Turkish Archives of Pediatrics

ORIGINAL ARTICLE
DOI: 10.5152/TurkArchPediatr.2025.25156

Comparison of Ketogenesis and Ketolysis Defects: A Retrospective Single-Center Study of 30 Patients

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What is already known on this topic?

- *Disorders of ketone body metabolism, including defects in ketogenesis and ketolysis, are rare inherited metabolic disorders that can cause life-threatening metabolic crises in early childhood.*
- *Early diagnosis and dietary management can prevent severe neurological sequelae and mortality.*

What this study adds on this topic?

- *This study is the largest cohort reported from Turkey and provides the first systematic comparison of ketogenesis and ketolysis defects in terms of age of onset, severity of acidosis, and clinical outcomes.*
- *This study highlights that patients with ketolysis defects tend to present later but with more severe acidosis, and may require renal replacement therapy.*

ABSTRACT

Objective: Despite overlapping features, these 2 groups of disorders may exhibit distinct clinical and biochemical profiles. This study aimed to evaluate and compare the clinical presentation, laboratory findings, neuroimaging characteristics, genotypic spectrum, and clinical outcomes of patients with ketogenesis and ketolysis defects.

Materials and Methods: Thirty patients diagnosed between 1986 and 2023 were retrospectively reviewed. Diagnosis was confirmed by clinical findings, biochemical, and genetic/enzymatic testing. Data included demographic details, clinical manifestations, neurodevelopmental status, laboratory results, imaging findings, genetic information, and treatments.

Results: Of the 30 patients, 13 (43.3%) were diagnosed with 3-hydroxy-3-methylglutaryl-CoA lyase deficiency (HMGCLD), 14 (46.7%) with 2-methylacetoacetyl-coenzyme A thiolase deficiency (MATD), and 3 (10%) with succinyl-CoA:3-ketoacid CoA transferase deficiency (SCOTD). Patients with ketolysis defects presented at a later median age (210 vs. 30 days, $P < .009$) and exhibited more profound metabolic acidosis (pH 7.06 ± 0.18 vs. 7.26 ± 0.12, $P = .028$). Common presenting symptoms included vomiting in 25 (83.3%), hypoglycemia in 9 (33.3%), and seizures in 5 (16.6%). Leigh-like neuroimaging findings were observed in 3 HMGCLD patients. Biallelic pathogenic variants in *HMGCL*, *ACAT1*, or *OXCT1* were identified in 14 patients. Dialysis was required in 1 MATD and 1 SCOTD case. Excluding those lost to follow-up, the mortality rates among the remaining 18 patients were 1/8, 12.5% in 2/9 HMGCLD, and 22.2% in MATD. One of the patients with SCOTD was alive at the time of the last follow-up.

Conclusion: Patients with ketolysis defects are more likely to present later and with severe metabolic acidosis, occasionally requiring renal replacement therapy. Delayed diagnosis may hinder timely intervention, potentially contributing to increased mortality.

Keywords: Beta-ketothiolase deficiency, HMG-CoA lyase deficiency, ketogenesis, ketolysis, metabolic acidosis, SCOT deficiency

INTRODUCTION

Ketone bodies, primarily acetoacetate and 3-hydroxybutyrate, are alternative energy substrates synthesized in the liver, especially during fasting. They provide a critical energy source for high-energy-demanding organs such as the brain, heart, and skeletal muscles, and unlike fatty acids, can cross the blood-brain barrier to supply up to two-thirds of the brain's energy needs during prolonged fasting.[1] While mainly derived from fatty acid oxidation, they can also be produced from ketogenic amino acids, particularly leucine (Figure 1). Ketone body metabolism involves 2 pathways: *ketogenesis* (production) and *ketolysis* (utilization).

Clinical suspicion should arise in infants or young children presenting with unexplained hypoglycemia, severe metabolic acidosis, recurrent vomiting, lethargy, or coma, especially

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Received: May 22, 2025
Revision Requested: June 15, 2025
Last Revision Received: July 20, 2025
Accepted: July 28, 2025
Publication Date: September 1, 2025

Cite this article as: Kahraman AB, Yıldız Y, Dursun A, Sivri S, Coşkun T, Tokatlı A. Comparison of ketogenesis and ketolysis defects: A retrospective single-center study of 30 patients. *Turk Arch Pediatr.* 2025;60(5):491-499.

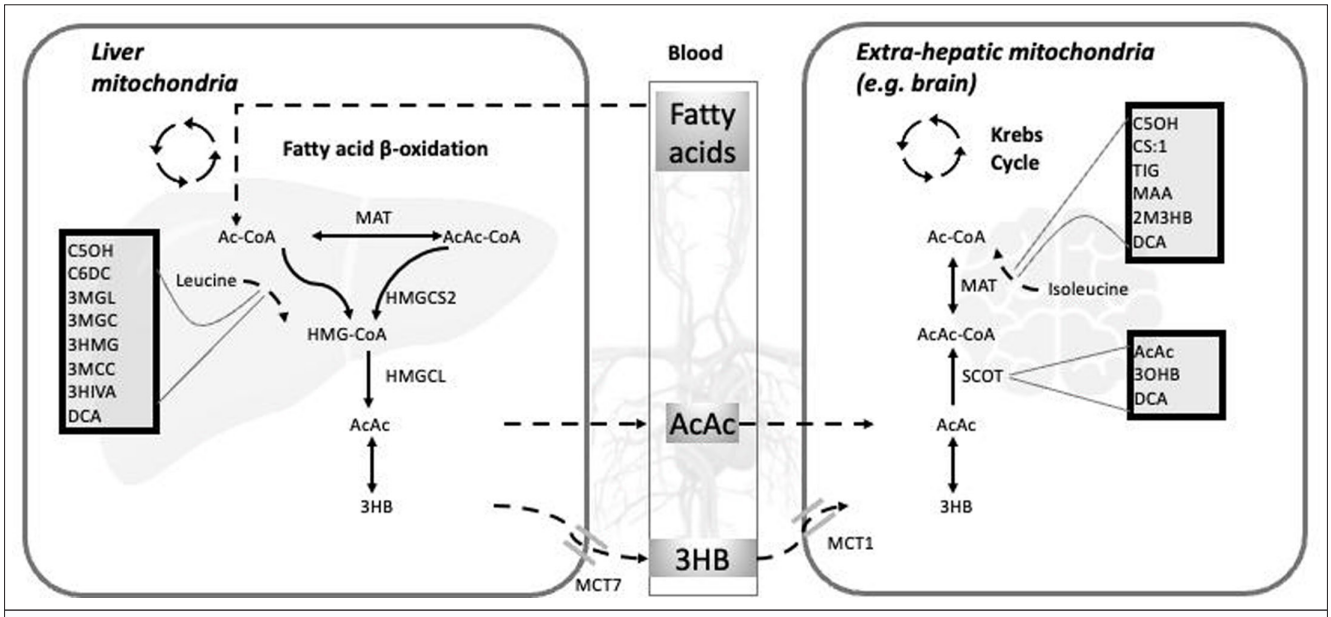

Figure 1. Ketone body metabolism pathway. This schematic illustration outlines the key steps involved in hepatic ketone body synthesis (ketogenesis) and peripheral utilization (ketolysis). In the liver, acetyl-CoA derived from fatty acid β-oxidation is converted to acetoacetyl-CoA (AcAc-CoA), which is then transformed into 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) by HMG-CoA synthase 2 (HMGCS2). Subsequently, HMG-CoA is cleaved by HMG-CoA lyase to yield acetoacetate (AcAc), which may be reduced to D-3-hydroxybutyric acid (3HB) or spontaneously decarboxylate to acetone (not shown). In extrahepatic tissues, acetoacetate is activated to acetoacetyl-CoA by succinyl-CoA:3-oxoacid CoA transferase and then cleaved into 2 acetyl-CoA molecules by mitochondrial acetoacetyl-CoA thiolase (ACAT1) for energy production. 3HB, D-3-hydroxy-n-butyric acid; Ac-CoA, acetyl-CoA; AcAc-CoA, acetoacetyl-CoA; AcAc, acetoacetic acid; HMG-CoA; 3-hydroxy-3-methylglutaryl-CoA; HMGCS2, 3-hydroxy-3-methylglutaryl-CoA synthase 2; TIG, tiglyglycine.

during fasting, infection, or catabolic stress. While hypoglycemia is a hallmark of ketogenesis defects, hyperglycemia may also occur in ketolysis defects due to compensatory mechanisms. Hepatomegaly, abnormal liver fat deposition, Reye-like syndrome, pancreatitis,[2] and dilated cardiomyopathy[3] may be present. Early recognition is critical, as timely diagnosis and management can prevent serious neurological damage or death.[4,5]

Ketogenesis defects, such as 3-hydroxy-3-methylglutaryl-CoA lyase deficiency (HMGCLD), often present with non-ketotic hypoglycemia and metabolic acidosis.[2,3] In contrast, ketolysis defects, including 2-methylacetoacetyl-coenzyme A thiolase deficiency (MATD; deficiency of mitochondrial acetoacetyl-coenzyme A thiolase T2/beta-ketothiolase) and succinyl-CoA:3-ketoacid CoA transferase deficiency (SCOTD), typically result in impaired ketone utilization, leading to accumulation of ketone bodies and severe ketoacidosis. To date, 211 patients with HMGCLD (including 46 from Türkiye), 244 with MATD, and 44 with SCOTD have been reported worldwide.[6-8]

The primary aim of this study was to compare ketogenesis and ketolysis defects regarding age of onset, metabolic acidosis severity, and clinical outcomes, to facilitate earlier recognition and guide management strategies.

MATERIALS AND METHODS

Study Design and Participants

The study was approved by the Hacettepe University Ethics Committee (Approval no: GO-21/878; Date: June 29, 2021). Patients diagnosed with ketone body utilization disorders at Hacettepe University İhsan Doğramacı Children's Hospital between 1986 and 2023 were included. This study was designed as a single-center, retrospective cohort study. Written informed consent was obtained from the patients' legal guardians.

Biochemical and Genetic Analysis

Acylcarnitine profile was analyzed in dried blood spots by tandem mass spectrometry, and organic acids in urine by gas chromatography/mass spectrometry. Molecular analyses were performed using Sanger sequencing. In some cases, functional studies were additionally conducted in fibroblast cultures to support the biochemical and genetic findings.

Diagnostic Criteria

Diagnosis was confirmed based on clinical manifestations, characteristic plasma acylcarnitine and urinary organic acid profiles, and enzymatic and/or genetic analyses.

3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency

Defined by elevated C5OH-carnitine in dried blood spot acylcarnitine profile, with or without decreased free carnitine (<10 μmol/L), and increased urinary excretion of 3-methylglutaric acid (3MGL), 3-hydroxy-3-methylglutaric acid (3HMG), 3-methylglutaconic acid (3MGC), 3-methylcrotonylglycine (3MCC), 3-hydroxyisovaleric acid (3HIVA), dicarboxylic acid (DCA).[7]

2-Methylacetoacetyl-Coenzyme A Thiolase Deficiency

Defined by elevated C5OH-carnitine and C5:1-carnitine (with or without decreased free carnitine) in dried blood spot acylcarnitine profile, and increased urinary excretion of 3-hydroxybutyrate (3-OHB), acetoacetate (AcAc), tiglyglycine, 2-methyl-3-hydroxybutyrate (2M3HB), 2-methylacetoacetate (2MAA), and DCA (with massive ketosis).[8]

Succinyl-CoA:3-Ketoacid CoA Transferase Deficiency

Characterized by a normal acylcarnitine profile in dried blood spots, and increased urinary excretion of 3OHB, AcAc, and DCA, indicating massive ketosis.[6]

Data Collection

The demographic characteristics, age at diagnosis, perinatal findings, family history, presenting complaints, biochemical and genetic investigations, clinical follow-up information, neuropsychiatric tests (including routine examinations), and radiological imaging features were retrospectively reviewed from medical records.

Statistical Analyses

Statistical analysis was performed with SPSS version 29.0 for Windows (IBM SPSS Corp.; Armonk, NY, USA). The normality of the numerical data was analyzed using visual (histogram and detrended plot) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk tests). Normally distributed values were presented as mean ± SD, and non-normally distributed values as median and interquartile range (25th-75th percentile). The Mann–Whitney *U* test was used to analyze the difference between 2 independent groups using non-parametric data. Venous blood parameters, including pH, were normally distributed. The Student's *t*-test was employed to compare these parameters between the ketogenesis defect and the ketolysis defect groups. Fisher's exact tests were used to compare categorical variables. The level of statistical significance was accepted as $P < .05$.

RESULTS

General Clinical Characteristics

Between 1986 and 2023, a total of 37 patients with inherited disorders of ketone metabolism were under follow-up, including 18 with HMGCLD, 16 with MATD, and 3 with SCOTD. Due to insufficient data, 5 patients with HMGCLD and 2 with MATD were excluded from the study. The final analysis of this study included a total of 30 patients, 14 with MATD, 13 with HMGCLD, and 3 with SCOTD. None of the patients in this cohort had a dual diagnosis of more than 1 metabolic disorder (Figure 2).

The median age at presentation among patients diagnosed with HMGCLD was 1 month (interquartile range [IQR]: 3 days to 4 months; range: 2 days to 16 months). Among patients diagnosed with HMGCLD (n = 13), the most common presenting features were vomiting, feeding difficulty, and Kussmaul breathing, observed in 9 patients (69.2%), and seizures in 4 patients (30.7%). A positive family history with an asymptomatic period was reported in 1 patient (7.7%). The median age of the HMGCLD patients (n = 7) under follow-up is 11 years (range: 3 to 30 years). One HMGCLD patient developed hypoglycemic metabolic acidosis during COVID-19 infection.

The median age at presentation among patients diagnosed with MATD (n = 14) was 7 months (interquartile range [IQR]: 3-15 months; range: 10 days to 3 years). A history of consanguinity was present in 10 patients (71.4%). The most common presenting features were vomiting, feeding difficulty, and Kussmaul breathing, observed in 13 patients (92.8%). Additional clinical findings included hepatomegaly in 1 patient (7.1%), hypoglycemia in 1 patient (7.1%), and seizure in 1 patient (7.1%). A positive family history with an asymptomatic period was reported in 1 patient (7.1%). The median age of the MATD patients (n = 7) under follow-up is 8 years (range: 5-35 years).

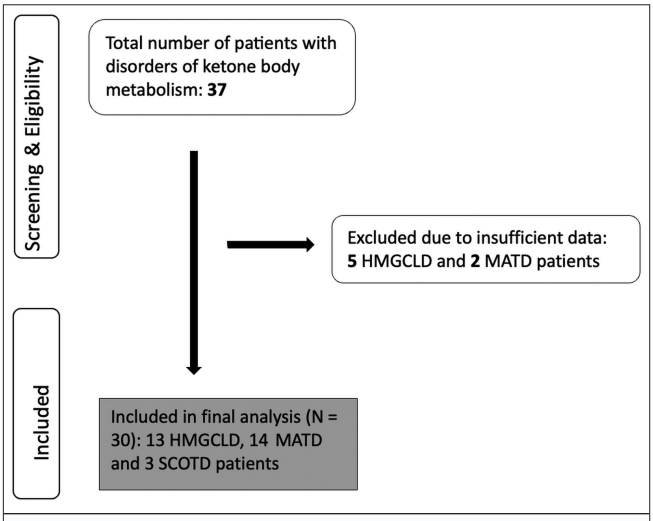

Figure 2. Flow chart showing patient inclusion and exclusion criteria for the study cohort, detailing the numbers of patients with HMGCLD, MATD, and SCOTD included in the final analysis. HMGCLD, 3-hydroxy-3-methylglutaryl-CoA lyase deficiency; MATD, 2-methylacetoacetyl-coenzyme A thiolase deficiency; SCOTD, succinyl-CoA:3-ketoacid CoA transferase deficiency.

The age at presentation for the 3 patients diagnosed with SCOTD was 2 days, 4 days, and 18 months, respectively. All 3 patients with SCOTD presented with vomiting, feeding difficulty, and Kussmaul breathing. One SCOTD patient under follow-up is 4 years old.

Among the 18 patients with available follow-up data, mortality was observed in 1/8 (12.5%) of HMGCLD cases and 2/9 (22.2%) of MATD cases. All deaths occurred in patients who were followed between 1990 and 2003. Demographic and clinical characteristics are summarized in Table 1.

Neurodevelopment and Imaging

Among HMGCLD patients, 2 underwent Wechsler Intelligence Scale for Children-Revised (WISC-R) testing: 1 (aged 6 years) scored in the low-average range, while another (aged 30 years) demonstrated above-average cognitive performance. One HMGCLD patient (aged 5 years) exhibited delayed developmental milestones with reduced white matter on cranial magnetic resonance imaging (MRI). Denver Developmental Screening Tests (DDST) results were available for 12 patients; 9 had abnormal results, with a median of 2 metabolic crises (range: 1-7), whereas 2 had normal results, each with 1 crisis. There was no statistically significant association between developmental delay and the number of metabolic crises ($P = .19$, Mann–Whitney *U* test).

Cranial MRI was available for 5 patients. Findings were normal in 2 MATD cases. In HMGCLD patients, MRI showed increased extra-axial cerebrospinal fluid spaces in the bilateral frontotemporal regions, decreased white matter volume, cerebral atrophy, and signal hyperintensities in the bilateral globus pallidus, putamen, caudate nucleus, periventricular white matter, and dentate nucleus, findings suggestive of Leigh syndrome.

Table 1. Demographic and Clinical Characteristics of 30 Patients with Ketone Body Metabolism Disorders (HMGCLD, MATD, SCOTD)

Sex, n (%)	
Female	13 (43.3)
Male	17 (56.7)
Region, n (%)	
Central Anatolia	9 (30)
S. Eastern Anatolia	7 (23.3)
Black Sea	5 (16.7)
Mediterranean	3 (10)
Marmara	4(13.3)
Abroad	2 (6.7)
Diagnostic distribution, n (%)	
HMGCLD	13 (43.3)
MATD	14 (46.7)
SCOTD	3 (10)
Patient follow-up status, n (%)	
Discontinued	12 (40)
Deceased	3 (10)
Ongoing	15 (50)[a]
Mortality, n (%)	
HMGCLD (n = 8)	1 (12.5)
MATD (n = 9)	2 (22.2)
Follow-up period, years*	8 (5-19), 3-35
Age at last follow-up	
HMGCLD (n = 7), years*	11 (5-21),
MATD (n = 7), years*	3-30
SCOTD (n = 1), years	8 (5-19), 5-35 4
Neonatal onset, n (%)	
HMGCLD (n = 13)	6 (46.2)
MATD (n = 14)	2 (14.2)
SCOTD (n = 3)	1 (33.3)
Presentation findings, n (%)	
Feeding intolerance	25 (83.3)
Vomiting	25 (83.3)
Kussmaul breathing	25 (83.3)
Hypoglycemia	9 (33.3)
Seizure	5 (16.6)
Hepatomegaly	1 (3.3)
Family history with an asymptomatic period	2 (6.6)

Data are presented as median (25th-75th percentile) with range (minimum–maximum)* or n (%).
HMGCLD, 3-hydroxy-3-methylglutaryl-coenzyme A lyase deficiency; MATD, 2-methylacetoacetyl-CoA thiolase deficiency; SCOTD, succinyl-CoA:3-ketoacid CoA transferase deficiency.
[a]Of the 15 patients under ongoing follow-up, 7 have a diagnosis of HMGCLD, 7 of MATD, and 1 of SCOTD, excluding lost to follow-up.

Biochemical and Genetic Investigations

Urinary ketone testing was negative in 12 (92.3%) of patients with HMGCLD, whereas markedly elevated ketone levels (++++ with dipstick) were detected in patients with ketolysis defects. Hyperammonemia was not observed in any group. All patients presented with metabolic acidosis at initial admission, except for 1 with HMGCLD and 1 with MATD, both of whom were diagnosed pre-symptomatically due to a positive sibling history.

Clinical and laboratory characteristics of patients with ketolysis and ketogenesis defects were compared (summarized in Table 2). Patients with ketolysis defects had a later age at initial presentation and experienced more severe metabolic acidosis episodes (Figure 3). Approximately half of the MATD 7 (50%) and HMGCLD 8 (54.5%) patients experienced at least 1 metabolic crisis, commonly triggered by gastroenteritis.

Twelve patients (40%) were diagnosed based on biochemical profiles (acylcarnitine and urine organic acid analyses) (Table 3).Molecular genetic analysis was performed in 14 patients, revealing biallelic pathogenic variants in *HMGCL* (n = 6), *ACAT1* (n = 6), and *OXCT1* (n = 2) (Table 4). Enzyme activity was studied in fibroblasts in 4 patients: 2 with MATD, 1 with SCOTD, and 1 with HMGCLD.

Treatment

Patients with HMGCLD were managed with frequent feedings and a diet low in protein and fat (20%-30% of daily energy intake). A low-leucine formula was used in patients under 12 years, while older patients transitioned to only a restricted diet. Patients with MATD and SCOTD were managed with a protein- and fat-restricted diet (20%-30%), supplemented with carbohydrate-rich formulas and frequent feedings; while a general protein restriction was initiated, no specific limitation of isoleucine intake was introduced. Cornstarch therapy was used in early years by 1 MATD patient and by 2 SCOTD patients to prevent hypoglycemia. Carnitine supplementation was provided to all HMGCLD and MATD patients.

Antiepileptic therapy is ongoing in 1 HMGCLD patient with seizures. During metabolic crises, 2 patients (1 with MATD and 1 with SCOTD) required renal replacement therapy due to progressive and refractory metabolic acidosis. Despite standard medical management, including high-dose glucose infusion, bicarbonate therapy, and correction of electrolyte disturbances, acidosis persisted in both cases. In addition to biochemical derangement, both patients exhibited clinical deterioration, including worsening consciousness and emerging hemodynamic instability, which prompted the decision to initiate peritoneal dialysis in the MATD case and hemodialysis in the SCOTD case. The SCOTD patient required continuous renal replacement therapy at the age of 6 months and intermittent hemodialysis at 8 months due to persistent refractory acidosis.

DISCUSSION

This is the first study to compare ketogenesis and ketolysis defects by integrating clinical and laboratory findings, contributing to a better understanding of their distinct biochemical and phenotypic characteristics. The differentiation between these disorders is crucial, as it directly influences the management approach, particularly during acute metabolic decompensation.

General Characteristics of Patients

Patients with HMGCLD typically present with acute metabolic decompensation in the early neonatal period, as seen in 42.8% of the cases and 40% in Grünert et al's[5] study. The rate of full-term births was 84.6% in this cohort compared to 93.7% in previous reports. The median age at presentation was 30 days versus 4 months or 56 days in prior studies.[5,7]

Table 2. Comparison of Clinical and Biochemical Features Between Patients with Ketogenesis (HMGCLD) and Ketolysis (MATD, SCOTD) Defects

	The Group with Ketogenesis Defect	The Group with Ketolysis Defect		
	Patient with HMGCLD (n = 13)	Patients with MATD and SCOTD (n = 17)[a]	*P*	Overall
Birth weight, gram*	3320 (3000-3800)	3400 (3050-3650)	.93¶	3400 (3000-3650)
Gestational age, n (%)			.56∇	
Term	11 (84.6)	16 (94.1)		27 (90)
Preterm	2 (15.4)	1 (5.9)		3 (10)
Consanguinity, n (%)			.67∇	
Yes	11 (84.6)	13 (76.5)		24 (80)
No	2 (15.4)	4 (23.5)		6 (20)
Family history of the same disorder, n (%)			.44∇	
Yes	5 (38.5)	4 (23.5)		9 (30)
No	8 (61.5)	13 (76.5)		21 (70)
Hypoglycemia at initial presentation, n (%)	7 (53.8)	2 (11.8)	**.02**∇	9 (30)
Denver Developmental Screening Test, n(%)			0.76∇	
Normal	2 (33.3)	1 (16.7)		3 (25)
Abnormal	4 (66.7)	5 (83.3)		9 (75)

Data are presented as median (25th-75th percentile)* or n (%). Statistically significant ($P < .05$) shown in bold.
HMGCLD, 3-hydroxy-3-methylglutaryl-coenzyme A lyase deficiency; MATD, 2-methylacetoacetyl-CoA thiolase deficiency; SCOTD, succinyl-CoA:3-ketoacid CoA transferase deficiency.
[a]MATD (n = 14), SCOTD (n = 3). Among patients with MATD, the median age at presentation was 7 months (IQR: 3-15 months; range: 10 days to 3 years).
¶Mann-Whitney *U* test.
∇ Fisher's exact test.

Grünert and Sass[7] reported a median symptom onset age of 12 months (range: 2 days to 8 years) in 244 MATD patients, compared to 7 months (range: 10 days to 3 years). Neonatal presentation was observed in 3.4% of their cases and 14.2% of ours.[8] In the largest SCOTD series, presentation ranged from 36 hours to 3 years (median: 7 months); the patients presented at 2 days, 4 months, and 18 months, all before age 3.[6] The study confirms that ketolysis defects tend to present later than ketogenesis defects, which may be explained by the ability of the mitochondrial medium-chain 3-ketoacyl-CoA thiolase (T1) to partially compensate for T2 deficiency under stable medical conditions, until a significant trigger, such as prolonged fasting or infection, occurs.[9] The reduced frequency of episodes with age may reflect lower energy demands relative to body weight and greater muscle mass supporting gluconeogenesis.[10]

In the largest MATD review, 33% of patients experienced multiple decompensations.[8] In this cohort, 50% of MATD patients had a single episode, while 50% had recurrent crises, demonstrating variability in disease course and the risk of severe episodes in some patients. Hepatomegaly, observed in one of the MATD cases and previously reported in HMGCLD and SCOTD, underscores the potential for hepatic involvement in these disorders. This finding is attributed to triglyceride accumulation secondary to impaired ketogenesis.[11,12]

Compared to reported mortality rates of 16.1% for HMGCLD, 3.1% for MATD, and 5% for SCOTD, the higher mortality in the MATD cohort may reflect the more severe metabolic acidosis characteristic of ketolysis defects.[5,6,8]

Developmental Milestones and Cognition

Neurological manifestations in HMGCLD include hypotonia, spasticity, movement disorders, seizures, and developmental delay. While Grünert and Sass reported seizures in 3 of 8 HMGCLD patients without decompensation (37.5%), all 4 of the patients with seizures (100%) had concurrent hypoglycemia and metabolic crises.[7] Normal DDST (Denver Developmental Screening Tests) results were seen in 33.3% of the HMGCLD patients versus 62.6% in Grünert and Sass's[7] study, with no association between neurological outcomes and number of crises. The oldest HMGCLD patient, aged 30, demonstrated above-average IQ (WISC-R: 119) with no further crises, supporting the potential for normal cognitive development with optimal management.[6] The presence of abnormal DDST in a patient without crises suggests neurodevelopment may be influenced not only by acute decompensations but also by chronic metabolic imbalance, highlighting the multifactorial nature of cognitive outcomes in these disorders.[5,13] Among the MATD patients, 80% had abnormal DDST results, with an average of 2 crises; seizures were seen during decompensations in 2 cases. In contrast, Grünert and Sass reported seizures in MATD patients without crises, indicating seizures may occur with or without acute decompensation, similar to HMGCLD.[8]

Laboratory Investigations

According to Grünert et al,[5] 3HMG and 3MGC were detected in all HMGCLD patients, while 3HIVA and 3MGL were present in 97% and 86% of cases; in this cohort, 3HMG and 3MGL were found in 92.3% and 84.6%, respectively.[4] C5OH was elevated in all the patients, slightly above the 95% reported by Grünert et al,[5] with free carnitine reduced in 23% compared to 18% in their study. Although urine organic acid and acylcarnitine profiles are useful, their diagnostic value may be limited by metabolite instability, residual enzyme activity, or technical variability. Trace ketonuria in one of the patients highlights that low-level ketones do not exclude HMGCLD, and isolated hepatic involvement without acidosis can occur.[14] Bulut et al[15]

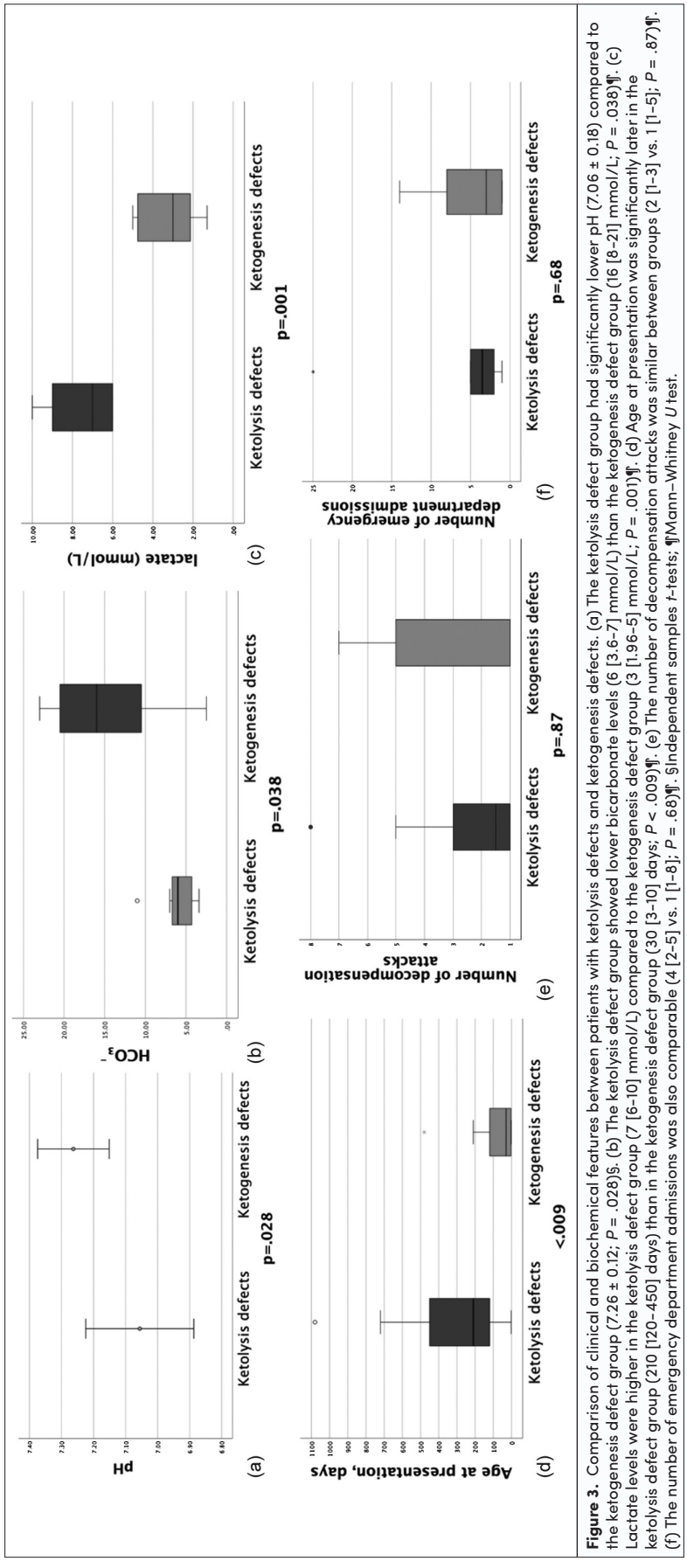

Figure 3. Comparison of clinical and biochemical features between patients with ketolysis defects and ketogenesis defects. (a) The ketolysis defect group had significantly lower pH (7.06 ± 0.18) compared to the ketogenesis defect group (7.26 ± 0.12; *P* = .028)§. (b) The ketolysis defect group showed lower bicarbonate levels (6 [3.6–7] mmol/L) than the ketogenesis defect group (16 [8–21] mmol/L; *P* = .038)¶. (c) Lactate levels were higher in the ketolysis defect group (7 [6–10] mmol/L) compared to the ketogenesis defect group (3 [1.96–5] mmol/L; *P* = .001)¶. (d) Age at presentation was significantly later in the ketolysis defect group (210 [120–450] days) than in the ketogenesis defect group (30 [3–10] days; *P* < .009)¶. (e) The number of decompensation attacks was similar between groups (2 [1–3] vs. 1 [1–5]; *P* = .87)¶. (f) The number of emergency department admissions was also comparable (4 [2–5] vs. 1 [1–8]; *P* = .68)¶. §Independent samples *t*-tests; ¶Mann–Whitney *U* test.

Table 3. Laboratory Investigations

The Group with Ketogenesis Defect		**The Group with Ketolysis Defect**	
Patient with ketogenesis disorders (HMGCLD, n = 13)		**Patients with ketolysis disorders (MATD and SCOTD, n = 17)**	
Initial DBS acylcarnitine profile, n (%)		**Initial DBS acylcarnitine profile in MATD patients [a](n = 14), n (%)**	
Low free carnitine	3 (23)	Low free carnitine	none
Elevated C5OH carnitine	13 (100)	Elevated C5OH carnitine	5 (62.5)
		Elevated C5:1 carnitine	3 (37.5)
Initial urinary organic acid elevations n (%)		**Initial urinary organic acid elevations in patients with MATD and SCOTD, n(%)**	
3-methylglutarate	8 (61.5)	3-hydroxybutyrate	17 (100)
3-hyrdoxy-3-methylglutarate	12 (92.3)	Acetoacetate	16 (94.1)
3-methylglutaconate	11 (84.6)	Tiglylglycine[b]	12 (85.7)
3-methylcrotonylglycine	1 (7.7)	Dicarboxylic aciduria	1 (5.8)
3-hydroxyisovaleric acid	13 (76.9)		
Dicarboxylic aciduria	3 (23.1)		

DBS, dried blood spot; HMGCLD, 3-hydroxy-3-methylglutaryl-coenzyme A lyase deficiency; MATD, 2-methylacetoacetyl-CoA thiolase deficiency; SCOTD, succinyl-CoA:3-ketoacid CoA transferase deficiency; C5OH, 3-hydroxyisovalerylcarnitine.
[a]Since the acylcarnitine analysis of patients with SCOTD is known to be normal, this part was excluded during the analysis.
[b]SCOTD was ruled out in the analysis because these parameters are expected only in MATD.
[c]One HMGCLD patient (elevated C5OH carnitine, urinary organic acids not available) and 1 MATD patient (elevated C5OH carnitine, urinary organic acids showed 3-hydroxybutyric acid and tiglylglycine) were diagnosed pre-symptomatically due to sibling death.

reported a mean blood pH of 7.07 ± 0.13 in MATD patients, similar to 7.06 ± 0.18 in this study. The data confirm that ketolysis defects are linked to more severe metabolic acidosis, likely due to ketone body accumulation. All MATD patients showed ketosis, though ketosis-negative cases have been reported due to secondary carnitine deficiency impairing fatty acid oxidation.[16] Fasting carnitine profiles may not always show C5OH or C5:1 elevation. While normoglycemia is expected in MATD, 2 of the patients had hypoglycemia, and hyperglycemia may develop from compensatory mechanisms.[17] These findings reflect the biochemical heterogeneity of these disorders and support individualized diagnostic and management strategies.

Genetic Heterogeneity

Similar to previously published series from Türkiye, including 16 and 9 patients reported by Bulut et al[15] and Canda et al,[11] respectively, the cohort also demonstrated considerable genotypic diversity. The most frequent variant in the series was the homozygous *HMGCL* c.31C>T (p.Arg11) mutation, and the c.876+1G>C variant, which is common in the Turkish population, was identified in 1 patient. According to Grünert and Sass,[7] the most common pathogenic *HMGCL* variant was c.109G>T (p.Glu37), reported in 36 of 211 patients (17%). In the study by Alfadhel et al,[18] a founder variant, *HMGCL* c.122G>A (p.Arg41Gln), was detected in 77.4% of 62 patients of Arabic origin with HMGCLD. These patients predominantly presented with hypoglycemia (61.3%), metabolic acidosis (79.0%), seizures (27.4%), and neurodevelopmental problems, including learning difficulties (24.1%). This variant was also detected in one of the patients. The genetic heterogeneity observed in this cohort aligns with previous reports from Türkiye and underscores the absence of a predominant mutation pattern.

In both this cohort and the series reported by Bulut et al,[15] the homozygous *ACAT1* c.865G>T (p.Gly289Val) variant was identified in 2 patients with MATD. However, there was no common mutation among those who experienced frequent metabolic decompensations. Nguyen et al,[19] in their study conducted in Vietnam with 41 patients with MATD, demonstrated that the differences in ketoacidosis episodes and their effects, even among patients from the same family under the same conditions, indicate a lack of genotype-phenotype correlation.[19]

Table 4. Genetic Analysis of Identified Cases

Group with Ketogenesis Defect (n = 6)			**Group with Ketolysis Defect (n = 8)**		
Gene	**Nucleotide Change (Protein Change)**	**Zygosity**	**Gene**	**Nucleotide Change (Protein Change)**	**Zygosity**
HMGCL	c.876+1G>C (IVS8+1G>C) (p.?)	Homozygous	*OXCT1*[a]	c.424G>C (p.Ala142Pro)	Homozygous
HMGCL	c.31C>T (p.Arg11*)	Homozygous	*OXCT1*	c.1433T>C (p.Val478Ala)	Homozygous
HMGCL	c.31C>T (p.Arg11*)	Homozygous	*ACAT1*	c.1040T>C (p.Ile347Thr)	Homozygous
HMGCL	c.31C>T (p.Arg11*)	Homozygous	*ACAT1*	c.865G>T (p.Gly289*)	Homozygous
HMGCL	c.31C>T (p.Arg11*)	Homozygous	*ACAT1*	c.865G>T (p.Gly289*)	Homozygous
HMGCL	c.122G>A (p.Arg41Gln), c.876+1G>C (p.?)	Compound heterozygous	*ACAT1*	c.416del (p.Ser139Ilefs*9)	Homozygous
			ACAT1	c.1163+2T>C (IVS11+2T>C) (p.?)	Homozygous
			ACAT1	c.366_369del (p.Asn123Lyfs*7), c.472A>G (p.Asn158Asp)	Compound heterozygous

[a]Previously reported by Yıldız et al.[20]

For SCOTD, the homozygous *OXCT1* c.424G>C (p.Ala142Pro) variant, previously reported as a novel mutation by Yıldız et al,[20] was identified. It can be stated that genotype-phenotype correlations have not been established for HMGCLD, MATD, and SCOTD, which are considered pan-ethnic diseases. These findings underline the genotypic diversity of ketolysis defects.

Treatment

In HMGCLD, 42.8% of the patients continued low-leucine formula use, similar to 43.8% in Grünert and Sass[7]; none over age 12 required formula. L-carnitine supplementation was used in all patients, aligning with 78% in the same study.[5] Although no universal consensus exists, the literature supports avoiding excessive fat and protein intake, encouraging frequent feeding, and administering carnitine in cases of secondary deficiency.[13] Family education on ketonuria monitoring may enable earlier intervention in ketolysis defects.[6-8] In severe cases, intensive treatments such as dialysis may be required; 11 of 244 MATD patients and 3 of 32 SCOTD patients needed dialysis, and one of the patients underwent hemodialysis for refractory acidosis.[6,8,20] Oral bicarbonate was used in 12.1% of Grünert et al's[5] cases and one of the HMGCLD patients.[8] Although dietary restriction is commonly recommended in SCOTD, its definitive benefit remains unproven.

Although the immediate management of both ketogenesis and ketolysis deficiencies is predicated upon analogous principles such as the administration of high-dose glucose infusion to inhibit lipolysis, the rectification of metabolic acidosis through the use of bicarbonate, and the management of hyperammonaemia when present patients exhibiting defects in ketolysis are at an elevated risk of experiencing more pronounced ketoacidosis. This condition may precipitate rapid physiological decompensation and, in certain instances, may require the implementation of renal replacement therapy. Consequently, in cases of ketolysis deficiencies, the prompt identification and timely initiation of these therapeutic interventions are imperative to avert neurological sequelae and enhance clinical outcomes.

Most patients in the cohort were diagnosed after developing symptoms. However, 2 cases were identified before the onset of symptoms due to a positive family history. Grünert et al[21] reported that among 32 patients with MATD identified through newborn screening, cognitive outcomes were favorable, highlighting the importance of early diagnosis in preventing metabolic crises. These findings support the implementation of expanded newborn screening in detecting affected individuals early, allowing timely treatment and helping to prevent metabolic crises.

Strengths and Limitations of the Study

This study represents the largest cohort of patients with ketone body metabolism disorders reported from Türkiye, providing a valuable national perspective on these rare conditions. However, the study has certain limitations. Its retrospective and single-center design may limit generalizability to broader populations and introduce potential biases related to data availability and documentation. In addition, the small sample size, particularly for SCOTD, restricts the power of subgroup analyses.

Conclusion

Ketone body metabolism disorders are characterized by diverse clinical manifestations. Individuals with ketolysis defects typically exhibit a later onset of symptoms and are more prone to severe metabolic acidosis, which may, in some cases, require renal replacement therapy. A delayed diagnosis may impede prompt therapeutic intervention, thereby potentially exacerbating mortality rates. Early biochemical and genetic testing in suspected cases is therefore essential to prevent avoidable metabolic crises. Despite advances in diagnostics, genotype-phenotype correlation remains unclear, underscoring the need for larger, collaborative studies. Further research is warranted to explore the long-term outcomes of these patients and the potential benefits of emerging therapies.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Hacettepe University (Approval No.: GO-21/878; Date: June 29, 2021.

Informed Consent: Written informed consent was obtained from the patients' legal guardians who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.B.K., Y.Y.; Design – A.B.K., Y.Y.; Supervision – A.D., S.S., T.C., A.T.; Data Collection and/or Processing – A.B.K.; Analysis and/or Interpretation – A.B.K., Y.Y.; Literature Search – A.B.K., Y.Y.; Writing – A.B.K., Y.Y.; Critical Review – A.D., S.S., T.C., A.T.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study has received no financial support.

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