მეტია სტრესის არამქონე დედების შვილებთან შედარებით (RR=2.042).

მიღებული შედეგები ადასტურებს ჰიპოთეზას, რომ **პრენატალური სტრესი იწვევს შთამომავლობაში** ADHD-ს განვითარებას პროგრამირების ეფექტის **მეშვეობით. გამომდინარე ზემოაღნიშნულიდან, სამომავლო კვლევები მიზანმიმართული** უნდა იყოს სხვა პრენატალური ფაქტორების ზემოქმედების შესწავლაზე, რაც შესაძლებელია გახდეს ADHD-ს განვითარების მიზეზი.

IMPACT OF MICROBIOME COMPOSITION ON QUALITY OF LIFE IN HEMODIALYSIS PATIENTS

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Chronic Kidney Disease (CKD) represents a great challenge for the whole world. Worldwide, approximately 242/1,000000 patients with CKD (The global estimated prevalence is 13.4% (11.7-15.1%) and the number of patients with kidney failure is expected to increase [1;2]. During the last years, the share of dialysis programs in health financing has increased from 6% to 12% especially, in developed countries and still proceeds to grow [3]. According to the official data of 2021, 2670 people, 716 out of the million-population received Kidney Replacement Therapy (KRT) in Georgia, with an average age of 58.4. The lack of a cadaver kidney transplant program in Georgia increases the vintage of the patients on dialysis. Long-term dialysis therapy often results in an increased risk of systemic inflammation.

Chronic inflammation in the CKD population can have a serious impact on patients' quality of life (QoL) [4-6]. Markedly altered intestinal flora plays an important role in the increased production of gut-derived uremic toxins such as indoxyl sulfate and p-cresol sulfate, promoting pro-inflammatory responses [7,8]. Systemic inflammation increases with the progression of CKD. Despite appropriate treatment with KRT, systemic inflammation may dramatically change the psychological, social, economic prosperity of hemodialysis (HD) patients [9]. Thus, intestinal microbiome disturbances may lead to serious changes in HD patients' QoL. The potential benefit from modulating the "healthy" colonic colonization may become improvement of QoL of this population.

The aim of our study was the assessment of QoL of the HD patients before and after therapy with refined probiotics. The Missoula-VITAS Quality of Life Index (MVQOLI) was used for this purpose. The MVQOLI evaluates 5 dimensions of patients' QoL: symptoms, function, interpersonal, well-being, and transcendence [10]. The questionnaire is specifically designed to assess the patients' personal experience in each of these dimensions. It is important to mention that factors that influence QoL in patients with kidney failure receive little attention

Material and methods. In this cohort-prospective study we included 272 patients on maintenance hemodialysis from a single-center loaded with 300 regular HD patients. All patients were on the same regime range of 12h per week with a mean single pool of Kt/V 1.55 [interquartile range IQR 1,45-1.65]. The median age of the patients was 54 [IQR, 44-68], sex distribution 160 men (57%) and 112 women (43%), and a dialysis vintage 3 years [IQR 3-7]. The study was designed as a two-step approach: the first step aimed the assessment of overall QoL of the HD patients and selection of those with gastrointestinal complaints – forming of the "GI group"; the second step included the fecal investigation and probiotic treatment of the patients from the "GI group" followed by reassessment of QoL by the end of the treatment. Initially, we used two questionnaires: the first - the Missoula-VITAS Quality of Life Index-15 (MVQOLI-15) translated into Georgian; the second - related to gastroenterological complaints. The purpose of the questionnaire was to reveal the number of patients with gastrointestinal complaints, and the severity of these symptoms. The second step of the study focused on the effect of probiotics on the quality of life of HD patients. HD patients were eligible to participate in the study if none of the following conditions were met: HD duration ≤3 months, active inflammatory diseases, bleedings and other chronic gastrointestinal diseases, viral hepatitis, severe mental and oncological diseases in past medical history. We have selected 33 patients for the "GI group" with mean age of 30 (IQR 18-65) and sex following distribution - 17 females and 16 males. Each patient has been studied under an individual schedule, the same scheme, for 12 weeks. We have studied intestinal flora, quality of life, and gastrointestinal complaints before and after treatment. Also, 7 HD patients were recruited as the control group with no gastrointestinal problems. All participants were informed about the research purposes. The patients included in the study have signed informed consent.

We treated each patient with a probiotic containing L. acidophilus KB27, B. longum–KB31, and S. thermophilus KB19. 34. The daily dose was 80X10'9CFU. The patients were instructed to continue the same dosage during the following 12 weeks. Qualitative and quantitative data of colon microflora, characteristics of QoL, and gastrointestinal complaints were collected individually and underwent statistical processing. The fecal samples were analyzed using microbiological methods of plating, enumeration, and counting colonies on specific growth media. The statistical program SPSS was used to statistically process the results.

Results and discussion. On the general question of MVQOLI-15- How would you rate the overall quality of life? - 65% of HD patients' answer was "fair" (Table 1).

The dataset obtained by the GI questioner showed that most of the selected patients had various complaints (nausea, bloating, constipation, diarrhea) presenting with multiple levels of severity (mild -24%, severe-51% and moderate – 35%).

Before the start of the specific therapy with probiotics, it was found, that in 33 patients the intestinal flora contained reduced amounts of CFU of Bifidobacterium and Lactic acid bacteria. The other types of dysbiosis were also revealed (for example, the presents of hemolytic E coli and so on). In 15 samples, among 33, there was a low amount of CFU of Bifidobacterium. 22 samples contained a low amount of CFU of Lactobacillus.

Intestinal flora has not been completely restored in four cases after 12 weeks of the treatment. In 4 more patients, intestinal microbial content was not reassessed due to incomplete treatment (patients dropped out for a while after getting infected with covid-19). The Wilcoxon-Mann-Whitney UU test was used to test the null hypothesis, to find out differences between the two samples. As a result of a statistical study, the following values of the UUU criterion were obtained: Bifidobacteria - UU = 221, Lactic acid bacteria UU = 126, Enterococci - UU = 227,E. coli typical - UU = 254, The value of the UU criterion according to the table U0.05 = 314.39 (95% probability), n = m = 29. In all cases, U U <U0.05, which confirms that the difference between two samples (pre- treatment and post-treatment) is significant (Table 2).

In 6 patients was positive result for hemolytic Escherichia coli (additional tests were performed to find out the genetic marker of hemolytic E coli.). After treatment with probiotics, in the repeated fecal samples, the bacteria were no longer observed. The value of the U criterion is 31, U and U0.05 = 13. The statistical difference between these two samples was insignificant. However, taking into account the significance of E. coli, the result achieved only by the use of probiotics should be considered as effective.

Correction of the microflora had a positive reflection on the patients' clinical condition. Almost all major symptoms diminished. According to the results obtained by the questionnaires, bloating, diarrhea, and the feeling of rapid fullness have been dramatically reduced. The opposite was observed in those with constipation and heartburn: patients reported only minor improvement but not significant. The latter can be explained by peculiarities related to HD treatment: recommended diet (lack of fiber-containing food), fluid restriction, high ultrafiltration rate, and some drugs often result in constipation in these patients.

A nonparametric method was used for determining the correlation coefficient (association coefficient) to find out the relationship between them. The research results were presented in the form (2X2) of a row table, according to which the value of the χ^2 criterion was determined by a significance level $\alpha = 0.05$ (95% probability) and a degree of freedom $\gamma = 1$ (equal to 3.84). As a result of statistical processing, the following values of the χ^2 criterion were obtained: Diarrhea - $\chi^2 = 17{,}19$; Constipation - $\chi^2 = 9.27$; feeling of rapid fullness - $\chi^2 = 12.68$ Heartburn - $\chi^2 = 2.21$; Bloating- $\chi^2 = 44.2$ Nausea - $\chi^2 = 0.54$. Statistical studies have shown that the significance of the χ^2 criterion for the incidence of diarrhea, constipation, feeling of rapid fullness, and bloating before and after treatment is $\chi^2 > \chi^2$ 0.05: 1, i.e. The null hypothesis is rejected, and a

Table 1. Self-assessment of QoL by HD patients (total 253 patients)

Overall QoL (How would you rate overall quality of life?)	frequency	%
worst possible	14	5.53
Poor	62	24.51
Fair	166	65.61
Good	11	4.35
best possible	0	0.00

Table 2. Mann–Whitney U test results

	Mann–Whitney U test	
Bifidobacteria	UU = 221	U< U0,05,
Lactic acid bacteria	UU = 126	U< U0,05,
Enterococci	UU = 227	U< U0,05,
E. coli typical	UU = 254	U< U0,05,

difference between the two is likely. As for the significance of the χ^2 test for indicators of heartburn and nausea, $\chi^2<\chi^20.05$: 1, that is, the difference between these two options is not significant. Based on the obtained results, it can be concluded that this treatment is effective for the relief of symptoms such as diarrhea, rapid fullness, bloating, and a little bit less effective for constipation.

The MVQOLI-15 questionnaire before the treatment showed an average score of 14 [SD 2.47, IQR 10 to 20.7]. After treatment, all patients filled out the same questionnaire again. The total average MVQOLI-15score was 17 (SD 2.53). The "GI group" study average score was less than the total average MVQOLI-15 score obtained from 253 HD patients (16.4 (SD 2.8)). It confirms the worth QoL of these patients. With the Wilcoxon-Mann-Whitney formula, UU criterion values were obtained: U = 297.5, U0.0 = 453.5 (95% probability) n = m = 33. Statistical studies have shown that the difference between the two clinical conditions (before and after treatment) is significant, and the effectiveness of treatment is obvious.

The disturbances of the normal gut microbiome have been recognized in the pathogenesis of various chronic diseases. Among them the most important are obesity [11], diabetes [12] and liver cirrhosis [13]. The role of the gut microbiome in CKD has been gradually increased. The intestinal barrier plays significant role in the pathogenesis of uremia as well. A lot of evidence proved that in CKD intestinal barrier is disrupted: high blood urea levels cause an influx of circulating urea into the gut; this leads to translocation of bacteria-derived uremic toxins into the systemic circulation and causes inflammation and leukocyte stimulation [14-16]. Endotoxemia is often developed in patients with uremia without clinically revealed infections. Intestinal flora may have become the source of endotoxin production [18].

In a prospective observational study of 268 patients with CKD, Wu and colleagues [19] found the baseline concentration of indoxyl sulfate to be predictive of CKD progression [20,21]. Meijers and colleagues measured p-cresol levels in 499 patients with mild-to-moderate CKD and showed that p-cresol sulfate levels increased with decreasing estimated glomerular filtration rate (GFR) [22-25].

This study aimed to investigate changes of QoL in HD patients through the correction of intestinal microflora. For this purpose, certain probiotics were prescribed during the 12 weeks among single-center hemodialysis (HD) patients. Our study observed the change in gut microbiota and QoL in HD patients, which was consistent with a lot of literature [26-29]. Factors that are associated with CKD may play a role in the promotion of gut microbiota imbalance, such as increasing intestinal uremic toxin availability, metabolic acidosis, intestinal wall edema, and reducing colonic passage and digestive capacity [15,30]. Pharmacological therapies (e.g., antibiotics and iron delivery) may also influence gut microflora dysbiosis [31].

The HD therapy has a significant impact on the gut microbiota in patients with kidney failure. Toxin accumulation, strict dietary restrictions, dialysis catheter intervention, and some other reasons, could damage intestinal microenvironments, promote pathogenic bacterial growth, and inhibit the growth of beneficial bacteria. The findings given in the literature can be explained as follows: Firstly, the reduction of visceral blood flow under the compensatory mechanism of HD maintaining hemodynamic stability during ultrafiltration may cause intestinal hypoperfusion, which disrupts intestinal barriers and increases the risk for bacterial translocation [32]. Secondly, gastrointestinal micro-bleeds induced by systemic anticoagulation therapies during HD treatments, in combination with uremic platelet dysfunction, may impair gut epithelial barrier structures and functions [15]. Lastly, it has been shown that diet plays a role in regulating the composition and metabolic activity of the human gut microbiota [33].

The therapeutic use of probiotics, prebiotics, and synbiotics is an area of increasing interest among renal healthcare professionals. Based on the data available in the literature, we can conclude that correction of the intestinal flora may have great benefits: bacteria belonging to the Lactobacillus and Bifidobacterium, may decrease blood urea nitrogen, and ammonia levels and plasma concentrations of p-cresol and indoxyl sulfate. Another benefit described after the use of probiotics is that increased strains of bifidobacteria populations have a significant effect on the intestinal mucosal barrier [23], that also helps to decrease several inflammatory cytokine and endotoxin concentrations and increase serum levels of anti-inflammatory IL-10 [34]. A little less significant tendencies were observed in white blood cell count, CRP, total indoxyl glucuronide, uremic toxins, markers of oxidative stress, and quality of life measures.

According to the questionnaire MWQOLI used in our study, all HD patients consider their illness as having a chronic cause, and in most cases, they accept the reality quite well [35]. However, the negative impact of the disease on patients' personal lives is considerable [36]. The answers collected by the both questionnaires showed, that the QoL of HD patients is low and nearly all of them have at least one GI problem.

This study has shown a significant association between dysbiosis and QoL. Our data revealed that the gut microbiota was altered in those HD patients, who have severe gastrointestinal complaints. All of them had low QoL. After treatment with probiotic the gut microbiomes and gastrointestinal complaints significantly improved. In turn that positively affected the quality of life.

Despite the promising results of our study, there are several weaknesses: the sample size was relatively limited, therefore, further studies with extended numbers are needed; all participants were enlisted from one center, which shared a limited geographical area. Our study did not estimate patients' drug intake or diets.

Conclusion. This study shows the impact of dysbiosis on Qol in the population of patients on HD. Correction of intestinal flora in hemodialysis patients improves the

quality of their lives. The use of probiotics has revealed a significant effect on some gastrointestinal complaints, such as meteorism, diarrhea, and fulness. For correction of microflora, it is recommended to use probiotics containing L. acidophilus, B. longum and S. Thermophilus for a long period of at least 12 weeks. It is necessary to conduct larger studies of higher methodological quality for further assessment of the impact of dysbiosis on QoL in hemodialysis patients.

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SUMMARY

IMPACT OF MICROBIOME COMPOSITION ON QUALITY OF LIFE IN HEMODIALYSIS PATIENTS

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Accumulating evidence showed that chronic inflammation is a risk factor for increased cardiovascular mortality in the population with Kidney Failure (KF) remaining on Kidney Replacement Therapy (KRT). The gut microbiome is altered in patients with Chronic Kidney Disease (CKD) and is one of the major sources of chronic inflammation. Uremic gut microbiome may have serious effects on patients' quality of life (QoL) and, especially, on their psychological, social, and economic prosperity. Factors that influence health-related quality of life (HRQOL) in patients with ESRD have received little attention**.**

Aim - this study aimed to investigate changes of QOL in HD patients by the correction of intestinal microflora.

The sample study consisted of 33 HD patients (age 18-75) from "The clinical center for development of nephrology". Data was collected through the completion of a specially designed questionnaire. For assessment of Qo

was used the “Missoula VITAS Quality of life index. Fecal samples were analyzed before and after treatment with probiotics.

It was revealed alteration of the colonic microbial composition in the sample of the hemodialysis patients. Also, there was a strict correlation between gut dysbiosis and HD patients’ QoL. Our study demonstrates important relationships between gut dysbiosis and QoL in HD patients. Correction of intestinal flora with probiotics-containing L. acidophilus, B. longum, and S. Thermophilus for a long period of at least 12 weeks improves the quality of their lives.

Keywords: kidney failure, hemodialysis, quality of life, gut microbiota, probiotics.

РЕЗЮМЕ

ВЛИЯНИЕ СОСТАВА МИКРОБИОМА НА КАЧЕСТВО ЖИЗНИ ПАЦИЕНТОВ, НАХОДЯЩИХСЯ НА ГЕМОДИАЛИЗЕ

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Новейшие данные подтверждают, что хроническое воспаление увеличивает риск летального исхода у больных почечной недостаточностью (ПН), которым проводят заместительную почечную терапию. При ПН меняется микробиом кишечника и он становится одним из основных источников воспаления. Микробиом кишечника уремического больного значительно влияет на качество его жизни (КЖ), особенно на психологическое, социальное и экономическое благоденствие.

Целью исследования является изучение качества жизни и флоры кишечника пациентов, находящихся на гемодиализе и их коррекция посредством применения пробиотиков.

В исследовании участвовали 33 пациента в возрасте 18-75 лет одного диализного центра –„Клинический Центр Развития Нефрологии”. Данные собраны с помощью специально разработанного вопросника. КЖ оценивали посредством индекса качества жизни по Missoula VITAS. Копрологические образцы анализировали до и после лечения пробиотиками.

Выявлено изменение микробного состава толстой кишки, установлена корреляция между дисбиозом кишечника и качеством жизни у пациентов, находящихся на гемодиализе (ГД). Проведенное исследование выявило значительную связь между дисбиозом кишечника и качеством жизни пациентов, находящихся на ГД. Коррекция флоры кишечника пробиотиком, содержащим L. acidophilus, B. longum и S. thermophilus в течение длительного времени (12 недель), улучшает качество их жизни.

რეზიუმე

ნაწლავური ფლორის გავლენა ჰემოდიალიზზე მყოფი პაციენტების ცხოვრების ხარისხზე

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უახლესი მონაცემებით მტკიცდება,რომ ქრონიკული ანთება ზრდის სიკვდილიანობის რისკს თირკმლის უკმარისობით (თუ) დაავადებულებში, რომლებსაც თირკმლის ჩანაცვლებითი თერაპია უტარდებათ. თუ-ს დროს ნაწლავის მიკრობიომი იცვლება და ანთების ერთ-ერთი მთავარი წყარო ხდება. ურემიული პაციენტის ნაწლავის მიკრობიომს შეუძლია მნიშვნელოვანი გავლენა მოახდინოს პაციენტების სიცოცხლის ხარისხზე (სხ), განსაკუთრებით ფსიქოლოგიურ, სოციალურ და ეკონომიკურ კეთილდღეობაზე.

კვლევა მიზნად ისახავს ჰემოდიალიზზე (ჰდ) მყოფი პაციენტების სიცოცხლის ხარისხისა და ნაწლავის ფლორის შესწავლას და მათ კორექციას პრობიოტიკების გამოყენებით.

კვლევა ჩატარდა „ნეფროლოგიის განვითარების კლინიკური ცენტრი“-ის 33 პაციენტზე (18-75 წლის ასაკი). მონაცემები შეგროვდა სპეციალურად შემუშავებული კითხვარის საშუალებით. სხ შეფასდა Missoula VITAS-ის სიცოცხლის ხარისხის ინდექსის გამოყენებით. კოპროლოგიური ნიმუშები გაანალიზებულია პრობიოტიკით მკურნალობამდე და მის შემდეგ.

გამოვლინდა მსხვილი ნაწლავის მიკრობული შემადგენლობის ცვლილება. გარდა ამისა,დადგინდა კორელაცია ნაწლავის დისბიოზსა და სიცოცხლის ხარისხს შორის ჰდ-ზე მყოფ პაციენტებში.

კვლევა აჩვენებს მნიშვნელოვან კავშირს ნაწლავის დისბიოზსა და სიცოცხლის ხარისხს შორის ჰდ-ზე მყოფ პაციენტებში. ნაწლავის ფლორის კორექცია L. acidophilus, B. longum da S. thermophilus შემცველი პრობიოტიკებით ხანგრძლივი პერიოდის (12 კვირა) განმავლობაში აუმჯობესებს მათი სიცოცხლის ხარისხს.