/L, compared to men, whose mean Hb was 99.5 ± 0.13 g/L. No statistically significant difference was found when comparing mean Hb levels between men and women who received ESA (Group A) ($p=0.833$).

In the global literature, there are no data comparing the results of the two patient groups (with or without ESA prior to HD) regarding Hb, weekly ESA dose, weekly ESA dose per kg of body weight, or ERI.

The following results were obtained in the calculations regarding the mean weekly ESA dose per kg of body weight: Women who did not receive ESA (Group B) had a significantly higher average ESA dose of 134.58 ± 6.835 IU/kg, compared to men, with a mean of 109.18 ± 6.2061 IU/kg. A statistically significant difference between genders was found ($p=0.011646$).

A statistically significant difference was also observed regarding resistance (ERI) between women who did not receive ESA (Group B) prior to HD and men (Group B) who also did not

receive ESA (p=0.0098). Women showed significantly higher resistance, with a mean ERI of 15.83±1.1862, compared to men, whose mean ERI was 12.00±0.55.

The results of a 12-year follow-up of patients at the Dialysis Unit of "St. Anna" University Hospital, Sofia, showed the following:

1. A large number of patients started periodic HD on an emergency basis without prior knowledge of their condition and without being followed by a nephrologist.
2. A significant percentage of patients on periodic HD had not received ESA treatment prior to dialysis.
3. A statistically significant difference was found regarding the mean Hb level in women who did not receive ESA (Group B) prior to HD compared to men (Group B) (p=0.047006), with women having significantly lower Hb levels: 93.45±0.25 g/L, compared to 99.5±0.13 g/L in men.
4. A statistically significant difference was found regarding the mean ESA dose per kg body weight in women who did not receive ESA (Group B) prior to HD compared to men (Group B) (p=0.011646). Women received a significantly higher mean dose: 134.58±6.835 IU/kg, compared to 109.18±6.2061 IU/kg in men.
5. A statistically significant difference was observed regarding resistance (ERI) between women who did not receive ESA (Group B) prior to HD and men (Group B) (p=0.0098), with women showing significantly higher resistance, with a mean ERI of 15.83±1.1862, compared to 12.00±0.55 in men.
6. No difference in age was observed between the two groups when compared by gender, nor in the mean weekly ESA dose.
7. No statistically significant difference between genders was found when comparing the mean weekly ESA dose per kg of body weight in Group A (those who received ESA before HD) (p=0.399).
8. No statistically significant difference between genders was found when comparing ERI in Group A (those who received ESA before HD) (p=0.473).

Women who did not receive ESA treatment during the pre-dialysis period, after starting HD with ESA, have lower Hb levels, higher ESA doses, and higher weekly ESA doses per kg of body weight. They also exhibit stronger resistance to treatment compared to men who did not receive ESA prior to HD. When administering ESA, the patient's gender must always be taken into account, and the specific characteristics of women should be considered.

Women without ESA treatment in the predialysis period, after starting HD with ESA, have lower Hb, higher ESA doses, and average weekly ESA doses per kg/weight; more

pronounced resistance to treatment compared to men without ESA before HD. When applying ESA, the gender of the patients should always be taken into account and the specific characteristics of the female sex should be taken into account.

Anemia in CKD is a complex process due to the relative deficiency of EPO, resistance to EPO and disturbances of iron homeostasis and all other factors involved in the pathogenesis of RA. Optimal management of RA remains a challenge. Here is what we have learned in recent years: In CKD patients with asymptomatic anemia or mild fatigue, strategies that are not based on ESA should be adopted. We need to think differently.

Anemia is usually present in patients with CKD, in whom GFR is below 20 ml/min. and worsens in parallel with increasing azotemia. In other cases, however, patients in ESRD, on HD for 1-2 or 3 years maintain hemoglobin above 128 g/l, even 140 g/l, and this has necessitated blood transfusion. There are reports of nephrectomized patients with normal Hb levels before the era of exogenously introduced EPO. The explanation in these cases is associated with Polycythemia rubra vera and/or hypersensitivity of erythroid progenitors to insulin-like growth factor/IGF-1/, which is formed in the liver and participates in erythropoiesis.

Solving the problems of patients with anemia is strictly individual - according to individual characteristics and compliance with standards, as well as in accordance with European and world guidelines: severity of the anemia syndrome, presence of infection and/or iron deficiency accompanying severe hyperparathyroidism, as well as sensitivity and tolerance to a certain type of ESA, presence of Diabetes Mellitus, Heart Failure.

In recent years, all these types of ESA have been used in the DTD of the University Hospital "St. Anna" Sofia. What is the principle for choosing the respective medication? A difficult answer to the question - of course, whatever supplies were received from the State Order under Regulation 34, no matter how insufficient they may be. Until 2006 - 50% EPO-Alpha and EPO-Beta. Then, in 2007 - 100% EPO Beta. In 2008 - 100% EPO - Alpha, small amounts of Darbepoetin and a donation from Roche EPO - Beta and CERA. In 2007, two patients received Hematide /according to a clinical study/. After that - alternating years of treatment with Retacrit and/or Binocrit according to the competitions under the Public Health Insurance Act. That is, the team in the department has good clinical experience with the different classes of ESA. What was the surprise when the Hb level in the patients was retrospectively monitored for the last years and it turned out that four patients maintained Hb above 110g/l without ESA. Why did a patient with gouty nephropathy, from 15.09.1998. on HD maintain Hb 65;71;84g/l until September 2007. and is on treatment with ESA, and then permanently without ESA, have Hb above 120g/l and have had to have blood transfusions several times? Then since 2011 received

ESA, Hb was over 120g/l and several blood transfusions were required.. The answer to this question is difficult to find. Unblocking Polycythemia vera, extrarenal synthesis of EPO, etc. are discussed.

Why is there no effect in other patients with the administration of very large doses of ESA? Why in many cases, with a continuous increase in the dose of ESA, there is no effect, Hb drops and the patient dies? The answer to these questions is difficult to find - the possible causes are: uncontrolled arterial hypertension, poorly treated infections and inflammatory conditions, administration of large doses of corticosteroids and cytostatics during the transplantation period and chronic rejection of the transplant.

Over the past 15 years, there have been 17 patients at the Dialysis Unit who have gradually restored kidney function over a period of 1 to 3 years and have discontinued hemodialysis (HD) treatment. These patients are now monitored in the nephrology clinic at the Diagnostic and Consultation Center (DCC Since 2022, patients with preserved diuresis have been treated with the so-called "Combined Dietary and Dialysis Program." During the inter-dialysis period, the patients adhere to a low-protein diet, while on dialysis days, they follow a high-protein diet. An individualized and holistic approach is applied to the treatment of comorbidities, as well as to kidney replacement therapy with HD and/or hemodiafiltration (HDF). This approach helps preserve the residual kidney function of the patient.

To achieve prolonged preservation of residual kidney function, an incremental program of kidney replacement therapy with HD and/or HDF is applied to 82.14% of patients in the Dialysis Unit. The results from the incremental program show: an 8-fold increase in diuresis, higher hemoglobin (Hb) levels, serum calcium, phosphorus, and potassium within reference ranges, as well as ferritin; lower serum creatinine, parathyroid hormone (PTH), and erythropoiesis resistance index (ERI). These results from incremental dialysis confirm findings from other authors and could be introduced into routine clinical practice. There are no publications regarding the "Combined Dietary and Dialysis Program" combined with incremental dialysis. Figures 30 and 31 compare the results of the two groups - with an incremental and conventional program of renal replacement therapy.

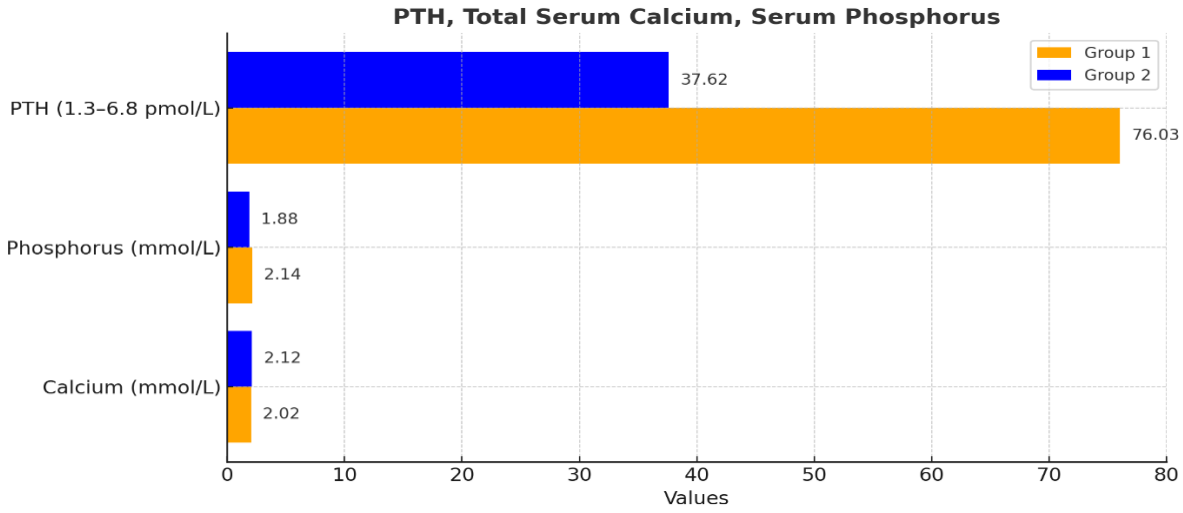

Figure 28. Comparison of results when applying the "Combined Diet, Dialysis Program" combined with incremental dialysis (in orange - results of patients with a conventional program; in blue - of the "Combined Diet, Dialysis Program" combined with incremental dialysis.

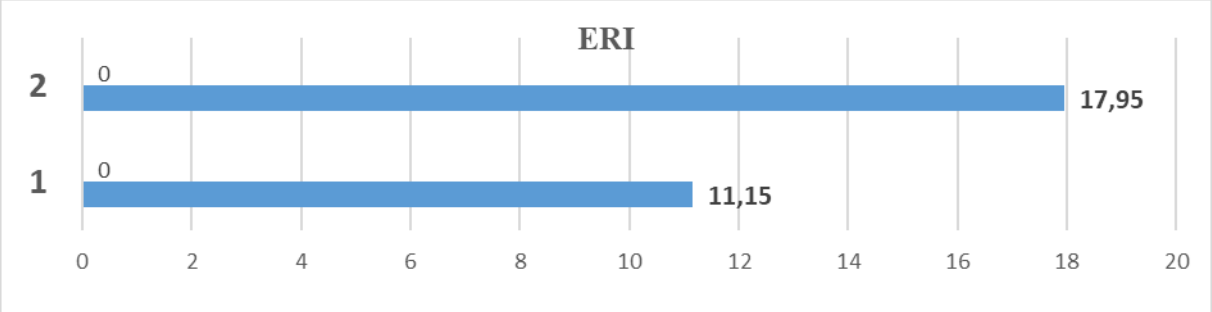

Figure 29. ERI (1- results of patients with a conventional program; 2- when applying the “Combined dietary, dialysis program” combined with incremental dialysis).

These results from incremental dialysis confirm the results of other authors and can be introduced into routine practice. No publications exist for the “Combined dietary, dialysis program” combined with incremental dialysis.

CONCLUSIONS from Task 1:

1. Calculating the ERI and identifying high values provide reliable evidence of resistance, saving costs on expensive investigations.
2. ERI correlates with the number of hospitalizations and serves as a short-term predictor of mortality.

3. In women with grade II obesity, a relationship is observed between BMI and mean hemoglobin levels.

CONCLUSIONS from Task 2:

1. The relationship between VHTP and RA is confirmed.

CONCLUSIONS from Task 3:

1. Combining medications leads to better management of calcium-phosphorus metabolism and improved quality of life, with an increase in hemoglobin levels.

CONCLUSIONS from Task 4:

1. Switching treatments between different types of ESAs is safe, regardless of the sequence.

CONCLUSIONS from Task 5:

1. A statistically significant difference is noted in mean hemoglobin levels, average ESA dose per kg body weight, and resistance between women and men who had not received ESA before HD.

CONTRIBUTIONS

The contributions are scientific-theoretical and practical, clarifying contemporary aspects of renal anemia treatment.

ORIGINAL:

- For the first time in Bulgaria, such a long-term (20 years) follow-up of a large cohort of 2,963 patients was conducted.
- For the first time in Bulgaria, a one-year follow-up was carried out on patients undergoing HD and non-HD treatment, assessing the state, safety, and benefits of switching from short- to long-acting ESAs and vice versa.
- For the first time in Bulgaria, the significance of ERI as a predictor of near-term mortality in HD patients was demonstrated.
- The significance of obesity in women regarding anemia syndrome in CKD was established for the first time.
- Gender differences in a 12-year follow-up of dialysis patients were demonstrated for the first time. Women not treated with ESA before HD showed lower hemoglobin, higher weekly ESA doses, and greater resistance compared to men.

- A large-scale study compared treatment outcomes for anemia syndrome based on vascular access type.
- A comprehensive analysis was conducted, comparing hemoglobin levels, BMI, ESA resistance, and vascular access.

CONFIRMATORY:

- Confirmed the importance of iron deficiency prevention and treatment in dialysis patients with PIVC as a critical factor for maintaining stable hemoglobin levels.
- Verified that applying a "combined dietary and dialysis program" with individualized and holistic approaches to comorbidity treatment and HD/OL-HDF therapy yields good results and can be routinely used.
- Confirmed that the incremental dialysis program reliably preserves RKF and can be routinely applied.

SCIENTIFIC PUBLICATIONS RELATED TO THE DISSERTATION

1. Ashikova, KA., Borisov, B., Asenova, I. Comparison of outcomes when switching treatment of renal anemia from short-acting to long-acting erythropoietin-stimulating agents and vice versa. Nephrology, Dialysis and Transplantation, 2024, 30(1): 32-43; ISSN: 1312-5257;
2. Ashikova, KA, Borisov, B. Diagnosis and treatment of complications during the peridialysis period in chronic kidney disease. Nephrology, Dialysis and Transplantation, 2023, 29(4): 18-27; ISSN: 1312-5257;
3. Ashikova KA, Linkova S. Chronic kidney disease - peridialysis period: predialysis, dialysis preparation, and initial dialysis prescription. Journal of Biomedical and Clinical Research, 2023, 16(2): 105-117; ISBN: 1313-6917;
4. Ashikova KA. Is there a Difference in the Resistance to Erythropoietin Stimulating Agents in Dialysis Patients Depending on Whether or not They received such Treatment Before Starting Hemodialysis? Journal Of Medical Science and Clinical Research, 2020, 8(8): 197-206; ISSN: 2455-0450
5. Ashikova KA. Results of two-year treatment with ZEMPLAR in patients with CKD, secondary hyperparathyroidism, and anemia. GP news, 2013, issue 4, pp. 9-12; ISSN: 1311-4727

CONFERENCE PARTICIPATIONS

1. Ashikova KA, Ignatova Z. "Do we preserve residual kidney function?" National Nephrology Conference, Oct 11–13, 2024, Flamingo Hotel, Albena. Oral presentation by Ashikova KA.
2. Ashikova KA, Ignatova Z. "How do we preserve residual kidney function in our patients?" National Nephrology Conference, Oct 11–13, 2024, Flamingo Hotel, Albena. Oral presentation by Ashikova KA.
3. Ashikova KA. "Obesity, chronic kidney disease, renal anemia: Hidden consequences of the obesity epidemic and kidney disease." Nephrology Academy," May 9–12, 2024, Grand Hotel Plovdiv. Oral presentation by Ashikova KA.
4. Ashikova KA. "Obesity, CKD, and renal anemia – diagnosis and treatment: A nephrologist's perspective." Nephrology Academy, May 9–12, 2024, Grand Hotel Plovdiv. Oral presentation by Ashikova KA.
5. Ashikova KA. "Particularities in our patients with obesity, CKD, and renal anemia. "Nephrology Academy," May 9–12, 2024, Grand Hotel Plovdiv. Oral presentation by Ashikova KA.
6. Ashikova KA, Borisov B, Asenova I. "Are stable hemoglobin levels truly stable with changes in ESA treatments?" National Nephrology Conference, Nov 9–12, 2023, Imperial Hotel, Plovdiv. Oral presentation by Ashikova KA.
7. Ashikova KA, Borisov B. "Case of a patient with multiple rare diseases and CKD." XX International Medical Scientific Conference for Students and Young Doctors, Oct 16–20, 2023, Pleven. Poster.