

Clinical and Biochemical Outcomes of Ketogenic Diet Therapy over a Decade: Experience from a Single Center

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Abstract

Purpose

The ketogenic diet, high in fat and low in carbohydrates, is used to treat metabolic diseases and drug-resistant epilepsy. This study evaluates the clinical outcomes, metabolic changes, and treatment adherence among patients receiving the ketogenic diet.

Methods

We retrospectively analyzed the hospital records of 18 pediatric patients who received ketogenic diet therapy at a single center between 2014 and 2024.

Results

Patient age ranged from 4 to 240 months, with a median treatment duration of 21 months. Follow-up revealed significant increases in total cholesterol, AST, and free carnitine; LDL and triglycerides rose in six months but decreased by twelve months, while HDL gradually declined. There were no significant changes in glucose, complete blood count, or vitamin levels. Seizure frequency decreased in 88.9% of patients; two discontinued due to lack of efficacy. Two patients developed kidney stones, but no cardiac complications were observed.

Conclusion

Over the ten years, the ketogenic diet proved to be a safe and sustainable treatment for children, with side effects manageable through careful monitoring.

What is Known?

Ketogenic diet therapy is an established treatment for selected children with drug-resistant epilepsy and certain metabolic disorders, but long-term nutritional and metabolic safety requires systematic monitoring.

What is New?

This real-world pediatric cohort provides longitudinal assessment of clinical efficacy together with hematological, biochemical, and nutritional parameters, demonstrating overall metabolic stability while identifying transient dyslipidemia and nephrolithiasis as relevant complications requiring follow-up.

1. Introduction

The ketogenic diet (KD) is a nutritional therapy characterized by its high fat, adequate protein, and low carbohydrate content, and is considered an effective treatment option for certain inborn errors of metabolic diseases, such as glucose transporter-1 (GLUT-1) deficiency, pyruvate dehydrogenase deficiency, etc., and drug-resistant epilepsy. Approximately 20–30% of patients with epilepsy fail to achieve seizure control with antiseizure medications, representing a major therapeutic challenge[1]. KD induces a metabolic shift from glucose to ketone bodies, enhances mitochondrial function, and modulates neurotransmitter balance, thereby reducing seizure frequency and improving quality of life[2]–[3]. Furthermore, variants such as the modified Atkins diet (MAD), medium-chain triglyceride (MCT) diet, and low glycemic index treatment (LGIT) have been reported to be used more frequently in recent years and to improve patient compliance[4].

Short- and medium-term studies have consistently demonstrated the effectiveness of KD; 30–40% of patients have reported complete seizure control, and 40–50% have reported a $\geq 50\%$ reduction in seizures[5]. However, questions remain regarding long-term safety, particularly regarding dyslipidemia, growth, and cardiovascular risk factors. Although transient metabolic disturbances (hypercholesterolemia, hypertriglyceridemia) have been reported, most are manageable with dietary modifications and supportive treatments[6]. On the other hand, some side effects such as kidney stones, gastrointestinal problems, and growth-related changes can be observed with long-term KD administration. Long-term assessments are critical to revealing whether KD maintains seizure control, the course of metabolic side effects over time, and the sustainability of treatment adherence. Such data will help clinicians weigh treatment benefits against potential risks, optimize dietary protocols, and provide families with realistic expectations.

Evaluating the clinical outcomes of patients followed with KD at our center over the last 10 years will contribute to the national literature and provide up-to-date data on the efficacy and safety of KD. This study aims to reveal the clinical responses, metabolic changes, and treatment adherence of patients who underwent KD at our center.

2. Materials and Methods

2.1 Study population and data collection

This retrospective longitudinal study identified patients through the center's electronic medical records using treatment codes for KD therapy. We systematically reviewed the records of patients treated with KD between 2014 and 2024 and collected data on demographics, dietary protocols, age at KD initiation, diagnosis, treatment duration, and reasons for discontinuation. We excluded patients with conditions in which KD is contraindicated—including fatty acid oxidation disorders, pyruvate carboxylase deficiency, defects of ketogenesis or ketolysis, primary carnitine deficiency, familial hyperlipidemia, fumarase deficiency, and acute intermittent porphyria—as well as those with chronic liver disease, nephrolithiasis, cardiomyopathy, or immunodeficiency.

At baseline and 6 and 12 months after treatment initiation, all participants underwent assessment of liver and renal function, urinary calcium and creatinine, lipid profiles, ketone levels, complete blood counts, serum vitamin B12, folate, and vitamin D, as well as metabolic screening with serum free carnitine and acylcarnitine profiles, urinary organic acid analysis, and plasma amino acid measurements. These time points were chosen to capture the short- and longer-term health effects of the ketogenic diet. Renal ultrasonography, echocardiography, and cerebral magnetic resonance imaging findings were also recorded.

Blood beta-hydroxybutyrate concentrations were measured with the FreeStyle Optium Neo Blood Glucose and Ketone Monitoring System (Abbott Diabetes Care Inc., UK) to assess ketone status. To standardize timing, fingertip capillary whole-blood samples were collected 2 hours after meals. Lipid profiles were evaluated concurrently; hyperlipidemia was defined as total cholesterol > 200 mg/dL, triglycerides > 130 mg/dL, LDL cholesterol > 130 mg/dL, or HDL cholesterol < 35 mg/dL [7]. Seizure types and etiologies were classified according to International League Against Epilepsy recommendations [8]. Drug-resistant epilepsy was defined as persistent seizures despite trials of at least two appropriately selected and adequately dosed antiseizure medications [9]. Treatment response was defined at each clinic visit as a > 50% reduction in seizure frequency from baseline.

2.2 Dietary protocol

The KD was initiated in all patients using a gradual, non-fasting protocol. Before initiation, a three-day dietary record was collected during hospitalization, and families were interviewed to complete a comprehensive nutritional assessment.

2.2.1 Diet Initiation and Energy Calculation

Each patient's initial energy requirement was individualized according to physical activity and ideal body weight for height in children younger than 2 years or ideal body mass index in those aged 2 years or older. Protein needs were based on age-specific Dietary Reference Intake (DRI) values: 1.5 g/kg/day for 0–12 months, 1.1 g/kg/day for 1–3 years, 0.95 g/kg/day for 4–13 years, and 0.85 g/kg/day for 14–18 years. Overall, prescribed energy and protein intakes were 60–80 kcal/kg/day and 1–1.5 g/kg/day, respectively.

The KD was introduced gradually, beginning with a 1:1 lipid-to-nonlipid ratio and increasing to 2.5:1–4:1 over 3–4 days until ketosis was achieved. Daily energy intake was distributed across 3–4 meals. Thereafter, the KD ratio was adjusted to sustain adequate ketosis while avoiding acidosis, hyperketosis, and hypoglycemia.

2.2.2 Ketone Monitoring and Follow-up

Blood beta-hydroxybutyrate levels were used to monitor ketosis. Measurements were performed using the *FreeStyle Optium Neo Blood Glucose and Ketone Monitoring System* (Abbott Diabetes Care Inc., UK) from fingertip whole-blood samples.

- Daily measurements during the first week,
- Twice weekly for the following three weeks,
- Weekly for two months,
- Then every two weeks thereafter.

Target ketone levels were maintained between 4–6 mmol/L, and all patients achieved therapeutic ketosis within 4–7 days (mean: 6 days). Parents reported daily ketone and glucose levels, seizure frequency, and adverse events via email or telephone in addition to routine clinic visits. Caloric intake and KD ratio were adjusted according to ketone levels, seizure control, and changes in body weight to maintain ideal body weight for height.

2.2.3 Diet Composition

Menus were tailored to child and family preferences and based on traditional Turkish foods to improve palatability and adherence. The Mediterranean-style KD derived 80–85% of total dietary fat from extra virgin olive oil, with additional fat supplied by cream, primarily in ice cream, as well as meat and butter used in soups. Palm, sunflower, hazelnut, coconut, and corn oils were excluded.

Milk, yogurt, kefir, cheese, and locally available foods were regularly included to improve dietary variety and acceptability. Low-carbohydrate, high-fiber vegetables and avocado were used liberally to prevent constipation, while almond, walnut, hazelnut, and coconut flours were used in bread and baked products.

All patients received sugar-free multivitamin and mineral supplements and maintained normal hydration throughout treatment, primarily with water and caffeine-free beverages.

Patients fed through nasogastric or gastrostomy tubes, infants younger than 1 year, and those with feeding difficulties received a commercial KD formula (KetoCal 4:1, Nutricia) and puréed ketogenic soups.

2.2.4 Medication Adjustment

Because liquid medications—including antiseizure drugs, antibiotics, and antipyretics—may contain varying amounts of carbohydrates, families were educated about hidden carbohydrate sources. Whenever possible, liquid preparations were replaced with tablets or capsules; otherwise, their carbohydrate content was calculated and incorporated into the daily diet plan.

2.3 Statistical analyses

The conformity of the data to normal distribution was assessed using histograms, Q-Q plots, and the Shapiro-Wilk test. The Mann-Whitney U test was used for quantitative variables in comparisons between paired groups. The Friedman test was used for comparisons between more than two repeated measurements. The Dunn-Bonferroni test was used for multiple comparisons. The relationship between quantitative data was assessed using Spearman correlation analysis. Data analysis was performed

using TURCOSA (Turcosa Analytical Analysis Co. Ltd., www.turcosa.com.tr) statistical software. The level of significance was accepted as $p < 0.05$.

3. Results

Of the 32 patients who initiated KD, 18 (11 female and 7 male) had complete medical records and met the study criteria. Age at KD initiation ranged from 4 to 240 months (median, 41 months), and treatment duration ranged from 6 to 168 months (median, 21 months). Table 1 summarizes the patients' general characteristics and the etiologies underlying KD use.

Laboratory follow-up showed significant increases in total cholesterol, AST, and free carnitine levels ($p=0.012$, $p=0.001$, and $p=0.002$, respectively; Table 2). LDL-C and triglyceride levels increased at 6 months and declined slightly by 12 months, whereas HDL levels decreased progressively. Glucose, complete blood count parameters, and vitamin levels showed no clinically significant changes (Figures 1 and 2).

Seizure frequency decreased in 16 patients (88.9%). Two patients discontinued treatment at 12 and 36 months because of insufficient efficacy. Nephrolithiasis developed in two patients during follow-up. One patient with a combined oxidative phosphorylation defect died from causes unrelated to the diet, and no cardiac adverse effects were observed.

4. Discussion

This study assessed clinical outcomes, metabolic changes, and treatment adherence during 10 years of KD follow-up at our center. Seizure frequency decreased in 16 of 18 patients (88.9%), demonstrating substantial therapeutic benefit. This response is consistent with established KD mechanisms: shifting cerebral metabolism from glucose to ketone bodies provides neurons with a stable energy source, enhances mitochondrial function, and reduces oxidative stress, which may explain the improvements observed at 6 and 12 months [1],[10]. Increased GABAergic inhibition, reduced glutamatergic excitotoxicity, and attenuated neuroinflammation may further contribute to the progressive improvement in drug-resistant seizure control [11].

These mechanisms are especially relevant to GLUT1 deficiency syndrome, in which impaired glucose transport across the blood–brain barrier causes chronic cerebral energy failure [12]. By providing an essential alternative fuel, ketone bodies directly address this metabolic deficit [13]. Although our cohort included few patients with GLUT1 deficiency, their favorable responses accord with evidence supporting KD as the first-line and most effective therapy for this disorder [14]. Previous studies also indicate that early KD initiation improves outcomes in GLUT1 deficiency [15],[16]. In our cohort, KD was initiated at 42–120 months in patients with GLUT1 deficiency, who also had the longest treatment durations. Their sustained adherence and improved clinical outcomes further support timely intervention.

The classic KD and modified Atkins diet (MAD) have comparable efficacy in childhood refractory epilepsy, although MAD is generally better tolerated [17],[18]. Consistent with this evidence, switching to MAD reduced seizures in patients in our study who had difficulty adhering to the classic diet.

Although dyslipidemia is an expected effect of high-fat dietary therapies, the main clinical concern is whether KD causes severe hyperlipidemia or complications such as pancreatitis or cardiovascular events [19]. In our cohort, lipid levels rose early in treatment, particularly by month 6, but subsequently stabilized and gradually declined. No patient developed pancreatitis or cardiac involvement, required lipid-lowering medication, or discontinued the diet, consistent with reports that severe dyslipidemia is uncommon and generally manageable through dietary modification [20]. The absence of a significant change in HDL levels also agrees with most published findings [21].

The high prevalence of dyslipidemia at baseline was consistent with previous reports; its subsequent improvement suggests that increasing mono- and polyunsaturated fats while reducing saturated fat was effective [22]. The olive oil-based KD used at our center may have moderated the lipid response, in line with evidence that ketogenic diets rich in unsaturated fats produce more favorable lipid profiles. Omega-3 and carnitine supplementation in selected patients also helped lower triglyceride and cholesterol levels [20],[21]. Lipid values improved over time, and reductions in antiseizure medications may have further contributed to this trend [23]. Overall, our findings indicate that KD-associated dyslipidemia is common but usually transient, manageable, and rarely clinically significant when appropriate dietary adjustments are made.

During follow-up, AST levels increased mildly without corresponding elevations in ALT or other indicators of hepatic dysfunction. Because AST is located in mitochondria and is also present in skeletal muscle, this isolated change likely reflects increased metabolic activity and fatty acid oxidation rather than hepatocellular injury. The concurrent rise in free carnitine may similarly indicate adaptive enhancement of fatty acid transport to support sustained mitochondrial β -oxidation during long-term KD therapy. Overall, these findings are more consistent with physiological metabolic adaptation than with hepatic or muscular toxicity. Carnitine and multivitamin supplementation initiated at the start of treatment may also have contributed to these changes.

KD can cause adverse effects involving the gastrointestinal, cardiac, renal, and skeletal systems [24]. In our cohort, two patients developed renal calculi. One had GLUT1 deficiency and the longest treatment duration (144 months), whereas the other had received KD for 19 months. These findings are comparable to previous reports: Freeman et al. identified renal stones in 6 of 150 children [25], another prospective study reported 6 cases among 112 patients followed for 2 months to 2.5 years [26], and a separate long-term pediatric study documented 7 cases [27]. Together, these data emphasize the need for close renal monitoring during prolonged KD therapy, particularly in patients with underlying metabolic disorders or extended treatment durations.

This study has several limitations. The small sample restricts generalizability and statistical power to detect subtle metabolic or clinical differences. Bone mineral density was not measured, precluding

assessment of long-term skeletal effects, an important concern in children receiving prolonged high-fat dietary therapy. Trace elements such as selenium, zinc, and copper were also not evaluated, although their levels may fluctuate during KD treatment and affect metabolic stability. These gaps limit a comprehensive assessment of the diet's nutritional and metabolic safety.

Despite these limitations, the study has important strengths. Its extended follow-up reflects real-world clinical practice and provides insight into the longitudinal metabolic effects of KD. Systematic lipid monitoring and individualized dietary adjustments strengthen confidence in the observed trends. Moreover, the heterogeneous cohort, which included many patients with severe drug-resistant epilepsy, increases the clinical relevance of the findings across diverse etiologies. Overall, the study adds meaningful evidence on the safety and metabolic course of KD in a challenging pediatric population.

5. Conclusion

Over 10 years of follow-up, KD was safe and sustainable in children with drug-resistant epilepsy when supported by structured metabolic monitoring and individualized dietary adjustments. Lipid levels commonly increased early but later stabilized without severe complications or treatment discontinuation, while other laboratory markers remained within acceptable ranges. These findings support long-term KD as a metabolically tolerable therapeutic option when combined with close follow-up, proactive dietary modification, and multidisciplinary care.

Declarations

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Conflict of Interest Disclosure

The authors declare that they have no conflicts of interest relevant to the content of this article.

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Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request. Due to ethical and privacy restrictions, individual patient data are not publicly available.

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Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Erciyes University Faculty of Medicine (Approval No:2025/03, Date:08/01/2025).

Conflict of Interest Disclosure

The authors declare that they have no conflicts of interest relevant to the content of this article.

Patient Consent Statement

Written informed consent was obtained from all patients or their legal guardians prior to inclusion in the study.

Author Contributions

H.Güneş: data curation (lead), formal analysis (supporting), writing –original draft (supporting).

A.Gülbahçe: data curation (supporting), writing –review & editing (supporting). **F.İpekten:** formal analysis (lead), writing –review & editing (supporting). **D. Öztekin:** data curation (supporting), writing – review & editing (supporting). **M. Canpolat, H.Per and H.Gümüş:** methodology(supporting), writing – review & editing (supporting). **H.Güneş and F.Kardaş:** conceptualization (lead), data curation (supporting), formal analysis(lead), methodology (lead), project administration (lead), resources (lead), supervision (lead), visualization (lead), writing – original draft (lead)

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Tables

Table 1: General demographic and clinical information of patients

Gender (F/M) (n, %)	11 (61,1) / 7 (38,9)
Age at KD initiation, months	41 (4-240) *
Duration of KD, months	21 (6-168) *
Continuation of KD (n, %)	16 (88,8)
Echocardiographic anomaly (n, %)	0 (0,0)
Nephrolithiasis (n, %)	2 (11,1)
Hypoglycemia (n, %)	5 (27,7)
KD ratios	n (%)
2:1	4 (22,2)
3:1	5 (27,7)
4:1	5 (27,7)
1,5:1	1 (5,5)
2,5:1	1 (5,5)
3,5:1	1 (5,5)
Indications for starting KD	
Etiology	n (%)
Refractory epilepsy	8 (44,4)
GLUT 1 deficiency	4 (22,2)
Congenital glycosylation defect	1 (5,6)
Herpes encephalitis	1 (5,6)
Dravet syndrome	1 (5,6)
Lennox-Gastaut epilepsy	1 (5,6)
Neuronal ceroid lipofuscinosis 14	1 (5,6)
Combined oxidative phosphorylation defect	1 (5,6)

* median (min-max)

Table 2: Laboratory values of patients before diet, at 6 months of diet and at 12 months of diet

	Time			<i>p</i>
	0 (<i>n</i> =18)	6 (<i>n</i> =18)	12 (<i>n</i> =18)	
T. cholesterol (mg/dl)	162.0(107.0-196.0) ^a	182.5(121.0-263.0) ^b	189.0 (87.0-271.0) ^{ab}	0.012
LDL-C (mg/dl)	84.9(57.7-447.0)	121.5(44.8-495.0)	108.2(48.8-503.0)	0.486
HDL-C (mg/dl)	52.6(30.0-509.0)	48.1(22.7-555.0)	46.5(32.1-444.0)	0.336
Triglycerides (mg/dl)	106.5(60.0-309.0)	187.0 (55.0-611.0)	123.0 (84.0-401.0)	0.078
Glucose (mg/dl)	85.5(64.0-157.0)	81.0 (62.0-104.0)	86.5(52.0-182.0)	0.497
Ketone	2.5(0.1-22.0)	3.0 (0.2-34.0)	2.8(0.4-38.0)	0.105
BUN (mg/dl)	12.1(5.0-164.0)	10.7(4.6-121.0)	10.7(0.3-135.0)	0.926
Creatinine (mg/dl)	0.4(0.2-37.0)	0.4(0.2-37.0)	0.5(0.2-33.0)	0.856
AST (u/L)	25.0(12.0-113.0) ^a	30.5(9.0-102.0) ^b	31.5(21.0-55.0) ^b	0.001
ALT (u/L)	22.5(4.0-92.0)	14.5(1.0-161.0)	16.5(7.0-42.0)	0.282
Uric acid (mg/dl)	3.6(1.4-44.0)	3.8(0.3-42.0)	4.4(2.5-46.0)	0.105
CPK (u/L)	84.5(25.0-370.0)	69.5(23.0-285.0)	94.0 (35.0-374.0)	0.078
C0 (μmol/L)	41.5(11.0-38817.0) ^a	42.5(12.0-3979.0) ^a	52.0 (15.0-11252.0) ^b	0.002
C2 (μmol/L)	44.7(13.0-7946.0)	42.1(13.0-4547.0)	42.0 (15.0-30606.0)	0.223
Glutamine (nmol/ml)	603.0(52.0-4509.0)	482.2(338.5-3978)	888.6(856.7-9324.0)	0.717
Hemoglobin (g/dl)	12.6(8.5-126.0)	13.6(7.8-153.0)	14.1(11.0-148.0)	0.249
White blood cell count (μL)	7620.0(1500.0-133200.0)	7840.0 (1290.0-12990.0)	6340(1140.0-17540.0)	0.472
Neutrophil count (μL)	2095.0(1000.0-4490.0)	2120.0 (1200.0-5500.0)	2335(1000.0-7800.0)	0.174
Platelet count (10³/μL)	331.5(184.0-451.0)	307.0 (116.0-574.0)	377.5(175.0-662.0)	0.205
Total protein (g/dl)	6.5(5.5-634.0)	6.7(3.9-688.0)	7.1(4.8-714.0)	0.353
Albumin (g/dl)	4.1(3.8-429.0)	4.4(2.2-496.0)	4.6(4.0-455.0)	0.264
25-OH vitamin D3 (ng/ml)	25.6(7.6-297.0)	25.0 (5.1-298.0)	16.4(6.0-35.6)	0.368

Vitamin B12 (pg/ml)	538.0(149.0-1167.0)	557.5(33.9-1140.0)	581.5(268.8-1095.0)	0.273
Folate (ng/ml)	13.7(6.9-993.0)	12.0 (3.7-111.0)	12.8(6.5-855.0)	0.999

The data are expressed as median (min-max). The same letters on the same line express the similarity between times, and different letters express the difference.

Figures

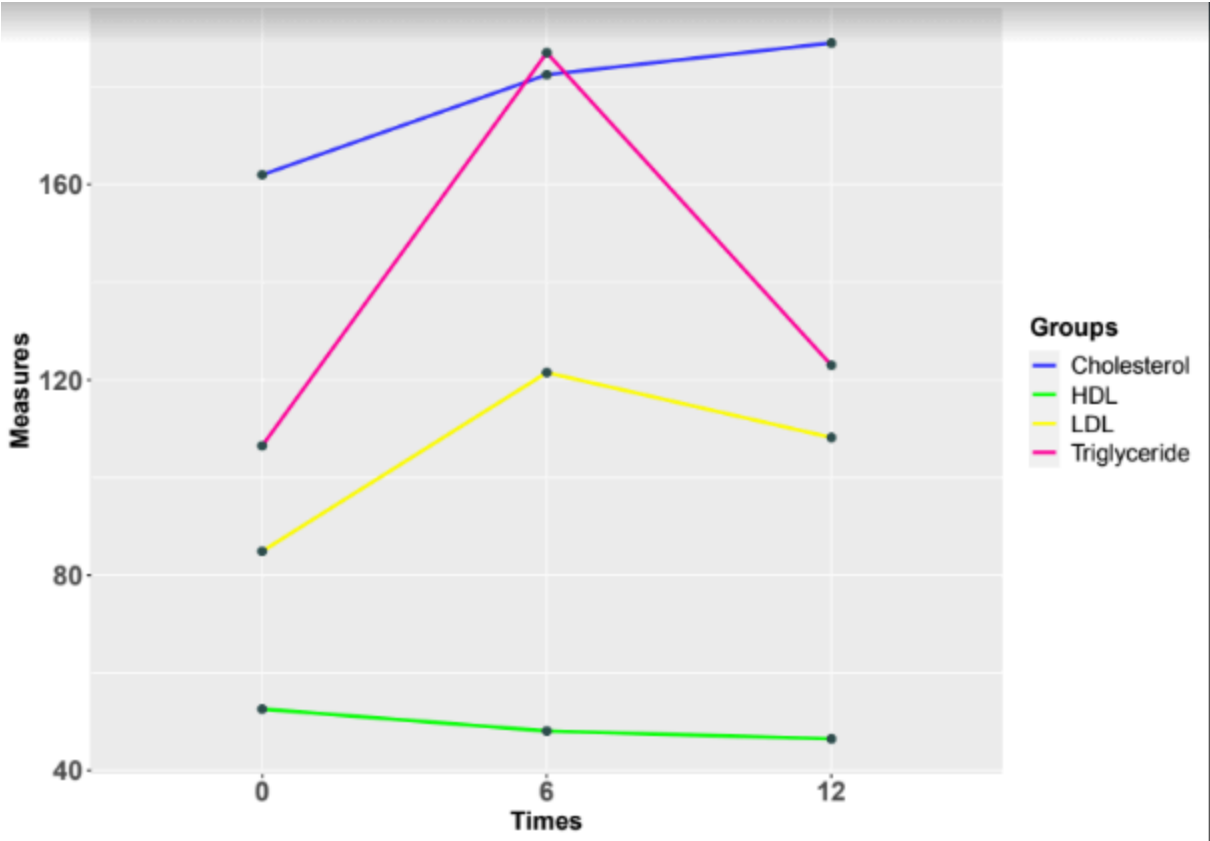


Figure 1
Course of lipid profile during treatment

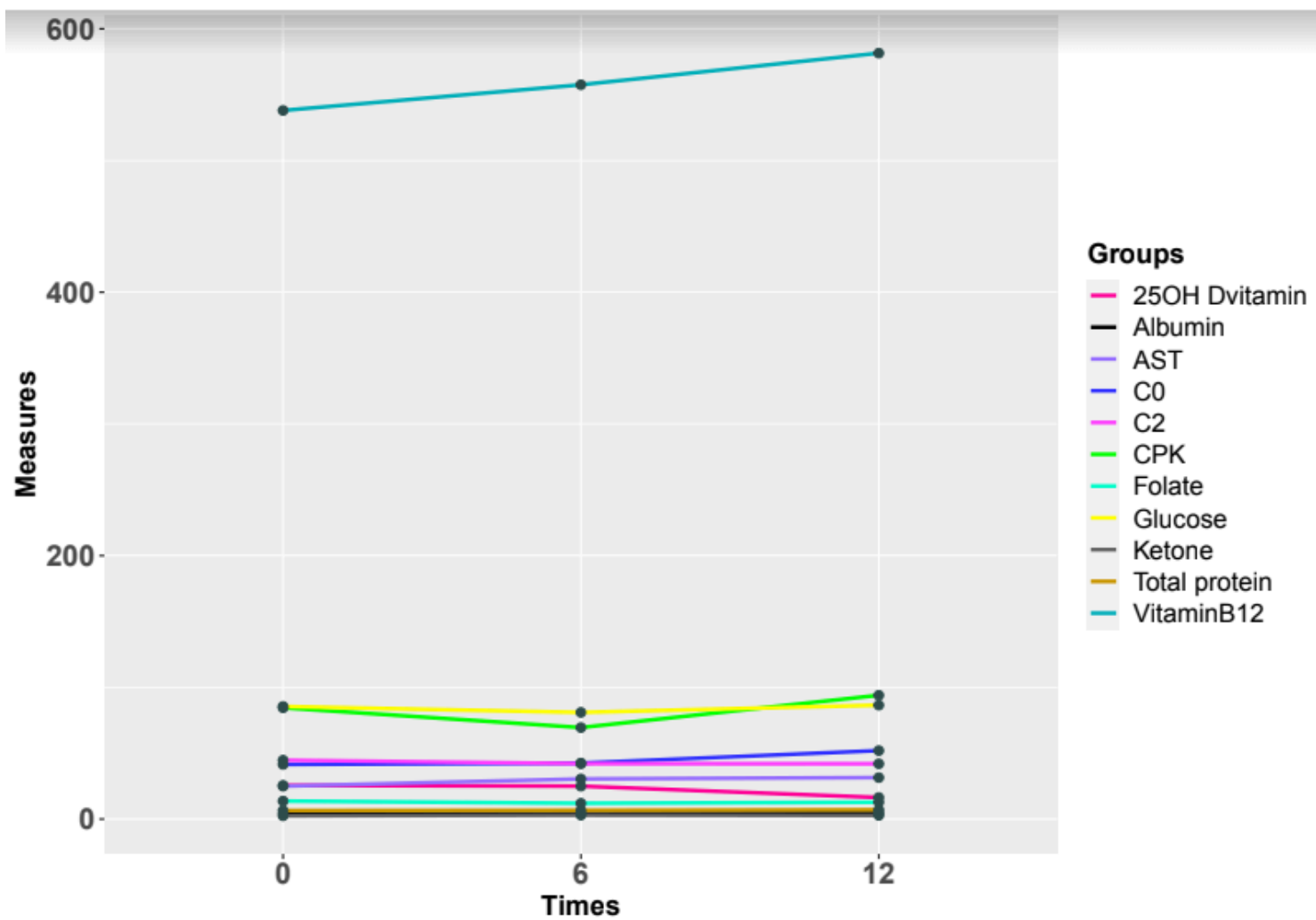


Figure 2

Course of laboratory values during treatment