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Genomic and Molecular Perspective on Ketone Metabolism: Effects on Energy Metabolism and Athletic Performance: A PICO & PRISMA 2020 Compliant Systematic Review

Manish Acharjee

Student, Department of Physical Education, Swarnim Gujarat Sports University, Desar- 391774 Gujarat, India.
*Corresponding author mail id: acharjeemanish07@gmail.com

A B S T R A C T :

This systematic review explores the genomic and molecular mechanisms underlying ketone metabolism and their implications for energy regulation and athletic performance. Guided by the PRISMA 2020 framework and PICO criteria, a comprehensive literature search across PubMed, Scopus, Web of Science, and Google Scholar identified 22 eligible studies published between 2000 and 2025. Findings reveal that ketone metabolism is tightly regulated by enzymatic, transcriptional, and signalling pathways. The hepatic enzyme HMGCS2 and the mitochondrial enzyme BDH1 were consistently identified as key modulators of ketogenesis and redox balance, while transcriptional regulators such as PPARα and mitochondrial deacetylase SIRT3 integrated nutrient availability with mitochondrial efficiency. Ketones, particularly β-hydroxybutyrate, function not only as energy substrates but also as signalling molecules that enhance mitochondrial biogenesis, redox stability, and epigenetic regulation. Human trials and animal studies demonstrated that ketogenic diets and exogenous ketone supplementation shifted substrate utilization from glucose toward fat and ketones, preserving glycogen, attenuating lactate accumulation, and in some cases improving endurance outcomes. However, evidence also revealed heterogeneous performance responses, with benefits more pronounced in endurance contexts and limitations observed in high-intensity efforts due to reduced glycolytic reliance. Genetic variability, including polymorphisms in HMGCS2 and PPARA, further explained inter-individual differences in adaptation. Collectively, this review highlights ketone metabolism as a dynamic interface between molecular regulation and exercise physiology, offering translational potential for personalized nutrition, training strategies, and broader clinical applications in metabolic disorders. Future research should integrate genomic profiling with performance trials to refine individualized approaches.

Keywords: Ketone, Metabolism, Genomics, Gene, Molecular Perspective, Energy Metabolism. And Athletic Performance

1 Introduction

The body switches its metabolic focus from glucose to other energy sources when there is low carbohydrate availability, such as during ketogenic diets, extended exercise, or fasting. The liver produces β-hydroxybutyrate (βHB), acetoacetate (AcAc), and acetone through a process called ketogenesis, which breaks down fatty acids into acetyl-CoA units. Following their release into the bloodstream, these ketone bodies are used as effective energy sources by peripheral tissues such as the heart, brain, and skeletal muscle (Evans et al., 2017). The two main ketone bodies used to produce energy are βHB and AcAc. After βHB is transformed into AcAc, it undergoes further metabolism to make acetyl-CoA, which then enters the tricarboxylic acid cycle to generate ATP. This metabolic change preserves glycogen stores and improves endurance performance by reducing dependency on glucose and offering an alternate fuel source (Evans et al., 2017; Hwang et al., 2022). The production and utilization of ketone bodies represent a critical adaptive response to periods of low carbohydrate intake, supporting sustained energy production and metabolic flexibility. Ketone metabolism supports metabolic flexibility and provides a strong energy source for endurance and high-intensity sports. Ketone substances, such as β-hydroxybutyrate, support mitochondrial efficiency and maintain performance during extended endurance activities when glucose stores diminish (Cox et al., 2016). Molecularly, ketones enhance the mitochondrial redox span, elevating ATP generation efficiency compared to glucose (Cox & Clarke, 2014). Ketones may inhibit excessive lactate synthesis and maintain glycogen, which would benefit recovery even though high-intensity exercises usually favor glycolysis (Ma & Suzuki, 2019). Importantly, ketolytic enzymatic adaptations and signalling through AMPK-SIRT1-PGC-1α pathways improve metabolic flexibility, or the ability to switch between energy substrates (Devrim-Lanpir et al., 2021).

To adjust cellular energy utilization amid nutritional scarcity, enzymes, transcription factors, and signalling pathways work in concert to regulate ketones strictly. While β-hydroxybutyrate dehydrogenase 1 (BDH1) controls the reversible interconversion between acetoacetate and β-hydroxybutyrate, optimizing redox balance for peripheral utilization, the mitochondrial enzyme 3-hydroxy-3-methylglutaryl-CoA synthase 2 (HMGCS2) is the rate-limiting catalyst of hepatic ketogenesis (Grabacka et al., 2016). Peroxisome proliferator-activated receptor-α (PPARα) maintains metabolic flexibility by increasing the transcriptional expression of genes involved in fatty acid oxidation and ketone body production (Kersten, 2014). Additionally, SIRT3, a mitochondrial deacetylase, links ketogenesis to redox homeostasis via modifying HMGCS2 activity and mitochondrial

efficiency (Dittenhafer-Reed et al., 2015). Collectively, these regulators integrate nutrient status with energy demands, ensuring that ketones function not merely as emergency fuels but also as signalling molecules with broad metabolic implications.

1.2 Objectives of the Study

1. To summarise current knowledge of genomic and molecular mechanisms of ketone metabolism.
2. To evaluate the effect of ketone metabolism on energy utilisation and exercise performance.
3. To identify gaps in the literature and suggest directions for future research in sports genomics and metabolism.

1.3 Significance of the Study

Human health and Sports Science can both benefit greatly from a better understanding of ketone metabolism from genetic and molecular viewpoints. Although more and more athletes are using ketogenic diets, individual responses are still very different, partly because of genetic and regulatory variations in enzymes, transcription factors, and signalling pathways. This study provides a framework for individualised training and diet by synthesising the most recent molecular insights to bridge fundamental biochemical regulation with performance outcomes. Determining how genes like HMGCS2 and regulators like PPARα and SIRT3 control energy flexibility may have implications for metabolic disorders such as obesity, diabetes, and neurological disorders that transcend beyond sports. As a result, this study highlights the translational potential of ketones in enhancing performance and metabolic resilience while also expanding our understanding of them as adaptable fuels.

2. Methodology

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines (Moher et al., 2009) and the PICO framework (Kloda et al., 2020). The protocol was prospectively registered on an open science platform, and any deviations from the original protocol were transparently documented.

2.1 Search Strategy

A comprehensive literature search was conducted across PubMed/MEDLINE, Scopus, Web of Science, & Google Scholar, covering the period from January 2000 to September 2025. Search strings combined controlled vocabulary (MeSH and Emtree terms) and free-text keywords related to ketone metabolism (“Ketone bodies”, “β-hydroxybutyrate”, “Ketogenesis”, “Ketolysis”), genomic and molecular regulation (“HMGCS2”, “BDH1”, “PPARA”, “SIRT3”, “transcriptomics”, “epigenetics”, “signalling”), and athletic performance outcomes (“VO_2 Max”, “time-to-exhaustion”, “strength”, “recovery”).

2.2. Eligibility Criteria

Studies were considered eligible if they met the following PICO criteria:

Population	Intervention	Comparator	Outcomes
Healthy adults or trained athletes were included only when addressing genomic or molecular regulation, and were synthesized separately.	Ketogenic diets, exogenous ketone supplementation, or exercise/fasting protocols inducing ketosis.	Usual diet, placebo, or alternative macronutrient-based interventions.	Primary—molecular and genomic markers (gene and protein expression, epigenetic regulation, signaling pathways); Secondary—exercise performance indices (VO_2 max, endurance, strength, recovery biomarkers)

Table No. 1: PICO Framework (Kloda et al., 2020).

2.3 Study Selection & Descriptives

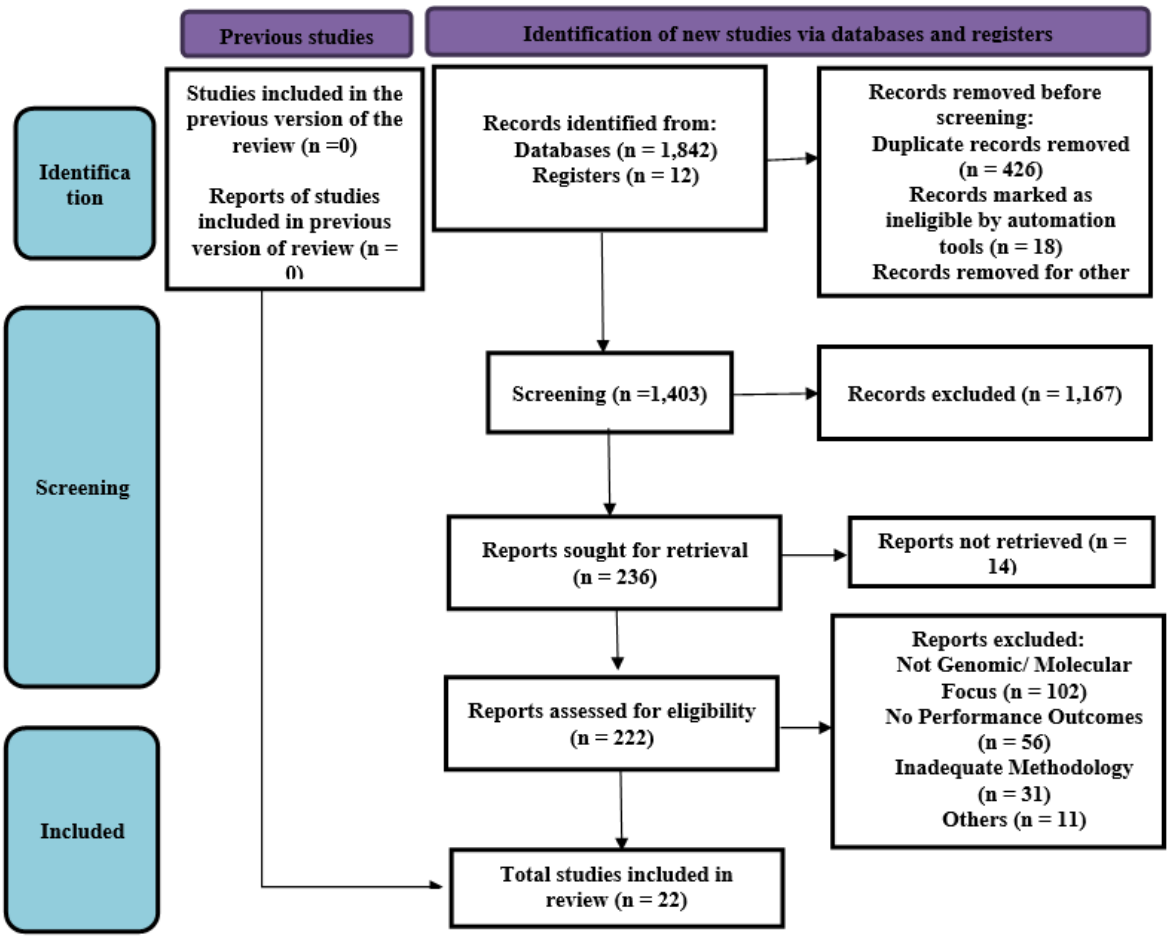

Figure No. 1: The PRISMA 2020 Framework (Moher et al., 2009).

An initial search across multiple databases yielded 1,842 records, with an additional 12 records retrieved from trial registries. After excluding 426 duplicates, 18 records flagged as ineligible by automation tools, and 7 records excluded for other reasons, a total of 1,403 articles proceeded to screening. During title and abstract screening, 1,167 studies were excluded because they were irrelevant to the review objectives. The remaining 236 reports were sought for full-text retrieval, of which 14 could not be accessed. A detailed eligibility assessment was then performed on 222 reports, resulting in the exclusion of studies for reasons including lack of genomic or molecular focus (n = 102), absence of performance-related outcomes (n = 56), methodological limitations (n = 31), and other miscellaneous factors (n = 11). Ultimately, 22 studies met the inclusion criteria and were incorporated into the final review.

3.0. Result & Discussion:

The study of ketone metabolism has evolved from treating ketones as emergency fuels to recognizing them as central regulators of energy homeostasis, with implications for both athletic performance and metabolic health. At the enzymatic level, 3-hydroxy-3-methylglutaryl-CoA synthase 2 (HMGCS2) remains the rate-limiting catalyst for ketogenesis in the liver, while β-hydroxybutyrate dehydrogenase 1 (BDH1) governs the interconversion of acetoacetate and β-hydroxybutyrate, thereby sustaining redox balance across peripheral tissues (Grabacka et al., 2016; Ruppert & Kersten, 2024). These enzymes are not merely metabolic switches, but also influence mitochondrial respiration and oxidative stress pathways, which are crucial for athletes exposed to repeated bouts of energetic stress. Transcriptional regulators add another layer of control. Peroxisome proliferator-activated receptor-α (PPARα) has been shown to upregulate genes linked to fatty acid oxidation and ketone production, reinforcing metabolic flexibility during fasting, ketogenic diets, or endurance exercise (Kersten, 2014; Rakhshandehroo et al., 2010). Similarly, the mitochondrial deacetylase SIRT3 modulates HMGCS2 activity and maintains NAD^+/NADH balance, thereby supporting ketone oxidation and redox stability (Dittenhafer-Reed et al., 2015; Shen et al., 2020). These regulators converge on AMPK-SIRT1-PGC-1α signalling, stimulating mitochondrial biogenesis and antioxidant defences (Tozzi et al., 2022). Importantly, β-hydroxybutyrate also acts as an epigenetic modulator, inhibiting histone deacetylases and altering transcription of antioxidant and metabolic genes, which influence adaptation to training (Memme et al., 2021; Shimazu et al., 2013).

Human intervention trials reinforce these molecular insights but reveal heterogeneity in performance outcomes. In one landmark study, Cox et al., (2016) demonstrated that exogenous ketone esters elevated circulating β-hydroxybutyrate and shifted substrate use towards fat and ketones, sparing glycogen and reducing lactate accumulation. Evans et al., (2017) confirmed similar shifts in fuel preference and redox balance during endurance cycling, though performance benefits were modest. By contrast, Leckey et al., (2017) in their study reported that ketone esters impaired professional cyclists' time-trial performance, likely due to gastrointestinal discomfort and altered carbohydrate availability. Similarly, McSwiney et al., (2019) found that the ketogenic diet adaptation improved time-to-exhaustion in endurance tests but hindered high-intensity performance, illustrating sports and context-specific outcomes. Evidence also suggests that ketones support recovery and metabolic resilience. Pinckaers et al., (2017) observed reductions in lactate accumulation and improved recovery markers following ketone supplementation, while Evans et al., (2017) noted attenuated exercise-induced inflammation and oxidative stress. Animal and transcriptomic studies extended these findings: Tozzi et al., (2022) demonstrated that overexpression of ketone-related genes in rodents enhanced endurance and delayed fatigue, while Miller et al., (2018) showed that ketogenic interventions lowered reactive oxygen species (ROS) and improved mitochondrial respiration in myocytes. Together, these findings emphasize that ketones serve not only as fuels but also as signalling agents that protect against oxidative damage and facilitate recovery.

More recent work deepens this perspective. Miller et al., (2020) reported that a 12-week ketogenic diet combined with exercise improved mitochondrial respiratory control and ATP efficiency in human skeletal muscle, suggesting that ketogenic diets enhance bioenergetic resilience in endurance athletes. Huang et al., (2021), using a murine model, found that long-term KD plus exercise upregulated genes involved in lipid oxidation while suppressing ketolysis-related genes in heart and skeletal muscles, demonstrating tissue-specific genomic remodelling. Hyatt et al., (2016) observed that KD improved mitochondrial coupling and antioxidant defences in rodents undergoing resistance training, highlighting benefits for oxidative resilience even under high mechanical loads. Finally, transcriptomic profiling in ultra-endurance athletes (2025 preprint) revealed that habitual low-carbohydrate, high-fat diets upregulated lipid and ketone metabolism genes at rest and altered recovery-related gene expression after exercise, underscoring how long-term diet shapes genomic responses to training. Despite compelling mechanisms, heterogeneity persists. Performance outcomes vary by intervention type (dietary vs. exogenous supplementation), study duration, sports discipline, and individual genetics. Polymorphisms in genes such as HMGCS2 and PPARA may partly explain inter-individual differences in ketone utilization and performance response (Lampe et al., 2013). Broadly, endurance athletes appear to benefit most from ketone-driven metabolic flexibility, whereas high-intensity or strength athletes may derive less benefit or experience impaired performance due to reduced glycolytic capacity. Taken together, the literature converges on several key insights: ketones enhance metabolic flexibility, mitochondrial efficiency, and recovery potential through enzymatic, transcriptional, and epigenetic regulation. Their ergogenic effect, however, is context-dependent and mediated by genomic variability. Understanding these mechanisms offers opportunities for personalized nutrition and training strategies in sport, while also extending to clinical contexts such as obesity, diabetes, and neurological disease.

4.0. Conclusion

This systematic review underscores ketone metabolism as a dynamic interface between molecular regulation and athletic performance. Beyond serving as alternative fuels, ketones orchestrate genomic and enzymatic adaptations that enhance mitochondrial efficiency, redox balance, and recovery. Key regulators—HMGCS2, BDH1, PPARα, and SIRT3—emerge as pivotal modulators of metabolic flexibility, with implications extending from endurance sports to clinical resilience. However, performance outcomes remain context-dependent, shaped by intervention type, sport specificity, and individual genetic variability. The translational potential of ketones lies not only in optimizing energy utilization but also in informing personalized nutrition and training strategies. Future research should integrate transcriptomic profiling and polymorphism mapping to refine these insights. Ultimately, ketone metabolism represents a promising frontier in sports genomics, bridging biochemical precision with human adaptability.

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