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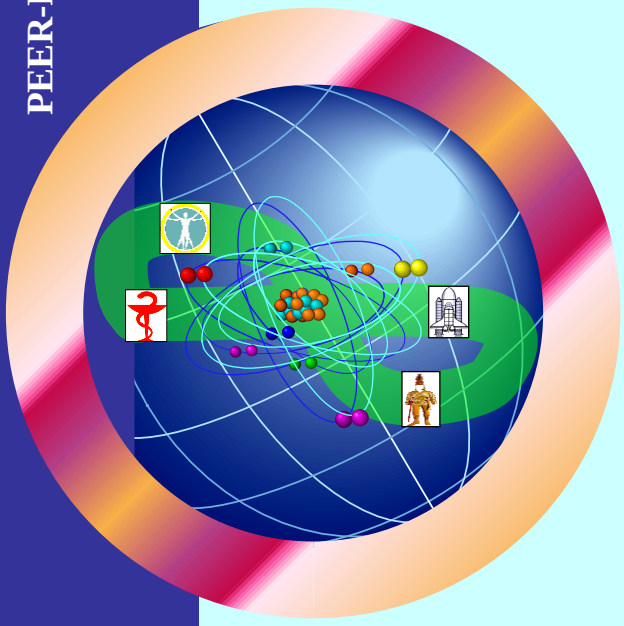
РЕЦЕНЗИЯЛАНАТЫН МЕДИЦИНАЛЫҚ
ҒЫЛЫМИ-ПРАКТИКАЛЫҚ ЖУРНАЛ



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MIDTERM RESULTS OF THE OBSERVATIONAL NON-INTERVENTIONAL CLINICAL STUDY "EVALUATION OF THE EFFECTIVENESS OF THE CARNITINE OROTATE AND BIPHENYLDIMETHYLDICARBOXYLATE COMPLEX IN THE PATHOGENETIC THERAPY OF METABOLIC-ASSOCIATED FATTY LIVER DISEASE: A PROSPECTIVE COHORT STUDY»

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Abstract

Introduction. Metabolic dysfunction-associated fatty liver disease (MAFLD) is a widespread pathology requiring effective treatment approaches. One promising direction is the use of a complex of carnitine orotate and biphenyldimethyldicarboxylate (COC and BDD), which possess antioxidant and hepatoprotective properties.

Materials and methods. As part of the observational, non-interventional, prospective cohort study KASVM-01 [NCT06078722], the impact of COC and BDD on the progression of MAFLD in patients in the Republic of Kazakhstan was investigated. From February 2023 to July 2024, a total of 121 participants from Almaty and Almaty Region were enrolled in the study and received COC and BDD. The observation period lasted 12 months, with an interim analysis conducted on 78 participants who completed a 24-week treatment course. Anthropometric parameters (BMI, waist circumference), liver steatosis and fibrosis levels measured via transient elastography (FibroScan) with CAP, ALT, AST, total cholesterol,

triglycerides, and FIB-4 (a non-invasive fibrosis marker) were assessed at baseline and after completing 24 weeks of therapy with COC and BDD.

Results. The interim analysis revealed a statistically significant reduction in ALT levels (from 32.4 to 20.1 U/mL, p<0.001), triglycerides (from 1.4 to 1.3 mmol/L, p=0.007), steatosis grade (from 304 to 283 dB/m, p<0.001), and fibrosis level (from 6.5 to 6.0 kPa, p=0.022). The prevalence of severe steatosis (S3) decreased from 52.7% to 45.7%, whereas mild steatosis (S1, S0) increased to 21.4% and 10%, respectively (p=0.001). The proportion of patients with F3 fibrosis declined from 8.1% to 1.4%, while F2 fibrosis decreased from 27% to 21.4% (p=0.022), indicating an improvement in fibrosis markers. During the observation period, BMI decreased (from 30.4 to 29.8 kg/m²), although the changes were not statistically significant (p=0.214). No significant changes were observed in total cholesterol and FIB-4 levels.

Conclusion. The interim analysis confirmed the effectiveness of COC and BDD in the treatment of MAFLD, demonstrating improvements in biochemical parameters as well as regression of liver steatosis and fibrosis. Further research and validation of these findings in later stages of observation are necessary to assess the final efficacy and long-term safety of the therapy.

Keywords: *Metabolic dysfunction-associated fatty liver disease, carnitine orotate, biphenyldimethyldicarboxylate, liver steatosis, liver fibrosis*

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Резюме

ПРОМЕЖУТОЧНЫЕ РЕЗУЛЬТАТЫ ОБСЕРВАЦИОННОГО НЕИНТЕРВЕНЦИОННОГО КЛИНИЧЕСКОГО ИССЛЕДОВАНИЯ «ОЦЕНКА ЭФФЕКТИВНОСТИ ПРИМЕНЕНИЯ КОМПЛЕКСА КАРНИТИН ОРОТАТА И БИФЕНИЛДИМЕТИЛДИКАРБОКСИЛАТА В ПАТОГЕНЕТИЧЕСКОЙ ТЕРАПИИ МЕТАБОЛИЧЕСКИ-АССОЦИИРОВАННОЙ ЖИРОВОЙ БОЛЕЗНИ ПЕЧЕНИ: ПРОСПЕКТИВНОЕ КОГОРТНОЕ ИССЛЕДОВАНИЕ»

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Введение. Метаболически-ассоциированная жировая болезнь печени (МАЖБП) является распространённой патологией, требующей эффективных методов терапии. Одним из перспективных направлений является использование комплекса карнитин-оротата и бифенилдиметилдикарбоксилата (КОК и BDD), обладающего антиоксидантными и гепатопротекторными свойствами.

Материалы и методы. В рамках обсервационного неинтервенционного проспективного когортного исследования KACBM-01 [NCT06078722] изучалось влияние КОК и BDD на течение МАЖБП у пациентов в Республики Казахстан. С февраля 2023 года по июль 2024 года в исследовании в Алматы и Алматинской области приняли участие 121 участник, принимавшие КОК и BDD. Длительность наблюдения составила 12 месяцев, а промежуточный анализ проведён на 78 участниках, завершивших 24-недельный курс лечения. Антропометрические данные (ИМТ, окружность талии), уровни стеатоза и фиброза печени, измеренные с помощью транзиторной эластографии (FibroScan) с CAP, АЛТ, АСТ, общий холестерин, триглицериды и FIB-4 (неинвазивный маркер фиброза), оценивались во время исходного визита и после завершения терапии КОК и BDD на 24-й неделе.

Результаты. По данным промежуточного анализа, отмечено статистически значимое снижение уровня АЛТ (с 32,4 до 20,1 ЕД/мл, p<0,001), триглицеридов (с 1,4 до 1,3 ммоль/л, p=0,007), степени стеатоза (с 304 до 283 дБ/м, p<0,001) и уровня фиброза (с 6,5 до 6,0 кПа, p=0,022). Частота выраженного стеатоза (S3) уменьшилась с 52,7% до 45,7%, тогда как легкие степени стеатоза (S1, S0) возросли до 21,4% и 10% соответственно (p=0,001). Доля пациентов с фиброзом F3 снизилась с 8,1% до 1,4%, а с F2 – с 27% до 21,4% (p=0,022), что свидетельствует об улучшении показателей фиброза. За время наблюдения ИМТ снизился (с 30,4 до 29,8 кг/м²), но статистически значимых различий не выявлено (p=0,214). Существенных изменений общего холестерина и FIB-4 не зафиксировано.

Заключение. Промежуточный анализ подтвердил эффективность применения КОК и BDD в терапии МАЖБП, продемонстрировав улучшение биохимических показателей, а также регрессию стеатоза и фиброза печени. Для окончательной оценки эффективности и долгосрочной безопасности терапии требуется продолжение исследования и подтверждение полученных данных на более поздних этапах наблюдения.

Ключевые слова: *метаболически-ассоциированная жировая болезнь печени, карнитин-оротат, бифенилдиметилдикарбоксилат, стеатоз печени, фиброз печени.*

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Түйіндеме

БАҚЫЛАУЛЫҚ ИНТЕРВЕНЦИЯСЫЗ КЛИНИКАЛЫҚ ЗЕРТТЕУДІҢ АРАЛЫҚ НӘТИЖЕЛЕРІ «КАРНИТИН ОРОТАТЫ МЕН БИФЕНИЛДИМЕТИЛДИКАРБОКСИЛАТ КЕШЕНІН МЕТАБОЛИЗММЕН БАЙЛАНЫСТЫ МАЙЛЫ БАУЫР АУРУЫНЫҢ ПАТОГЕНЕТИКАЛЫҚ ТЕРАПИЯСЫНДА ҚОЛДАНУ ТИІМДІЛІГІН БАҒАЛАУ: ПЕРСПЕКТИВТІ КОГОРТТЫҚ ЗЕРТТЕУ»

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Кіріспе. Метаболизммен байланысты майлы бауыр ауруы (МБМБА) кең таралған патология болып табылады және тиімді емдеу әдістерін қажет етеді. Перспективті бағыттардың бірі – антиоксиданттық және гепатопротекторлық қасиеттері бар карнитин-оротат пен бифенилдиметилдикарбоксилат (КОК және BDD) кешенін қолдану.

Әдістер. КАСВМ-01 [NCT06078722] обсервациялық, араласпайтын, перспективті когорттық зерттеуі аясында Қазақстан Республикасында КОК және BDD препаратының МБМБА ағымына әсері зерттелді. 2023 жылғы ақпан мен 2024 жылғы шілде аралығында Алматы және Алматы облысында 121 қатысушы осы препараттарды қабылдады. Бақылау ұзақтығы 12 айды құрады, ал аралық талдау 24 апталық емдеу курсын аяқтаған 78 қатысушыда жүргізілді. Антропометриялық көрсеткіштер (ДСИ, бел айналымы), бауыр стеатозы мен фиброз деңгейі (FibroScan CAP көмегімен), АЛТ, АСТ, жалпы холестерин, триглицеридтер және FIB-4 (фиброздың инвазивті емес маркері) бастапқы және 24-апталық терапиядан кейін бағаланды.

Нәтижелер. Аралық талдау бойынша АЛТ деңгейінің (32,4-тен 20,1 ЕД/мл-ге дейін, p<0,001), триглицеридтердің (1,4-тен 1,3 ммоль/л-ге дейін, p=0,007), стеатоз дәрежесінің (304-тен 283 дБ/м-ге дейін, p<0,001) және фиброз деңгейінің (6,5-тен 6,0 кПа-ға дейін, p=0,022) статистикалық тұрғыдан маңызды төмендеуі анықталды. Айқын стеатоздың (S3) жиілігі 52,7%-дан 45,7%-ға дейін төмендеді, ал жеңіл стеатоз деңгейлері (S1, S0) сәйкесінше 21,4% және 10%-ға дейін артты (p=0,001). F3 дәрежесіндегі фиброзы бар науқастар үлесі 8,1%-дан 1,4%-ға дейін, ал F2 деңгейі 27%-дан 21,4%-ға дейін төмендеді (p=0,022), бұл фиброз көрсеткіштерінің жақсарғанын көрсетеді. Бақылау кезеңінде ДСИ 30,4-тен 29,8 кг/м²-ге дейін төмендеді, бірақ статистикалық тұрғыдан маңызды айырмашылықтар анықталған жоқ (p=0,214). Жалпы холестерин мен FIB-4 көрсеткіштерінде айтарлықтай өзгерістер байқалмады.

Қорытынды. Аралық талдау КОК және BDD препараттарын МБМБА емдеуде қолданудың тиімділігін растады, биохимиялық көрсеткіштердің жақсарғанын, сондай-ақ бауыр стеатозы мен фиброзының регрессиясын көрсетті. Терапияның түпкілікті тиімділігі мен ұзақ мерзімді қауіпсіздігін бағалау үшін зерттеуді жалғастыру және алынған мәліметтерді бақылаудың кейінгі кезеңдерінде растау қажет.

Түйінді сөздер: *метаболизммен байланысты майлы бауыр ауруы, карнитин-оротат, бифенилдиметилдикарбоксилат, бауыр стеатозы, бауыр фиброзы.*

Дәйексөз үшін:

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Introduction

The prevalence of metabolic dysfunction-associated fatty liver disease (MAFLD) continues to rise rapidly, with some studies indicating a prevalence exceeding 30% [15], highlighting the importance of developing effective pharmacological treatment algorithms to prevent disease progression. The complexity of MAFLD pathophysiology significantly complicates the search for a universal and effective treatment approach.

The fundamental approaches in MAFLD therapy remain lifestyle modifications, including increased physical activity, weight reduction, and smoking cessation. An important addition to these measures is the correction of metabolic factors such as diabetes, obesity, and dyslipidemia [6].

In March 2024, resmetirom was approved for the treatment of MAFLD. The primary mechanisms of this drug include liver fibrosis correction and inflammation reduction. It is essential to understand that the drug was approved, alongside diet and exercise, for adults with MAFLD who have moderate to advanced liver fibrosis (stage F2 or F3) but have not yet developed cirrhosis. Resmetirom remains under clinical investigation, with its efficacy and safety still being studied, and treatment duration has yet to be established. Consequently, the search for optimal MAFLD treatment regimens continues.

One mechanism of MAFLD progression is reduced fatty acid oxidation in hepatocytes, which is closely linked to liver steatosis. It has been proven that mitochondrial dysfunction leads to fat accumulation in the liver, and oxidative stress may explain the mitochondrial dysfunction observed in MAFLD. Carnitine is a well-known modulator of free fatty acid transport and oxidation in mitochondria [16,18], and several studies have demonstrated its antioxidant activity in hepatocytes [5,10,12].

The carnitine orotate complex (Godex®) is a pharmaceutical drug that has demonstrated efficacy in reducing cytolysis in liver diseases [11,20,22]. Recent in vitro and in vivo studies have shown that the carnitine orotate complex can improve metabolic health by influencing glucose and lipid metabolism and significantly reducing liver steatosis [3,8,9,21]. Furthermore, experimental research has identified the molecular mechanism by which the carnitine orotate complex reduces insulin resistance [9].

Given its positive metabolic effects and widespread use, it became relevant to investigate the relationship between carnitine orotate complex use in MAFLD patients in Kazakhstan. A similar study was conducted in 2014 in the country, assessing the efficacy and safety of this complex in a smaller patient cohort with a shorter treatment duration (up to eight weeks) [1].

In November 2022, a Korean study was published examining the long-term use of the carnitine orotate complex (Godex®) (up to 30 days, 30-180 days, and over 180 days) and its impact on mortality. The study found that the most significant reduction in mortality risk was observed in individuals with metabolic risk factors such as obesity, fatty liver disease, dyslipidemia, type 2 diabetes, and metabolic syndrome with prolonged use of the carnitine orotate complex, whereas the effect was weaker in alcohol consumers [19].

Thus, **the aim of this study** was to evaluate the efficacy of carnitine orotate complex and BDD in the pathogenetic therapy of MAFLD in Kazakhstan in routine clinical practice.

Materials and Methods.

An observational, non-interventional, prospective cohort cluster study KASVM-01 [NCT06078722] was conducted to examine the effects of the carnitine orotate complex + biphenyldimethyldicarboxylate (COC and BDD) on the progression of MAFLD. The study included adult residents of Kazakhstan. To ensure consistency in enrollment, the recruitment period lasted six months, and the follow-up period was 12 months (*Scheme 1*). As part of routine clinical practice, patients visited their attending physician every six months. According to the study protocol, visits included specific examinations and questionnaires that are part of the standard routine management of MAFLD patients. Only patients with a formally documented and confirmed diagnosis (primary medical documentation) were eligible for inclusion in the study.

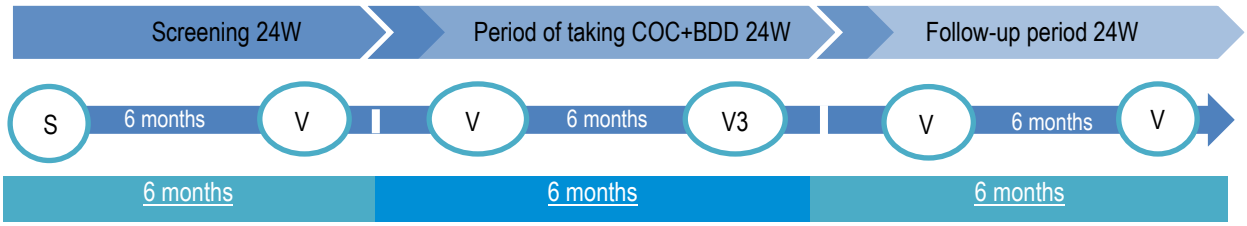
Study cohorts (*Scheme 1*):

• Study cohort: Patients taking COC and BDD, regardless of study participation. Treatment duration: six months, followed by six months of post-treatment observation.

• Control cohort: Patients not taking COC and BDD, regardless of study participation. Observation duration: 12 months.

The study included patients taking or not taking COC and BDD, regardless of sex and age, who were registered as MAFLD patients. Enrollment was conducted by researchers involved in the study across six regions of Kazakhstan: Almaty, Astana, Aktobe, Shymkent, Semey, Turkestan region, and Almaty region.

Inclusion criteria: Patients of both sexes aged 18 to 75 years, who are citizens of the Republic of Kazakhstan; patients with a clinically and laboratory-confirmed diagnosis of MAFLD without severe comorbidities; patients not receiving other adjunctive therapy (metabolic therapy drugs, essential phospholipids, ursodeoxycholic acid, glycyrrhizic acid, ademetionine, and others); patients with a minimum seven-day washout period between discontinuing other adjunctive therapy and starting COC and BDD; patients who voluntarily signed the informed consent form.



Cohort	Observation cohort	Regions
Study cohort	Patients using COC and BDD	Almaty, Almaty region
Control cohort	Patients not using COC and BDD	Astana, Aktobe, Shymkent, Semey, Turkestan region

Scheme 1. Observation period with patient visits depending on COC and BDD intake, cluster distribution of cohorts.

Exclusion criteria: Patients with alcohol abuse according to the AUDIT-C questionnaire; patients taking the carnitine orotate complex for more than four weeks before signing informed consent; patients with contraindications to the carnitine orotate complex; patients diagnosed with diabetes; pregnancy and lactation; concurrent use of levodopa, altretamine, cisplatin, metformin, statins; patients with co-infections (HIV, HBV, HCV); decompensated liver cirrhosis (CTP≥7 points); eGFR ≤15 mL/min/1.73 m²; drug-induced liver injury; use of narcotic and psychotropic substances; malignant liver or other organ tumors (history or present) or clinically significant elevation of alpha-fetoprotein >5 times the normal value; patients with significant biochemical activity (ALT, AST >10 ULN) and total bilirubin >2 ULN; participation in an interventional clinical study.

The enrollment period lasted 18 months with follow-up visits every three months. Based on sample size calculations for parallel groups with binary outcome parameters, the required number of patients in each group was 120. Applying a 10% dropout rate, the final number of study participants in each group was 132, requiring a total of 264 participants.

From February 2023 to July 2024, a total of 121 participants taking COC and BDD were enrolled in the study in Almaty and Almaty region. This interim analysis included 78 participants who completed COC and BDD therapy by September 2024. Anthropometric data (BMI, waist circumference), steatosis and fibrosis levels measured by transient elastography (TE), FibroScan, with CAP, ALT, AST, total cholesterol, triglycerides, and FIB-4 (a non-invasive fibrosis marker) were assessed at the baseline visit and after completing COC and BDD therapy at week 24.

Data presentation and processing methods.

"Waist circumference" and "Total cholesterol" showed normal data distribution, so parametric descriptive methods and tests were applied, while non-parametric methods were used for other parameters. Mean and standard deviation were used to describe "Waist circumference" and "Total cholesterol," while median and interquartile range were used for others. Paired Student's t-test was applied to compare mean values, and the Wilcoxon rank-sum test was used for median values. Frequency analysis was used to describe fibrosis stage, steatosis stage, and interpretation of the FIB-4 test result. To compare frequencies at baseline and week 24, variables were converted into ordinal data and compared using the Wilcoxon rank-sum test. All results were considered statistically significant at $p<0.05$.

Statistical analysis was conducted using Jamovi 2.4.8. The statistical abbreviations and terms used in this article are as follows: Mean - the arithmetic average of the given numbers, SD – standard deviation, Me – median, Min - the smallest value present in the data, Max - the largest value present in the data, Q1 - the lower quartile, the value under which 25% of data points are found when arranged in increasing order, Q3 - the upper quartile, or third quartile, the value under which 75% of data points are found when arranged in increasing order, P-value - defined as the probability, under the assumption of no effect or no difference (null hypothesis), of obtaining a result equal to or more extreme than what was actually observed.

Results

Over 24 weeks of COC and BDD administration, a statistically significant reduction was observed in ALT levels (U/mL) from 32.4 [19-51.5] to 20.1 [14.9-28.4] ($p<0.001$), triglycerides from 1.4 [1.1-2.2] to 1.3 [1.0-2.0] mmol/L ($p=0.007$), steatosis level based on TE (dB/m) from 304 [268-325] to 283 [246-312] ($p<0.001$), and fibrosis level (kPa) from 6.5 [5.3-8.3] to 6.0 [4.7-7.2] ($p=0.022$).

AST levels showed a slight increase over time: median at the first visit was 23.3 [17.9-38.6], and at week 24, the median was 23.5 [19.1-28.4] mmol/L ($p=0.021$), but at week 24, the variation remained within reference values. The median BMI decreased over 24 weeks from 30.4 to 29.8 kg/m²; however, these differences were not statistically significant ($p=0.214$). Changes in waist circumference over time could not be reliably assessed ($p=0.943$).

The frequency of grade 3 fibrosis based on TE data decreased from 8.1% to 1.4%, and grade F2 fibrosis from 27% to 21.4% ($p=0.022$) over 24 weeks. The frequency of F1 fibrosis increased from 28.4% to 32.9%, and F0 from 35.1% to 42.9%, indicating improvements in fibrosis markers after four weeks of COC and BDD administration.

The frequency of severe steatosis S3 according to TE data decreased from 52.7 to 45.7%, S2 degree also decreased from 29.7 to 22.9%. At the same time, the frequency of a milder degree S1 increased from 17.6 to 21.4% and previously absent cases with S0 – 10% appeared at 24 weeks of treatment with COCs and BDD ($p=0.001$).

When comparing total cholesterol data (Table 1) and interpreting the FIB-4 test results over time, no statistically significant differences were observed (Table 2).

Table 1.

Dynamic changes in indicators of a patient group taking COC and BDD who completed 24-week follow-up.

Indicator	Visit				P value
	Screening		24 weeks		
	Me [Q1-Q3] / Mean±SD	Min-Max	Me [Q1-Q3] / Mean±SD	Min-Max	
BMI, kg/m2	30,4 [28,1-33,1]	22,4-43,1	29,8 [27,3-32,4]	20,7-44,6	0,214
Waist circumference, cm	105±12,5	71-150	105±12,5	73-150	0,943
Fibrosis, kPa	6,5 [5,3-8,3]	3,1-21,1	6 [4,7-7,2]	3-25,8	0,022
Steatosis, dB/m	304 [268-325]	240-400	283 [246-312]	7,1-400	<0,001
AST, U/l	23,3 [17,9-38,6]	1,1-229	23,5 [19,1-28,4]	10-104	0,021
ALT, U/l	32,4 [19-51,5]	8-305	20,1 [14,9-28,4]	8,2-88,7	<0,001
Total cholesterol, mmol/l	5,4±1	3-8,2	5,3±0,9	2,9-8	0,392
Triglycerides, mmol/l	1,4 [1,1-2,2]	0,5-4,2	1,3 [1,0-2,0]	0,5-10,7	0,007
FIB-4 test result	1,1 [0,9-1,3]	0,28-7,5	1,3 [0,9-1,6]	0,21-8,8	0,051

Table 2.

Changes in the dynamics of the FIB-4 test results while taking COC and BDD.

Interpretation of FIB-4 test result	Screening		24 weeks		P
	n	%	n	%	
No significant fibrosis	38	80.9 %	35	63.6 %	0,071
Gray zone	8	17.0 %	18	32.7 %	
Fibrosis stage 4-6 on the Ishak scale	1	2.1 %	2	3.6 %	

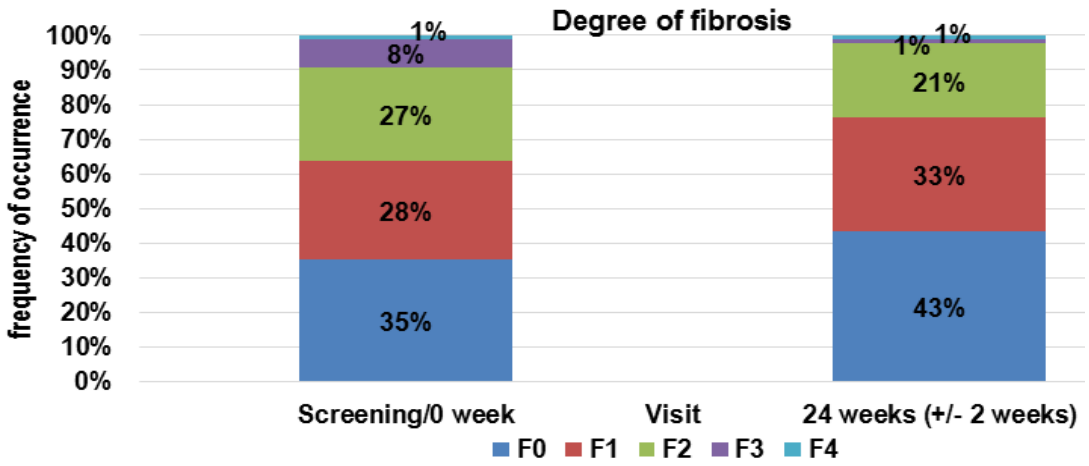


Diagram 1. Frequency of fibrosis according to TE data over time while taking COC and BDD.

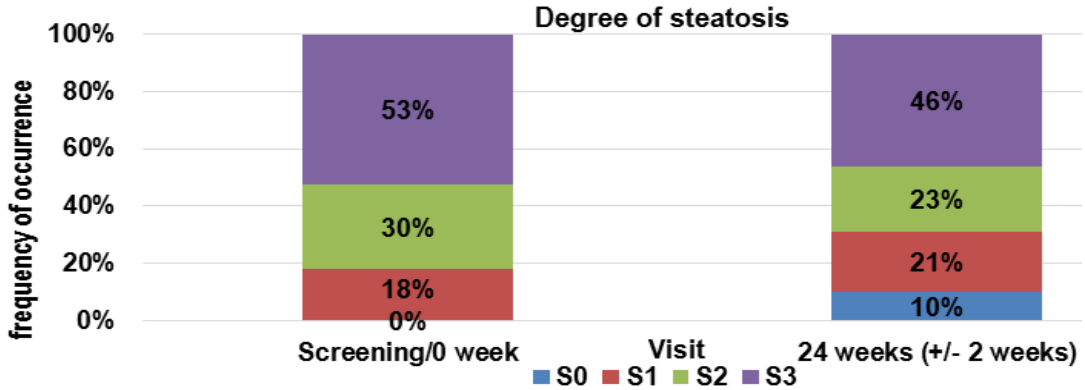


Diagram 2. Frequency of steatosis according to TE data in dynamics against the background of COC and BDD intake.

Discussion

The complex of carnitine orotate and BDD is a pharmaceutical agent used as part of combination therapy for liver diseases. It exhibits detoxifying, antioxidant, and metabolic effects, contributing to the maintenance and restoration of liver function. The drug exerts both functional and histological reparative effects on damaged hepatocytes and acts as a lipotropic factor in hepatic steatosis. It promotes β-oxidation of free fatty acids and their metabolism within hepatocyte mitochondria. The synergistic action of its components enhances glycogen storage, synthetic, and antitoxic functions of the liver. Furthermore, the drug increases hepatic cell sensitivity to insulin, facilitates its secretion, and normalizes ALT levels in the blood, which are elevated due to various liver diseases.

An interim analysis of the observational study KASVM-01 confirmed the potential of COC and BDD in the treatment of MAFLD. The study data demonstrate significant improvements in key biochemical, anthropometric, and instrumental parameters in patients who completed a 24-week therapy course.

A statistically significant reduction in ALT levels was observed over the 24-week treatment period with COC and BDD, indicating a reduction in hepatic inflammation. This effect is further supported by decreased triglyceride levels and hepatic steatosis grade as assessed by transient elastography (TE). These changes are mediated by the positive impact of COC and BDD on β-oxidation of fatty acids in mitochondria, thereby improving lipid metabolism by enhancing fatty acid uptake and consequently reducing lipotoxicity. *Zhang et al.* (2020) [24] and *Li N & Zhao H* (2021) [13] suggest that inhibition of β-oxidation may potentially contribute to reduced mortality in patients with metabolic risk factors upon prolonged administration of COC and BDD [19].

Additionally, the reduction in fibrosis severity, as determined by TE, particularly the decrease in the prevalence of advanced fibrosis (F3) from 8.1% to 1.4%, indicates a favorable long-term prognosis. The increase in mild fibrosis cases (F0 and F1) alongside the decrease in more severe forms supports the potential antifibrotic effect of COC and BDD. This finding aligns with experimental data demonstrating the beneficial role of carnitine in fibrosis regression in the liver [4,14,17,19].

Reducing hepatic fat accumulation in MAFLD is a key aspect of preventing disease progression. Excess lipid accumulation in hepatocytes promotes inflammation, fibrosis, and increases the risk of progression to cirrhosis or hepatocellular carcinoma. Reducing hepatic steatosis not only improves liver function but also decreases cardiometabolic risks, which is particularly important for patients with comorbid obesity and type 2 diabetes. The reduction in severe steatosis cases (S3) and the increase in mild steatosis (S1) or its complete absence (S0) underscore the efficacy of COC and BDD in reducing hepatic fat infiltration. This effect is consistent with the results of the CORONA study conducted by Korean colleagues in patients with type 2 diabetes [3].

Special attention should be given to the impact of COC and BDD on anthropometric parameters. Carnitine plays a crucial role in the transport of fatty acids into mitochondria, where they undergo oxidation with energy release, thereby contributing to lipolysis [23]. Additionally, biphenyldimethyl dicarboxylate activates enzymes involved in lipolysis, collectively leading to a reduction in fat accumulation in the body [7].

A systematic review previously demonstrated that L-carnitine supplementation may contribute to improvements in body weight and body mass index (BMI), particularly in overweight and obese individuals [2].

In the present study, the interim analysis showed a reduction in BMI from 30.4 to 29.8 kg/m². However, this change did not reach statistical significance, which may be due to the limited duration of observation. Nonetheless, the observed trend suggests that these changes may be attributed not only to lifestyle modifications but also to COC and BDD therapy. A longer follow-up and further analysis are required for an objective assessment of this effect.

It should be noted that the presented results are interim and based on data from a cohort of patients receiving COC and BDD in routine clinical practice. The final study analysis will include an evaluation of the efficacy of COC and BDD in managing MAFLD, as well as an inter-cluster comparison to demonstrate the internal validity of the findings and subgroup homogeneity. Despite existing publications supporting the efficacy of COC and BDD in MAFLD therapy [3,8,9,11,20,22], this study is the first to present real-world clinical practice data from the Republic of Kazakhstan.

Thus, the interim findings of the KASVM-01 study demonstrate the promise of COC and BDD in MAFLD treatment, particularly in reducing hepatic inflammation, steatosis, and fibrosis. However, a final assessment of the efficacy of these drugs requires further analysis, including long-term patient follow-up and comparative evaluation with other therapeutic approaches.

Conclusion

The interim analysis results demonstrate that COC and BDD exert a comprehensive positive effect on key parameters in MAFLD patients, including reductions in steatosis and fibrosis. However, for a definitive assessment of treatment efficacy and long-term safety, continued study and confirmation of the obtained data at later observation stages are required. Despite these promising results, additional research is necessary to evaluate the effectiveness of COC and BDD in MAFLD therapy.

The results presented in this publication represent interim data obtained from the cohort receiving COC and BDD for MAFLD as part of routine clinical practice. The final analysis will include an assessment of the effectiveness of COC and BDD in routine MAFLD management between study cohorts, as well as inter-cluster comparisons to demonstrate the internal validity of the results and subgroup homogeneity within clusters. Although the positive experience of using COC and BDD in MAFLD therapy has been extensively covered in prior publications [3, 8,9,17,20,22], this study is the first to present real-world application results of COC and BDD in a patient population receiving treatment as part of routine clinical practice in Kazakhstan.

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References:

1. *Aldasheva Zh.A.* Use of carnitine in the complex treatment of non-alcoholic steatosis and steatohepatitis. Journal "Vestnik KRSU", 2013, Vol. 13, No. 11, pp. 32-34. UDC 616.36: 616-003.826

2. *Askarpour M., Hadi A., Miraghajani M., Symonds M.E., Sheikhi A., Ghaedi E.* Beneficial effects of l-carnitine supplementation for weight management in overweight and obese adults: An updated systematic review and dose-response meta-analysis of randomized controlled trials. Pharmacol Res. 2020 Jan;151:104554. doi: 10.1016/j.phrs.2019.104554. Epub 2019 Nov 17. PMID: 31743774.

3. *Bae J.C., Lee W.Y., Yoon K.H., Park J.Y., Son H.S., Han K.A., Lee K.W., Woo J.T., Ju Y.C., Lee W.J.,* et al. Improvement of Nonalcoholic Fatty Liver Disease with Carnitine-Orotate Complex in Type 2 Diabetes (CORONA): A Randomized Controlled Trial. Diabetes Care. 2015;38:1245–1252. doi: 10.2337/dc14-2852.

4. *Demiroren, Kaan; Dogan, Yasar; Kocamaz, Halil; Ozercan, Ibrahim Hanifi; Ilhan, Selcuk; Ustundag, Bilal; Bahcecioglu, Ibrahim Halil* . (2014). Protective effects of L-carnitine, N-acetylcysteine and genistein in an experimental model of liver fibrosis. Clinics and Research in Hepatology and Gastroenterology, 38(1), 63–72. doi:10.1016/j.clinre.2013.08.014

5. *Dobrzyńska I., Szachowicz-Petelska B., Skrzydlewska E., Figaszewski Z.* Effect of L-carnitine on liver cell membranes in ethanol-intoxicated rats. Chem Biol Interact 2010;188:44–51

6. EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD) Tacke, Frank et al. Journal of Hepatology, Volume 81, Issue 3, 492 – 542

7. *Garcia C., Rodriguez M. et al.* Biphenyldimethyl dicarboxylate: a novel lipolytic agent. Lipids. 2018. Vol. 53. No. 4. P. 287-295.

8. *Hong E.S., Kim E.K., Kang S.M., Khang A.R., Choi S.H., Park K.S., Jang H.C., Lim S.* Effect of Carnitine-Orotate Complex on Glucose Metabolism and Fatty Liver: A Double-Blind, Placebo-Controlled Study. J. Gastroenterol. Hepatol. 2014;29:1449–1457. doi: 10.1111/jgh.12536.

9. *Hong J.H., Lee M.K.* Carnitine Orotate Complex Ameliorates Insulin Resistance and Hepatic Steatosis through Carnitine Acetyltransferase Pathway. Diabetes Metab. J. 2021;45:933–947. doi: 10.4093/dmj.2020.0223.

10. *Jun D.W., Cho W.K., Jun J.H.* et al. Prevention of free fatty acid-induced hepatic lipotoxicity by carnitine via reversal of mitochondrial dysfunction. Liver Int 2011;31:1315–1324

11. *Jun D.W., Kim B.I., Cho Y.K., Kim H.J., Kwon Y.O., Park S.Y., Han S.Y., Baek Y.H., Jung Y.J., Kim H.Y.,* et al. Efficacy and Safety of Entecavir plus Carnitine Complex (GODEX®) Compared to Entecavir Monotherapy in Patient with ALT Elevated Chronic Hepatitis B: Randomized, Multicenter Open-Label Trials. The GOAL Study. Clin. Mol. Hepatol. 2013;19:165–172. doi: 10.3350/cmh.2013.19.2.165.

12. *Li J.L., Wang Q.Y., Luan H.Y., Kang Z.C., Wang C.B.* Effects of L-carnitine against oxidative stress in human hepatocytes: involvement of peroxisome proliferator-activated receptor alpha. J Biomed Sci 2012;19:32

13. *Li N., Zhao H.* Role of Carnitine in Non-alcoholic Fatty Liver Disease and Other Related Diseases: An Update. Front. Med. 20218:689042. doi: 10.3389/fmed.2021.689042.

14. *Lyu J., Okada H., Sunagozaka H., Kawaguchi K., Shimakami T., Nio K., Murai K., Shirasaki T., Yoshida M., Arai K., Yamashita T., Tanaka T., Harada K., Takamura T., Kaneko S., Yamashita T., Honda M.* Potential utility of l-carnitine for preventing liver tumors derived from metabolic dysfunction-associated steatohepatitis. Hepatol Commun. 2024 Apr 12;8(5):e0425. doi: 10.1097/HC9.0000000000000425. PMID: 38619434; PMCID: PMC11019826

15. *Miao L., Targher G., Byrne C.D., Cao Y.Y., Zheng M.H.* Current status and future trends of the global burden of MASLD. Trends Endocrinol Metab. 2024 Aug;35(8):697-707. doi: 10.1016/j.tem.2024.02.007. Epub 2024 Feb 29. PMID: 38429161

16. *Murosaki S., Lee T.R., Muroyama K.* et al. A combination of caffeine, arginine, soy isoflavones, and L-carnitine enhances both lipolysis and fatty acid oxidation in 3T3-L1 and HepG2 cells in vitro and in KK mice in vivo. J Nutr 2007;137:2252–2257

17. *Nimbalkar V., Vyawahare N.* L-carnitine ameliorates bile duct ligation induced liver fibrosis via reducing the nitrosative stress in experimental animals: preclinical evidences. Heliyon. 2021 Nov 26;7(11):e08488. doi: 10.1016/j.heliyon.2021.e08488. PMID: 34901512; PMCID: PMC8642613

18. *Noland R.C., Koves T.R., Seiler S.E.* et al. Carnitine insufficiency caused by aging and overnutrition compromises mitochondrial performance and metabolic control. J Biol Chem 2009;284:22840–22852

19. *Park K.Y., Hong S, Kim K.S., Han K, Park C.Y.* Prolonged Use of Carnitine-Orotate Complex (Godex®) Is Associated with Improved Mortality: A Nationwide Cohort Study. J Pers Med. 2022 Nov 28;12(12):1970. doi: 10.3390/jpm12121970. PMID: 36556191; PMCID: PMC9787718

20. *Park M.S., Kang J.S., Chon C.Y., Paik S.W., Rim K.S., Kwak M.J., Jeon Y.C., Lee M.H.* Oral Godex Capsule for Chronic Liver Disease:A Double-Blind, Randomized, Multicenter Controlled Trial. J. Korean Soc. Clin. Pharmacol. Ther. 2001;9:151–162. doi: 10.12793/jkscpt.2001.9.2.151.

21. *Ringseis R., Keller J., Eder K.* Role of Carnitine in the Regulation of Glucose Homeostasis and Insulin Sensitivity: Evidence from in Vivo and in Vitro Studies with Carnitine Supplementation and Carnitine Deficiency. Eur. J. Nutr. 2012;51:1–18. doi: 10.1007/s00394-011-0284

22. *Sin J.S., Jung E.Y., Lee M.H., Kang J.K.* Therapeutic Effect of the Godex on the Liver Cirrhosis Induced by CCl4 and Ethanol in the Rat. J. Appl. Pharmacol. 2002. 10:200–207.

23. *Smith J.D., Jones A.B.* The role of carnitine in fatty acid metabolism. Journal of Nutritional Biochemistry. 2020. Vol. 85. P. 123-130.

24. *Zhang, Y., et al.* Enhancing fatty acids oxidation via L-carnitine attenuates obesity-related atrial fibrillation. Front. Pharmacol. 2021. 12:771940.

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