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EFFECT OF A LIFESTYLE MODIFICATION ON INFLAMMATORY STATE IN OBESITY WITH CONCOMITANT NONALCOHOLIC FATTY LIVER DISEASE*

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For the last 40 years obesity has displayed unfavorable epidemiological dynamics. According to the data accumulated in 2013–2016 from 18 NHANES US studies, the latest prevalence estimated at 36.6% (male) and 41.0 % (female) [1].

Countries with a high prevalence of obesity also include both Western and Eastern Europe [2], and Ukraine, in particular.

Epidemiological studies have demonstrated that overweight and obesity can be regarded as a crucial predecessor to other noncommunicable diseases and an important risk factor for would-be morbidity [3], in nonalcoholic fatty liver disease (NAFLD), in particular [4, 5]. Significantly, NAFLD is one of the fast emerging as global health priorities, which bears a sensitive public health burden in the USA and Europe, affecting 64 million and 52 million patients, respectively [6, 7].

Both these conditions potentiate emergence and progression of each other. The meta-analysis by Dr. Younussi demonstrated that worldwide prevalence of obesity among NAFLD and NASH patients estimated at 51% and 81%, respectively [8, 9]. Correspondingly, Dr. Pallapayova and Dr. Perrumpail showed that in population with obesity, NAFLD prevalence varied from 60% to 95% [8, 10, 11].

Despite noticeable progress in the development of pharmacotherapy for obesity treatment, lifestyle modification remains an essential part of a successful weight loss intervention [12]. Furthermore, weight loss health improvements extend beyond anthropometric changes. A weight loss by 7% or more is associated with resolu-

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tion of nonalcoholic steatohepatitis in 65–90 % cases and improvement in the nonalcoholic steatosis [8].

In addition, a weight loss through lifestyle modification (diet, exercise) has been established as an integral part of the treatment of NAFLD patients [13].

The latest trends show that a low-grade inflammation represents one of the pathogenic mechanisms common in both obesity and NAFLD [14]. Chronic inflammation is associated with an increased serum concentration of proinflammatory cytokines and C-reactive protein. In turn, adipose tissue dysfunction is characterized by excess development and infiltration by inflammatory cells — an important source of adipokines. With this in mind, weight loss due to dietary interventions, as well as bariatric surgery, can help to suppress the intensity of chronic inflammation [15].

However, even with an account of the anti-inflammatory potential of nutrition and the beneficial effect of the diet in treatment of both obesity and NAFLD, scientific reports on the efficacy of lifestyle modification on proinflammatory state are scarce [16, 17].

Hence, the aim of this study was to assess the effect of weight loss due to lifestyle modification as part of obesity treatment in patients with obesity and concomitant NAFLD on inflammatory state.

METHODS AND MATERIALS

The study enrolled 52 NAFLD patients as a comparison group (group I) and 53 outpatients with obesity and concomitant NAFLD (main group or group II). The control group consisted of 23 healthy volunteers. All subjects signed an informed consent prior to the enrollment in the study and exposure to laboratory and instrumental procedures. We diagnosed obesity in compliance with EASO guidelines [18] and NAFLD in compliance with the recommendations of the European Association for the Study of the Liver (EASL) «EASL-EASD-EASO Clinical Practice Guidelines for the Management of Non-Alcoholic Fatty Liver Disease» [19]; the nationally-adapted clinical guidelines «Non-alcoholic fatty liver disease» and «Non-alcoholic steatohepatitis» with excluding secondary fatty liver etiologic factors. We determined the anthropometric indices, i.e. height in meters; body weight in kilograms with the following quantification of the body mass index (BMI). To assess physical endurance and physical state, according to K. Cooper, we performed bicycle exercise. All patients were evaluated for their liver function, carbohydrate metabolism and lipid metabolism. We estimated steatosis in compliance with the NAS index, and a fibrosis degree by the METAVIR scale with the hepatobiliary system ultrasound visualization (Soneus P7 ultrasound scanning system) by the wave attenuation coefficient and shear wave elastometry, respectively. Patients with severe steatohepatitis and cirrhosis, and other conditions possibly affecting the low-grade inflammation state were excluded from the study. As proinflammatory markers we assessed serum C-reactive protein (CRP) (hs-CRP ELISA KIT — DRG International Inc. (USA)), interleukin-6 (IL-6) (Vector-Best (Russia)) and IL-15 («RayBiotech» (USA)). In order to determine the effect of weight loss due to a lifestyle modification as obesity treatment on proinflammation markers in patients with obesity and concomitant NAFLD, the patients were randomized to follow-up groups who received only general recommendations (Groups IA and IIA), and active lifestyle modification (ALM), who underwent an adjustment of the diet composition and regimen with an energy deficit up to 500–1000 kkal according to the recommendations of a nutritionist and the expansion of physical activity under the guidance of a rehabilitation therapist (Groups IB and IIB). The duration of the follow-up stage was 24 weeks.

The statistical analysis was performed with the use the software package 'STATISTICA 13.1' (Statsoft, USA). According to the Kolmogorov–Smirnov criterion, the distribution of all parameters under study was established as different from normal (Gaussian), so we resorted to non-parametric statistical methods for the data processment, hereinafter referred to as Me [LQ; UQ], where Me is the median, and LQ and UQ are the lower and upper quartiles, respectively.

RESULTS AND DISCUSSION

An analysis of clinical manifestations demonstrated a statistically significant relation between the hepatic steatosis severity grade and the BMI (Kruskal-Wallis test, H = 23.55, $p < 0.01$); WC and W/H (WC: H = 20.45, $p < 0.01$; W/H: H = 36.27, respectively, $p < 0.01$).

The results of a bicycle ergometry showed that a satisfactory physical condition was observed in Group I by 29.30% more frequently than in Group II, while poor physical condition was by 20.00% more frequently observed in Group II ($p < 0.05$). Eight patients (15.09%) from Group II had their exercise tolerance level reduced to a very low level indicating a deterioration in physical condition due to a low level of motor activity and inappropriate nutrition.

A study in carbohydrate metabolism showed an elevation in fasting glycaemia by 12.38% ($p < 0.05$), insulin concentration by 74.27% ($p < 0.05$) in Group II, while index of insulin resistance HOMA in Group II exceeded that of Group I by 1.7 times.

Studies in the lipid spectrum showed that the Group II patients as compared with Group I had their serum total cholesterol (TCH) elevated by 14.87% ($p < 0.05$), triglycerides (TG) by 20.98% ($p < 0.05$), low density lipid (LDL) cholesterol by 25.08% ($p < 0.05$), and very low density lipid (VLDL) cholesterol by 50% ($p < 0.05$). Conversely, high density lipid (HDL) cholesterol level with Group II was lower by 11.21% ($p < 0.05$).

A study in proinflammatory markers showed that both Group I and Group II patients displayed an elevation in their concentrations. The CRP serum concentration in Group I exceeded that in NAFLD patients by 76.22% ($p < 0.05$) and IL-6 by 65.78% ($p < 0.05$). We did not find any age- and gender-related peculiarities both in CRP and IL-6 ($p > 0.05$). In juxtaposition, the control group revealed an increase in IL-15 concentration in Group I by 51.40% ($p < 0.05$), and almost twice as high as in Group II ($p < 0.05$). No gender and age-related differences were found for IL-15 levels ($p > 0.05$).

24-week administration of ALM contributed to weight loss, which averaged 6.76 [3.33; 10.45]% from the initial level in Group IB and 13.89 [6.88; 19.62]% in group IIB. In Groups IA and IIA, we indentified a mere tendency to weight loss, which, however, did not reach a statistical significance. The target weight loss (over 7% of the baseline) was determined only in patients from the groups of ALM (groups IB and IIB) and was more significant in the obesity group (70.37% vs. 44, 44% of patients; $p < 0.05$). Weight loss was accompanied by an improvement in clinical symptoms, general physical condition (according to K. Cooper) and physical endurance, i. e. in group IB this index increased by 19.56%, and in group IIB by 26.58%.

24-week ALM administration contributed to a decrease in hepatic steatosis grade, which was observed in 7 (25.93%) patients of group IB ($p < 0.05$) and in 7 (25.93%) patients of group IIB ($p < 0.05$). In addition, ALM was associated with an increased insulin sensitivity, confirmed by a decrease in insulin level in the Group IB by 20.99 [15,92; 27.95]% ($p < 0.05$), in group IIB by 42.03 (24.03; 50.34]% ($p < 0.05$), as well as the dynamics of the HOMA index, which decreased in group IB by 32.76 [21.93; 46.72]%, in group IIB — by 47.94 [33.38; 63.84]% ($p < 0.05$). Groups IA and IIA revealed a mere tendency towards a decrease in these indices ($p > 0.05$).

The TCH dynamics analysis showed a decrease in the concentration in all groups with significant changes found only in ALM group, i.e. in group IB by 5.92 [2,78; 9.93]% ($p < 0.05$) in group IIB by 25.64 [23.30; 30.38]% ($p < 0.05$).

The study in the dynamics of pro-inflammatory markers showed that after 24 weeks of follow-up in patients with group IA, the content of CRP tended to decrease by 25.00 [–2,63; 44.14]%, which did not reach statistical significance ($p > 0.05$). However, in patients from group IB, who received ALM, the CRP level decreased by 32.79 [19.05; 53,57]%, i.e. reached a statistical significance ($p < 0,05$). Relevant changes were observed in the group of patients with obesity and concomitant NAFLD (Group II).

In group IIA, the level of CRP decreased by only 10.58 [–3.96; 23.13]% ($p > 0.05$), and in group IIB became statistically significant decreased by 68.90 [17.18; 89.21]% ($p < 0.05$).

The study in the IL-6 level determined a decrease by 11.49 [–19.91; 24.69]% ($p > 0.05$)

after 24-weeks follow-up in group IA, and in group IIA by 14.34 [–22.10; 22.28] % ($p > 0.05$). In juxta position, the ALM groups dispayed a statistically significant decrease in IL-6 in the Group IB by 26.84 [19,28; 37.15] % ($p < 0.05$), and in group IIB by 37.50 [18.81; 55.40] % ($p < 0.05$).

After 24-week follow-up IL-15 decreased insignificantly in group IA by 1.44 [–0.42; 3.22] % ($p > 0.05$) and in group IIA by 2.25 [–0.53; 9.49] % ($p > 0.05$). However, the patients receiving ALM showed a significant decrease in the IL-15 level in Group IB by 2.47 [1,23; 7.25] % ($p < 0.05$), and in Group IIB by 37.32 [33.41; 40.61] % ($p < 0.05$).

Thus, our study demonstrated that patients with obesity and NAFLD displayed significant changes in physical state, glucose, lipid metabolic parameters and proinflammatory markers. Administrations of ALM led to statistically significant improvement in metabolic and proinflammatory state in patients with obesity and NAFLD, i.e. a decrease in IL-15 by 37,32 %, IL-6 by 37,50 % and CRP by 68,90 %. These results correlate with data obtained by Bianchi V. E. and Tyrovolas S. [15, 17]. Furthermore, we deepened understanding of effect of life style modification on complex underlying mechanisms of these comorbid pathologies.

CONCLUSIONS

The ALM-related weight loss, which includes dietary correction and increased physical activity, exerts a positive effect on the clinical course of both obesity and NAFLD; leads to an objectivized improvement in the patients' physical condition and the physical activity tolerance level; contributes to the improvement of anthropometric parameters and reduce the hepatic steatosis grade; and affects the main pathogenetic links of both diseases, i.e. insulin resistance and lipid metabolism disorders; inhibits systemic inflammation by reducing the levels of pro-inflammatory cytokines, i.e. has an immunocorrective effect; and is a pathogenetically proven treatment of both obesity and NAFLD.

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Resume. The aim of this study was to assess the effect of weight loss due to lifestyle modification as part of obesity treatment in patients with obesity and concomitant NAFLD on inflammatory state.

Methods and materials. The study enrolled 53 outpatients with obesity and concomitant NAFLD (Group II) and 52 NAFLD patients as a comparison group (Group I). The control group consisted of 23 healthy volunteers. For all patients we measured serum C-reactive protein, interleukin-6 (IL-6) and IL-15. The patients were randomized to follow-up groups who received only general recommendations (Groups IA and IIA) and active lifestyle modification (ALM) for 24 weeks (Groups IB and IIB).

Results. The results of our study showed that patients with obesity and NAFLD displayed statistically significant changes in metabolic and proinflammatory state. Furthermore, we found that after 24 weeks of follow-up in patients with group IA, the content of CRP tended to decrease by 25.00 [–2,63; 44.14]%, which did not reach statistical significance ($p > 0.05$). However, in patients from group IB, who received ALM, the CRP level decreased by 32.79 [19.05; 53,57]%, i.e. reached a statistical significance ($p < 0,05$). Relevant changes were observed in the group of patients with obesity and concomitant NAFLD (Group II). Patients of the group IIA displayed the level of CRP decreased by only 10.58 [–3.96; 23.13]% ($p > 0.05$), but the group IIB showed a statistically significant decrease in CRP by 68.90 [17.18; 89.21]% ($p < 0.05$). The study in the IL-6 level determined a decrease by 11.49 [–19.91; 24.69]% ($p > 0.05$) after 24-weeks follow-up in group IA, and in group IIA by 14.34 [–22.10; 22.28]% ($p > 0.05$). In juxta position, the ALM groups dispayed a statistically significant decrease in IL-6 in the Group IB by 26.84 [19,28; 37.15]% ($p < 0.05$), and in group IIB by 37.50 [18.81; 55.40]% ($p < 0.05$). After 24-week follow-up IL-15 decreased insignificantly in group IA by 1.44 [–0.42; 3.22]% ($p > 0.05$) and in group IIA by 2.25 [–0.53; 9.49]% ($p > 0.05$). However, the patients receiving ALM showed a significant decrease in the IL-15 level in Group IB by 2.47 [1,23; 7.25]% ($p < 0.05$), and in Group IIB by 37.32 [33.41; 40.61]% ($p < 0.05$).

Conclusions. The ALM-related weight loss exerts a positive effect on the clinical course of both obesity and NAFLD, including inhibition systemic inflammation by reducing the levels of pro-inflammatory cytokines, i. e. has an immunocorrective effect; and is a pathogenetically proven treatment of both obesity and NAFLD.

ВПЛИВ МОДИФІКАЦІЇ ЖИТТЯ НА ПРОЗАПАЛЬНИЙ СТАН ПРИ ОЖИРІННІ З СУПУТНЬОЮ НЕАЛКОГОЛЬНОЮ ХВОРОБОЮ ПЕЧІНКИ

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Резюме. Метою цього дослідження було оцінити вплив втрати ваги внаслідок модифікації способу життя як частини лікування ожиріння на запальний стан у пацієнтів із ожирінням та супутньою НАЖХП.

Методи та матеріали. У дослідженні брали участь 53 пацієнти з ожирінням та супутньою НАЖХП (Група II) та 52 пацієнти з НАЖХП як група порівняння (Група I). Контрольну групу складали 23 здорових добровольця. Всім хворим було виміряно концентрацію С-реактивного білку у сироватці крові, інтерлейкіну-6 (ІЛ-6) та ІЛ-15. Пацієнтів рандомізували в групи спостереження, які отримували лише загальні рекомендації (Групи ІА та ІІА) та активну модифікацію способу життя (АМС) протягом 24 тижнів (Групи ІВ та ІІВ).

Результати. Результати нашого дослідження показали, що у пацієнтів із ожирінням та НАЖХП спостерігаються статистично значущі зміни в метаболічному та прозапальному стані. Крім того, ми виявили, що після 24 тижнів спостереження у пацієнтів з групою ІА вміст СРБ, як правило, зменшувався на 25,00 [–2,63; 44,14]%, що не досягло статистичної значущості ($p > 0,05$). Однак у пацієнтів із групи ІВ, які отримували АМС, рівень СРБ знизився на 32,79 [19,05; 53,57]%, тобто досягла статистичної значущості ($p < 0,05$). Відповідні зміни спостерігались у групі пацієнтів із ожирінням та супутніми НАЖХП (ІІ група). У пацієнтів ІІА групи рівень СРБ знизився лише на 10,58 [–3,96; 23,13]% ($p > 0,05$), але група ІІВ продемонструвала статистично значуще зниження СРБ на 68,90 [17,18; 89,21]% ($p < 0,05$). Дослідження на рівні ІЛ-6 визначило зменшення на 11,49[–19,91; 24,69]% ($p > 0,05$) після 24-тижневого спостереження в групі ІА та в групі ІІА на 14,34[–22,10; 22,28]% ($p > 0,05$). У сусідньому положенні групи АМС виявили статистично значуще зниження ІЛ-6 у групі ІВ на 26,84 [19,28; 37,15]% ($p < 0,05$), а в групі ІІБ — на 37,50 [18,81; 55,40]% ($p < 0,05$). Після 24-тижневого спостереження ІЛ-15 незначно зменшився в групі ІА на 1,44 [–0,42; 3,22]% ($p > 0,05$), а в групі ІІА — на 2,25 [–0,53; 9,49]%

(p > 0,05). Однак у пацієнтів, які отримували АМС, продемонстровано значне зниження рівня ІЛ-15 у групі ІБ на 2,47 [1,23; 7,25] % (p < 0,05), а в ІІБ групі на 37,32 [33,41; 40,61] % (p < 0,05).

Висновки. Втрата ваги, пов'язана з активною модифікацією образа життя, позитивно впливає на клінічний перебіг як ожиріння, так і НАЖХП, включаючи пригнічення системного запалення за рахунок зниження рівня прозапальних цитокінів, тобто має імунокорегуючий ефект; і є патогенетично доведеним лікуванням ожиріння та НАЖХП.

ВЛИЯНИЕ МОДИФИКАЦИИ ОБРАЗА ЖИЗНИ НА ПРОВОСПАЛИТЕЛЬНУЮ АКТИВАЦИЮ ПРИ ОЖИРЕНИИ И СОПУТСТВУЮЩЕЙ НАЖБП

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Резюме. Целью этого исследования было оценить влияние потери веса вследствие модификации образа жизни как части лечения ожирения на воспалительное состояние у пациентов с ожирением и сопутствующей НАЖБП.

Методы и материалы. В исследовании участвовали 53 пациенты с ожирением и сопутствующими НАЖБП (Группа II) и 52 пациента с НАЖБП как группа сравнения (Группа I). Контрольную группу составили 23 здоровых добровольца. Всем пациентам было проведено измерение концентрации С-реактивного белка в сыворотке крови, интерлейкина-6 (ИЛ-6) и ИЛ-15. Пациентов рандомизировали в группы наблюдения, получавших только общие рекомендации (Группы IA и IIA) и активную модификацию образа жизни (АМО) в течение 24 недель (Группы IB и IIB).

Результаты. Результаты нашего исследования показали, что у пациентов с ожирением и НАЖХП наблюдаются статистически значимые изменения в метаболическом и провоспалительных состоянии. Кроме того, мы обнаружили, что после 24 недель наблюдения у пациентов с группой IIA содержание СРБ уменьшался на 25,00 [–2,63; 44,14] %, не достигшим статистической значимости (p > 0,05). Однако у пациентов из группы IB, которые получали АМО, уровень СРБ снизился на 32,79 [19,05; 53,57] %, то есть достигла статистической значимости (p < 0,05). Соответствующие изменения наблюдались в группе пациентов с ожирением и сопутствующими НАЖХП (II группа). У пациентов группы IIA уровень СРБ снизился лишь на 10,58 [–3,96; 23,13] % (p > 0,05), но группа IIB продемонстрировала статистически значимое снижение СРБ на 68,90 [17,18; 89,21] % (p < 0,05). Исследования уровня ИЛ-6 определило его уменьшение на 11,49 [–19,91; 24,69] % (p > 0,05) после 24-недельного наблюдения в группе IA и в группе IIA на 14,34 [–22,10; 22,28] % (p > 0,05). При сопоставлении у пациентов групп АМО обнаружено статистически значимое снижение ИЛ-6 в группе IB на 26,84 [19,28; 37,15] % (p < 0,05), а в группе IIБ — на 37,50 [18,81; 55,40] % (p < 0,05). После 24-недельного наблюдения уровень ИЛ-15 незначительно уменьшился в группе IA на 1,44 [0,42; 3,22] % (p > 0,05), а в группе IIA — на 2,25 [–0,53; 9,49] % (p > 0,05). Однако у пациентов, получавших АМО, продемонстрировано значительное снижение уровня ИЛ-15 в группе IБ на 2,47 [1,23; 7,25] % (p < 0,05), а в II Б группе на 37,32 [33,41; 40,61] % (p < 0,05).

Выводы. Потеря веса, связанная с активной модификацией образа жизни, положительно влияет на клиническое течение как ожирения, так и НАЖБП, включая угнетение системного воспаления за счет снижения уровня провоспалительных цитокинов, то есть имеет иммунокоррегирующий эффект; и является патогенетически обоснованным лечением как ожирения, так и НАЖБП.