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Adherence to lifestyle modification in patients with nonalcoholic fatty liver disease

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) makes a major impact on morbidity and mortality among the working-age population in developed countries. In the lack of effective pharmacological methods, the leading role in treatment of NAFLD belongs to lifestyle modification, consistent and gradual weight loss, and its maintenance. The qualitative and quantitative structure of the diet, intensity of physical activity, and most importantly, regularity and consistency of implementation of lifestyle modification activities are the key to successful management of patients with NAFLD.

To date, there are very few studies on adherence to lifestyle modification activities in this group of patients, which is mainly due to a deficiency of methodological tools. The questionnaire "QAA-25" recommended by the Russian Scientific Medical Society of Therapists for quantitative assessment of adherence to treatment allows to assess both adherence to therapy in general and adherence to its individual components (adherence to drug therapy, adherence to medical counseling, and adherence to lifestyle modification), which requires further study taking into account features of therapeutic strategies in treating NAFLD.

Key words: nonalcoholic fatty liver disease, lifestyle modification, adherence, insulin resistance, metabolic syndrome.

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Приверженность модификации образа жизни при неалкогольной жировой болезни печени

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РЕЗЮМЕ

Неалкогольная жировая болезнь печени (НАЖБП) вносит серьезный вклад в заболеваемость и смертность трудоспособного населения развитых стран. При отсутствии эффективных фармакологических подходов

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ведущую роль в лечении НАЖБП играет модификация образа жизни, в первую очередь последовательная и постепенная потеря массы тела, а также ее поддержание. Качественный и количественный состав диеты, уровень физической активности, а главное, регулярность выполнения мероприятий по модификации образа жизни являются залогом успешного ведения пациентов с НАЖБП.

На сегодняшний день исследований, посвященных изучению вопросов приверженности мероприятиям по изменению образа жизни у данной группы больных, крайне мало, что во многом связано со скудностью методологического инструментария. Рекомендованный российским научным медицинским обществом терапевтов опросник количественной оценки приверженности лечению «КОП-25» позволяет оценить как приверженность терапии в целом, так и по отдельным ключевым компонентам (приверженность лекарственной терапии, приверженность медицинскому сопровождению и приверженность модификации образа жизни), что требует изучения, учитывая особенности терапевтических стратегий при НАЖБП.

Ключевые слова: неалкогольная жировая болезнь печени, приверженность, модификация образа жизни, инсулинорезистентность, метаболический синдром.

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RELEVANCE

Nonalcoholic fatty liver disease (NAFLD) includes a range of liver changes which are morphologically characterized by excessive accumulation of fat in hepatocytes (associated with insulin resistance) in patients who do not consume significant amounts of alcohol and/or steatogenic drugs and do not have other possible causes of secondary steatosis [1]. The established risk factors for the development and progression of this disease include obesity, type 2 diabetes mellitus, and dyslipidemia [2, 3].

Currently, NAFLD is one of the most common liver diseases worldwide, affecting 20–40% of the population in developed countries [4, 5]. This trend is expected to worsen as obesity rates increase [6, 7]. NAFLD is considered as a hepatic manifestation of the metabolic syndrome, whose pathogenetic mechanisms of formation determine the interdisciplinary relationship between the progression of the disease (steatohepatitis, fibrosis, cirrhosis) and cardiovascular events, renal pathology, etc. This, in turn, becomes the reason for high mortality among these patients.

Despite the growing interest in the study of NAFLD in the global and Russian research community, the issue of effective specific treatment of NAFLD remains unresolved. The main directions of drug therapy for NAFLD are increasing tissue sensitivity to insulin and reducing the stage of liver damage [8], which are used only with lifestyle modification [9–12]. Therefore, lifestyle modification is the cornerstone of any NAFLD treatment regimen and implies namely changes in the quantity and quality of nutrition, weight loss, and increased physical activity. Changing habits and lifestyle as established functional systems in human behavior requires significant efforts. Long-term effectiveness of non-pharmacological treatment depends on patient motivation and adherence [13–15].

In few studies available on adherence to treatment in patients with NAFLD, there is evidence of significant effectiveness of non-pharmacological treatment, but information on adherence to these treatment methods is extremely limited. This may be determined by difficulties of studying the adherence to lifestyle modification, as well as by imperfection of the methodology.

EATING BEHAVIOR MODIFICATION IN THE TREATMENT OF NAFLD

The 2016 guidelines of the European Association for the Study of the Liver, European Association for the Study of Diabetes, and European Association for the Study of Obesity describe the main provisions of diet therapy: weight loss by 7–10% from the initial weight, which should be achieved by reducing the daily calorie intake by 500–1,000 kcal; a change in the ratio of macronutrients in favor of an increase in the amount of complex carbohydrates, plant-based proteins, and fiber and a decrease in the proportion of fat; exclusion of food containing fructose from the diet; consumption of alcoholic beverages not exceeding the daily safe dose (30 ml for men, 20 ml for women in terms of ethanol) [16].

The most effective therapeutic intervention in the treatment of NAFLD is diet modification, which promotes weight loss in patients [16]. Despite this, some diets that involve excessive and/or rapid weight loss (for example, diets very low in carbohydrates and high in fat) contribute to the development of insulin resistance. This, in turn, worsens the course of the disease [17]. The use of elimination diets and the so-called healthy fasting for the treatment of patients with NAFLD is absolutely unacceptable, since fatty liver disease is aggravated, and a relatively favorable stage of steatosis can advance to steatohepatitis and fibrosis [18].

Given a strong association between NAFLD and obesity, it is not surprising that significant histological and biochemical improvements are seen in patients after weight loss. A study by M. Palmer and S. Schaffner demonstrated that weight loss of more than 10% in obese patients with NAFLD is associated with a significant decrease in serum aminotransferase levels [19]. In another study, S. Zelber-Sagi et al. found that a 9% decrease in body weight leads to significant morphological changes [20].

Diet therapy to achieve the target body weight should have both quantitative and qualitative changes. Most studies demonstrate that energy restriction alone is not enough to treat NAFLD, modulation of both macro- and micronutrients in the diet is critical, so a balanced diet and moderate weight loss may now be considered the best therapeutic approach [21]. The balance and qualitative composition of the diet are even more important in a situation when we face the so-called metabolically inactive NAFLD in patients with initially normal body weight. The main goal in diet therapy is to maintain normal body weight and realize the antifibrinogen effects of the corresponding diets [22, 23].

Diet is the main moderator of triglyceride accumulation in the liver parenchyma and can be crucial for potentiating antioxidant activity [2, 24–26]. To date, there are no solid data on the effect of certain products on the development and course of NAFLD, but such studies are being conducted globally [22, 24, 27, 28]. There have been reports that diets high in carbohydrates and low in fat, but with the same amount of protein and total calories are associated with greater severity of NAFLD [24], or that patients with NAFLD consume more saturated fatty acids compared with healthy individuals [23].

A population-based study in Germany showed that it is typical of people with NAFLD to consume less tea, confectionery, fat, bread, cereals, and cheese and have higher consumption of soups, beer, wine, juice, poultry, and eggs [29]. Among 999 Chinese adults included in the study by C.Q. Yang et al., patients who had a vegetarian diet had the lowest risks of developing NAFLD [30].

A number of European studies also suggested that a plant-based diet is beneficial for patients with liver diseases [31–33]. In a crossover study of the Chinese population, a vegetarian diet was associated with a lower risk of developing fatty liver disease [34]. However, there are studies that do not confirm this effect [27, 35]. For example, in another crossover study involving 615 Buddhists, a vegetarian diet was not shown to be effective in preventing NAFLD [35]. According to the Rotterdam study of 3,882 patients with NAFLD, it was found that a diet rich in animal proteins was associated with the development of NAFLD, regardless of the traditional risk factors. According to that study, sugar consumption did not increase the risk of the development and progression of NAFLD [36].

One of the most preferred diets in patients with NAFLD is the Mediterranean diet [37]. This diet is a traditional approach to eating among the population in the states surrounding the Mediterranean Sea. Although due to cultural, religious, and agricultural characteristics, each region is characterized by its own variant of the diet, the general features of

the diet are as follows: eating a large amount of unrefined grains, vegetables, fresh fruits, olive oil and nuts; fish, white meat and legumes in moderation; limiting the intake of red meat, meat products, and sweets. The main characteristics of the Mediterranean diet are a healthy fatty acid profile, consisting in low intake of saturated fat and cholesterol and, conversely, high intake of monounsaturated fatty acids with a balanced ratio of omega-6 to omega-3, along with a high content of complex carbohydrates and dietary fiber [38].

The MEDINA study in a large cohort of patients with NAFLD demonstrated that a Mediterranean diet, regardless of weight loss, can lead to significant improvements in biochemical liver markers, and these changes were maintained for at least 12 months [39]. It was suggested that the positive effect of the Mediterranean diet is partly due to the high content of substances with high antioxidant and anti-inflammatory activity [40–42].

Cognitive behavioral therapy (CBT) can be an important aspect of lifestyle modification therapy. S. Moscatiello et al. compared the effectiveness of psychotherapy support in weight loss in patients with NAFLD [43]. After 2 years, in the group of patients receiving psychotherapy, there was a statistically significant decrease in body weight, normalization of liver parameters and a greater likelihood of maintaining it within the required therapeutic interval, compared with the group receiving diet therapy alone. Evidence on long-term treatment efficacy and adherence to lifestyle modifications and diet emphasizes the role of psychotherapy support in the treatment of NAFLD [44].

PHYSICAL ACTIVITY IN THE TREATMENT OF PATIENTS WITH NAFLD

In the aforementioned consensus statement of the European Association for the Study of the Liver, European Association for the Study of Diabetes, and European Association for the Study of Obesity, increasing physical activity to 120–150 minutes per week (in 3–5 workouts) is one of the main recommendations for non-drug treatment of NAFLD. Preference should be given to aerobic activities (brisk walking, exercise bike, swimming) [16].

In a retrospective analysis of 813 adults with biopsy-confirmed NAFLD, physical activity was assessed using clinical questionnaires [45]. Similarly, the level of physical activity was assessed in the crossover study by S. Zelber-Sagi, which involved 375 patients with NAFLD [46]. Patients with NAFLD were significantly less physically active than those without NAFLD. An important limitation of these studies is the use of survey and questionnaire data rather than objective measures of physical activity.

The relationship between low physical activity and NAFLD was also studied among adolescents [28, 47–49]. L.N. Hattar et al. in a prospective cohort study compared the physical activity of pediatric patients (aged 8–16 years) with NAFLD in patients without liver diseases [50]. The results showed that the group of obese children with NAFLD had the lowest physical activity scores, and more than 50% of them did not exercise actively at all.

All this led to a new concept that a simple decrease in the level of "inactivity", even in the absence of proper physical education sessions, can be useful [51–53]. The lack of adequate physical activity in patients with NAFLD prompted the American Association for the Study of Liver Diseases, the American College of Gastroenterology, and the American Gastroenterological Association to revise the guidelines on the role of physical exercise in 2012 [54]. The Association Joint Clinical Guidelines mention physical exercise as an effective method for reducing hepatic steatosis, however, it should be noted that only a limited number of studies use physical exercises as the main treatment for NAFLD, and the significance of improvements in the course of the disease, provided no weight loss, is yet to be studied.

Several studies focused on finding the optimal frequency and intensity of physical exercise that would lead to clinically significant reduction of hepatic steatosis [55–58]. The study by K.D. Kistler et al. showed that patients who performed high-intensity exercise, such as exercising on a treadmill or using a step machine, were significantly less likely to develop NAFLD [45]. The average time spent on performing intense physical exercise by the studied patients was 3 hours per week. A decrease in the risk of developing progressive fibrosis was also noted, when the recommended duration of high-intensity exercise was doubled. In contrast, patients who did moderate-intensity exercise, such as brisk walking, did not show a difference in the risk of

developing NAFLD or fibrosis compared with those who did not exercise.

These results are consistent with previously published studies showing great cardiovascular health benefits of intense exercise [46]. Based on the available data, it can be concluded that high-intensity exercise appears to be of the greatest benefit to patients with NAFLD and should be considered the preferred option when discussing the treatment strategy [59, 60].

Strength training deserves special attention, due to its wider application. Often, patients with NAFLD have underlying medical conditions that can complicate aerobic exercises. To date, there are few studies examining the effectiveness of strength training in the treatment of patients with NAFLD, but the available data suggest this area is promising [61, 62].

The study by K. Hallsworth et al. evaluated the effect of resistance training on the biochemical parameters of patients with NAFLD [63]. The training consisted of eight strength exercises with a total duration of 45–60 minutes, done 3 times a week. At the end of the 8-week test period, a decrease in steatosis and lipid oxidation and an increase in muscle tissue sensitivity to insulin were recorded. These effects were recorded regardless of body weight loss. Since the data on the effect of resistance training on the course and outcome of NAFLD are insufficient, attention should be paid to studies evaluating the effectiveness of such exercises in patients who meet the criteria for metabolic syndrome, given high probability of their having NAFLD.

A meta-analysis of 13 randomized controlled trials using resistance training to improve metabolic syndrome showed that this approach can significantly influence such parameters as obesity, glycated hemoglobin levels, and systolic blood pressure [64]. There was also a decrease in the amount of visceral fat and the level of proinflammatory cytokines [65].

COMBINING DIET AND EXERCISE IN THE TREATMENT OF NAFLD

Sustained weight loss is most effectively achieved by combining diet changes with a specific level of exercise. Thus, in the prospective study by S.S. Baba et al. 44 patients with histologically confirmed NAFLD underwent aerobic physical activity for at least 45 minutes a day 5 times a week in combination with a diet aimed at reducing body weight (daily deficit in the range of 500–1000 kcal). After 3 months, these patients showed a significant decrease in aspartate aminotransferase (from 70.5 to 41.4 U/l, $p < 0.0001$) and alanine aminotransferase (from 104 to 63.2 U/l, $p < 0.0001$). In approximately 45% of patients adhering to the recommended regimen for 3 months, the level of aminotransferases became fully normal [66].

A similar study of 96 patients with NAFLD compared the effectiveness of intensive lifestyle interventions (exercise and dietary changes) to achieve a minimum weight loss of 7% and exceptional nutritional education. According to magnetic resonance spectroscopy, a significant decrease in the degree of steatosis was noted in the intensive intervention group (50.8 and 22.8%, respectively; $p = 0.04$) [67].

Despite the fact that statistically significant results were achieved in all of the above-mentioned studies, a number of limitations may prevent the use of these approaches in real clinical practice. Thus, in the study by C.S. Baba et al., 25% of the participants were unable to complete their prescribed exercise program due to difficulty and physical fatigue. In addition, significant specialized assistance was required to achieve the results obtained.

In the aforementioned study by K. Promrat et al., all patients were closely monitored by a nutritionist and a professionally trained physical education instructor for a 48-week trial period [68]. This study included extensive psychological support throughout the period. These financial, human, and physical obligations significantly increase the burden of managing the NAFLD patient.

ADHERENCE IN NAFLD PATIENTS

Even without significant weight loss, lifestyle changes improve the course of NAFLD, especially when adherence is high. Meanwhile, it is the adherence to lifestyle modification that is the main problem of all such interventions [69]. To date, there are very few studies examining the issues of adherence to lifestyle change in this group of patients. This is largely due to a deficiency of methodological tools, since the widely used questionnaires of patient adherence to MMAS-4 and MMAS-8 therapy do not adequately assess adherence to lifestyle modification [70–72].

The Russian Scientific Medical Society of Therapists recommends to use the Russian questionnaire for quantitative assessment of adherence to treatment "QAA-25" to determine adherence to therapy [73]. It allows to estimate (in %) patient's adherence to therapy by its main components: adherence to drug therapy, medical counseling, and lifestyle modification, which makes it extremely promising [74].

A number of studies which were carried out in 2001–2006 in Greece and dedicated to the influence of the Mediterranean diet on the development of cardiovascular diseases in the Greek population are of interest. To assess the adherence and effectiveness of the Mediterranean diet, the Mediterranean diet score system was used, which implies a score assigned to respondents depending on what foods and with what frequency they consume. Typically, the score ranges from 0 (minimum adherence to the Mediterranean diet) to 9 (maximum adherence) [75, 76].

Another tool for assessing adherence to a particular type of nutrition is the international diet quality indicator (DQI-I), which examines four main aspects: its composition and variety, adequacy, moderation, and balance (the sources of energy that a person receives from food are analyzed). The score is estimated from 0 to 100; the higher the score, the higher the quality of the diet [77, 78].

Bearing in mind that pharmacological and surgical methods of NAFLD treatment are a backup therapy strategy, the prevalence of their use can indirectly indicate the degree of ineffectiveness of non-drug methods, due to low adherence of patients to the doctor's recommendations in the long term. In this regard, it is worth noting that there are data that in the vast majority of patients after bariatric surgeries, no manifestations of fibrosis were registered; however, after a short period of time, they relapsed and progressed at a higher rate [8].

The use of metabolic surgery techniques in the treatment of patients with NAFLD remains a matter of debate. To date, there is no evidence for the safety and efficacy of bariatric surgery in the treatment of patients with nonalcoholic steatohepatitis. In addition, there is evidence of both progression of fibrosis in patients with NAFLD after surgical treatment of obesity and cases of NAFLD manifestation in patients undergoing similar operations [79, 80].

CONCLUSION

Diseases associated with metabolic syndrome, in particular, NAFLD, make a significant contribution to the morbidity and mortality of the working population in developed countries. In the absence of effective pharmacological approaches, lifestyle modification, primarily consistent and gradual weight loss, as well as its maintenance are crucial in the treatment of NAFLD. Diet and exercise should be the main elements of any NAFLD treatment plan. The macro- and microelement composition of the diet has a significant impact on the progression of liver damage. Diets that are low in carbohydrates and saturated fats should be preferred.

Exercise is clearly essential in the management of NAFLD and should be recommended for all patients with hepatic steatosis. Even regardless of weight loss, physical activity improves disease progression rates. Increasing the intensity of exercise leads to a gradual increase in the beneficial effect in the treatment of NAFLD. The effect of strength training is less studied, but preliminary results show that it is highly effective in patients with NAFLD, even in the absence of significant weight loss.

As with many therapies, there is no single approach that would apply to every patient. At this stage of understanding the problem, there is a need for strategies focused on patient's individual characteristics. Regularity and consistency are the most important characteristics of any NAFLD management program.

Previous studies have investigated adherence to in patients with NAFLD treatment in general, while it is fundamentally important to study the nature of patients' adherence to lifestyle modifications in the short and long term, since eating behavior and physical activity are currently the only effective treatments for this pathology. Until recently, there have been no tools to assess adherence to lifestyle modification. However, at present, the Russian questionnaire for quantitative assessment of adherence to treatment "QAA-25" makes it possible to determine both adherence to therapy in general and adherence by individual key components: adherence to drug therapy, medical counseling, and lifestyle modification, which undoubtedly takes into account treatment strategies in patients with NAFLD.

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