

Effect of A Modified Ketogenic Diet on The Hepatobiliary System in Experimental Metabolic Syndrome: Dynamics of Apolipoprotein E and Lipoprotein Lipase

Alimov S.M.

Tashkent State Medical University, Tashkent, Uzbekistan

Tursunov D.Kh.

Tashkent State Medical University, Tashkent, Uzbekistan

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Abstract

Background: Metabolic syndrome (MetS) is accompanied by dyslipidemia, impaired glucose homeostasis, systemic inflammation, and hepatobiliary dysfunction [1, 2]. Apolipoprotein E (ApoE) and lipoprotein lipase (LPL) are key components of triglyceride-rich lipoprotein metabolism [7–9]. **Objective:** To evaluate the effects of a modified ketogenic diet (MKD; 60% fat, 30% protein, 10% carbohydrate) on hepatobiliary, metabolic, inflammatory, and lipoprotein-related parameters in an experimental rabbit model of MetS, with particular emphasis on ApoE and LPL dynamics. **Methods:** Sixty Chinchilla rabbits entered the experiment. Eight formed the intact control group, whereas MetS was induced in 52 animals for 60 days using crystalline cholesterol (250 mg/kg), 5% sucrose solution, and subcutaneous insulin (0.1 U/100 g every other day) [5]. Four animals died during induction. The remaining 48 animals with MetS were allocated to six groups (n=8 each): MetS control, traditional ketogenic diet (TKD), MKD, MKD+ezetimibe (0.14 mg/kg/day), MKD+metformin (25 mg/kg/day), and MKD+metformin+ezetimibe. Treatment lasted 30 days. Biochemical variables were assessed on days 10, 20, and 30; ApoE and LPL were measured by ELISA. **Results:** In the MKD group, ALT decreased from 64.4 ± 5.8 U/L on day 10 to 49.9 ± 4.8 U/L on day 30, GGT from 14.9 ± 1.6 to 12.4 ± 1.2 U/L, and albumin increased from 35.9 ± 3.2 to 40.5 ± 3.9 g/L. ApoE decreased from 26.2 ± 1.2 to 23.2 ± 1.2 and 21.2 ± 1.1 mg/dL, whereas LPL increased from 25.8 ± 0.8 to 27.0 ± 0.8 and 30.8 ± 0.9 ng/mL on days 10, 20, and 30, respectively. **Conclusion:** MKD was associated with improvement in hepatobiliary, metabolic, inflammatory, and lipoprotein-related indices in experimental MetS. ApoE and LPL showed clear time-dependent responses and warrant further investigation as research indicators of lipoprotein metabolic changes.

Keywords: Metabolic syndrome; modified ketogenic diet; apolipoprotein E; lipoprotein lipase; hepatobiliary system; dyslipidemia; rabbit model.

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1. Introduction

Metabolic syndrome is a cluster of interrelated

cardiometabolic abnormalities, including central adiposity, impaired glucose regulation, dyslipidemia, and systemic inflammation [1, 2, 24]. The liver has a central role in these

disturbances, and metabolic dysfunction-associated steatotic liver disease is closely linked to the MetS phenotype [4, 6, 11, 22, 23]. ApoE participates in receptor-mediated clearance of triglyceride-rich lipoprotein remnants, whereas LPL hydrolyzes triglycerides in circulating chylomicrons and very-low-density lipoproteins [7–9]. Their coordinated disturbance may therefore provide additional information on lipoprotein metabolism in MetS. Low-carbohydrate and ketogenic dietary interventions can modify hepatic triglyceride accumulation and cardiometabolic variables, although their effects depend on macronutrient composition, duration, and experimental context [10, 12, 13, 25]. The present MKD reduced the fat proportion and increased the protein proportion relative to the traditional ketogenic diet while maintaining carbohydrate restriction. The aim of this study was to evaluate the effects of MKD (60:30:10) on hepatobiliary biochemical indices, glucose and lipid metabolism, C-reactive protein (CRP), ApoE, LPL, and liver morphology in experimental MetS, and to compare these effects with TKD and pharmacological correction added to MKD.

2. Methods

2.1. Animals and study design

Sixty Chinchilla rabbits were initially included. Eight animals formed the intact control group. MetS was induced in the remaining 52 rabbits for 60 days. Four animals died during induction; consequently, 48 animals with established MetS remained and were allocated to six groups of eight animals each. Together with the intact group, the final analysis comprised seven groups (n=8 per group).

2.2. Induction of metabolic syndrome

MetS was induced according to the experimental protocol used in the dissertation study: crystalline cholesterol (250 mg/kg) was administered with carrot, drinking water was replaced by a 5% sucrose solution, and insulin was administered subcutaneously at 0.1 U/100 g every other day for 60 days [5].

2.3. Interventions

The 30-day correction period included the following groups: intact control; MetS control; MetS+TKD; MetS+MKD; MetS+MKD+ezetimibe (0.14 mg/kg/day); MetS+MKD+metformin (25 mg/kg/day); and MetS+MKD+metformin+ezetimibe. TKD provided approximately 70% fat, 20% protein, and 10% carbohydrate, whereas MKD provided 60% fat, 30% protein, and 10% carbohydrate. Egg white was used as the

additional protein source in the MKD formulation. The pharmacological rationale is consistent with the established actions of metformin and ezetimibe [15, 16].

2.4. Laboratory measurements

Blood samples were obtained on treatment days 10, 20, and 30. ALT, AST, alkaline phosphatase (ALP), GGT, total protein, albumin, total and direct bilirubin, glucose, insulin, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and CRP were assessed. ApoE and LPL were quantified by enzyme-linked immunosorbent assay (ELISA).

2.5. Histomorphological assessment

At the end of the experiment, liver tissue was assessed histologically using hematoxylin-eosin and Oil Red O staining. Steatosis, lobular inflammation, hepatocellular injury, and the NAFLD Activity Score (NAS) were evaluated.

2.6. Statistical analysis

Data are presented as mean±standard error (M±m), with n=8 per final group. Normality was assessed using the Shapiro–Wilk test. Group comparisons were performed using analysis of variance followed by Tukey post-hoc testing where applicable. Pearson correlation analysis was used for associations between selected biochemical and morphological variables. Statistical significance was accepted at $p < 0.05$.

3. Results

3.1. Development of experimental metabolic syndrome

After 60 days of induction, the experimental MetS phenotype was characterized by marked anthropometric and biochemical abnormalities. ApoE increased by 573.1%, LPL decreased by 47.6%, ALT increased by 60.2%, and GGT increased by 126.6% relative to the initial/intact reference values. These changes reflected pronounced disruption of lipoprotein and hepatobiliary metabolism.

3.2. Hepatobiliary response to MKD

MKD produced progressive improvement in the principal hepatobiliary indices. ALT decreased from 64.4 ± 5.8 U/L on day 10 to 53.5 ± 5.1 U/L on day 20 and 49.9 ± 4.8 U/L on day 30. AST decreased from 38.6 ± 3.6 to 34.8 ± 3.2 and 31.8 ± 3.0 U/L, respectively. GGT decreased from 14.9 ± 1.6 to 13.4 ± 1.2 and 12.4 ± 1.2 U/L, while albumin increased from 35.9 ± 3.2 to 37.7 ± 3.6 and 40.5 ± 3.9 g/L.

3.3. ApoE and LPL dynamics

In the MKD group, ApoE decreased from 26.2 ± 1.2 mg/dL on day 10 to 23.2 ± 1.2 mg/dL on day 20 and 21.2 ± 1.1 mg/dL on day 30. LPL increased from 25.8 ± 0.8 ng/mL to 27.0 ± 0.8 and 30.8 ± 0.9 ng/mL, respectively. On day 30, the untreated MetS group showed ApoE of 35.8 ± 1.15 mg/dL and LPL of 19.8 ± 1.1 ng/mL.

3.4. Metabolic, inflammatory, and morphological outcomes

By day 30, MKD reduced glucose to 4.8 ± 0.46 mmol/L, total cholesterol to 3.3 ± 0.26 mmol/L, triglycerides to 1.22 ± 0.12 mmol/L, LDL cholesterol to 0.59 ± 0.058 mmol/L, and CRP to 2.0 ± 0.2 mg/L; HDL cholesterol increased to 0.70 ± 0.07 mmol/L. Histomorphological examination demonstrated lower steatosis, lobular inflammation, and hepatocellular injury than in untreated MetS. The total NAS in the MKD group was 3.7 ± 0.4 versus 8.8 ± 0.7 in the MetS control group.

Table 1. Selected day-30 outcomes across experimental groups

Parameter	Intact	MetS	TKD	MKD	MKD+EZE	MKD+MET	MKD+MET+EZE
ALT, U/L	49.8 ± 4.8	87.7 ± 8.6	62.7 ± 6.2	49.9 ± 4.8	65.6 ± 6.5	63.7 ± 6.2	49.85 ± 4.8
GGT, U/L	9.4 ± 0.93	22.0 ± 2.0	17.8 ± 1.7	12.4 ± 1.2	17.7 ± 1.8	17.0 ± 1.7	12.4 ± 1.1
Albumin, g/L	41.3 ± 4.0	25.2 ± 2.4	36.7 ± 3.5	40.5 ± 3.9	33.2 ± 3.2	34.7 ± 3.4	40.5 ± 4.0
ApoE, mg/dL	5.4 ± 0.4	35.8 ± 1.15	26.5 ± 0.9	21.2 ± 1.1	19.24 ± 1.12	17.1 ± 0.74	15.6 ± 0.89
LPL, ng/mL	35.2 ± 0.92	19.8 ± 1.1	28.6 ± 1.1	30.8 ± 0.9	28.31 ± 0.95	31.4 ± 0.65	33.1 ± 1.21
CRP, mg/L	1.8 ± 0.17	4.0 ± 0.4	2.63 ± 0.3	2.0 ± 0.2	2.9 ± 0.3	2.8 ± 0.27	2.0 ± 0.19
NAS, points	0.6 ± 0.2	8.8 ± 0.7	5.8 ± 0.5	3.7 ± 0.4	—	—	3.4 ± 0.4

4. DISCUSSION

The principal finding was a coordinated improvement in hepatobiliary, metabolic, inflammatory, and lipoprotein-related indices during MKD. The progressive decrease in ApoE and increase in LPL across the 30-day correction period support a time-dependent response of triglyceride-rich lipoprotein metabolism. ApoE and LPL are biologically relevant to remnant clearance and triglyceride hydrolysis, respectively [7–9].

Compared with TKD, MKD contained less fat (60% vs 70%) and more protein (30% vs 20%), while carbohydrate remained at 10%. Egg white, not fish meal, was the additional protein source. Consequently, the observed effects should not be specifically attributed to fish-derived EPA or DHA. They are more appropriately interpreted as an integrated response to carbohydrate restriction and the overall composition of the MKD. Previous studies indicate that carbohydrate restriction can reduce hepatic triglyceride content, but the magnitude and clinical relevance of

ketogenic-diet effects vary across settings [10, 12, 13, 25].

The pharmacological groups received the respective drugs on the background of MKD. Therefore, these comparisons estimate the additional effect of ezetimibe, metformin, or their combination rather than a direct comparison between MKD and isolated drug monotherapy. Metformin has established glucoregulatory actions, whereas ezetimibe inhibits intestinal cholesterol absorption through NPC1L1 [15, 16].

The histological improvement was concordant with the biochemical response. Nevertheless, morphology was evaluated only at the endpoint, and molecular pathways such as Nrf2 or NLRP3 were not directly measured. Although β -hydroxybutyrate has been shown to inhibit NLRP3 inflammasome signaling [21], such a mechanism remains inferential in the present experiment.

The study has several limitations: it used an animal model; each final group contained eight animals; correction lasted

30 days; only male animals were used in the source study; histology was assessed only at the endpoint; and the proposed molecular mechanisms were not directly tested. Accordingly, the results should not be interpreted as evidence of clinical efficacy in humans.

5. Conclusion

Experimental MetS was accompanied by marked disturbances in ApoE, LPL, and hepatobiliary indices. MKD (60% fat, 30% protein, 10% carbohydrate) was associated with progressive improvement in ALT, AST, ALP, GGT, albumin, ApoE, LPL, glucose, lipid profile, CRP, and liver morphology over 30 days. ApoE and LPL should be regarded as informative research indicators of lipoprotein metabolic response rather than validated clinical diagnostic markers. The findings support further mechanistic and translational investigation of MKD, but do not establish clinical efficacy in humans.

Declarations

Ethics approval: The source manuscript does not provide the name of the approving ethics committee, approval number, or date. These factual details must be inserted before submission.

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Conflict of interest: The authors declare no conflict of interest.

Data availability: Data supporting the findings were generated within the authors' dissertation research. The availability of individual-level data should be stated according to the policy of the selected journal.

Author contributions: Author roles should be finalized according to the CRediT taxonomy before submission.

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