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Low-carbohydrate and Ketogenic Diets: Mechanisms for Weight Loss and Diabetes Remission

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Abstract

The rising global prevalence of obesity and type 2 diabetes necessitates a deeper understanding of effective dietary interventions beyond conventional paradigms. Low-carbohydrate and ketogenic diets have demonstrated significant clinical efficacy, yet their multifaceted physiological mechanisms are often fragmented in the literature. This paper synthesizes current evidence to provide a cohesive explanation of how these diets drive weight loss and facilitate diabetes remission. This paper details the primary metabolic shift from glucose to ketone body utilization, driven by glycogen depletion and sustained low insulin levels, which enables continuous lipolysis. It further explores the hormonal regulation underpinning fat mobilization, the debate surrounding increased energy expenditure, and the direct mechanisms for glycemic control, including the removal of dietary glucose and restoration of hepatic insulin sensitivity. The discussion extends to favorable alterations in body composition, including the preferential loss of visceral and ectopic fat, and analyzes the complex impact on lipid metabolism and cardiovascular risk factors. Finally, the evidence from clinical trials is contextualized by a comparative analysis with other dietary patterns, highlighting short-term advantages and the critical role of long-term adherence. Future research must prioritize long-term, randomized controlled trials to definitively establish the sustainability and safety of these diets. Further investigation is needed to elucidate the precise role of gut microbiota and bile acid signaling in mediating metabolic benefits. Personalized nutrition approaches will be essential to identify which individuals are most likely to achieve long-term success and optimal health outcomes on a low-carbohydrate or ketogenic diet.

Keywords: Beta-hydroxybutyrate, Glycemic control, Insulin resistance, Ketogenic diet, Low-carbohydrate diet, Type 2 diabetes, Visceral adipose tissue, Weight loss

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Introduction

A comprehensive examination of current literature underscores the multifaceted mechanisms through which low-carbohydrate and ketogenic diets facilitate weight loss and promote diabetes remission [1-4]. These dietary approaches, characterized by significant carbohydrate restriction and high fat intake, have garnered attention for their potential to induce profound metabolic changes, improve glycemic control, and alter body composition [5-8].

One of the primary mechanisms attributed to the efficacy of ketogenic diets in weight management and diabetes remission involves metabolic adaptation to ketosis. As outlined by Malinowska and Żendzian-Piotrowska [9], the ketogenic diet induces a shift from glucose-based energy metabolism to fat-based oxidation, leading to increased production of ketone bodies such as beta-hydroxybutyrate. This metabolic switch not only provides an alternative energy substrate but also influences appetite regulation, often resulting in reduced caloric intake and subsequent weight loss. The role of ketone bodies extends beyond energy provision; they may exert signaling functions that modulate inflammation and insulin sensitivity, further contributing to metabolic improvements [9].

The impact of carbohydrate restriction on insulin dynamics is another critical aspect. Long et al. [10] demonstrated that ketogenic diets could induce hepatic insulin resistance and fatty liver disease in animal models, suggesting complex effects on liver metabolism. Conversely, human studies, such as those reviewed by Rafiullah et al. [11], indicate that very-low-carbohydrate ketogenic diets can significantly improve glycemic control in patients with type 2 diabetes. These diets reduce postprandial glucose excursions and decrease insulin demand, which may facilitate remission of type 2 diabetes. Unwin et al. [12] further support this, showing that a primary care-based low-carbohydrate approach achieved drug-free remission in a substantial proportion of patients, emphasizing the diet's potential to restore normal glucose homeostasis.

The modulation of gut microbiota has emerged as an intriguing mechanism mediating the benefits of ketogenic diets. Defeudis et al. [13] highlighted that very-low-calorie ketogenic diets positively influence gut microbiota composition, which may, in turn, improve metabolic parameters and reduce inflammation. This microbiome-mediated pathway could be pivotal in understanding long-term outcomes, although current evidence remains primarily observational and short-term. In addition to metabolic shifts, the influence of ketogenic diets

on body composition is well-documented. Correa et al. [14] reported significant anthropometric improvements, including weight loss and reduced body fat, which are crucial for managing obesity-related insulin resistance. The rapid weight reduction observed with very-low-calorie ketogenic diets is partly attributed to decreased appetite, increased satiety, and enhanced fat oxidation, as discussed by Laddu et al. [15]. These effects are often achieved through stages of induced ketosis, followed by reintroduction of calories and maintenance strategies, which help sustain weight loss over time.

Furthermore, the role of bile acids in mediating weight loss and metabolic health has been explored. Li et al. [16] found that ketogenic diet consumption elevates serum taurodeoxycholic acid and tauroursodeoxycholic acid, which may reduce calorie absorption and promote weight loss. This mechanism suggests that beyond caloric restriction, ketogenic diets may influence enterohepatic signaling pathways that regulate energy balance. The potential for ketogenic diets to induce diabetes remission is also supported by clinical case reports and retrospective studies. Correa et al. [14] and Moriconi et al. [17] documented cases where significant glycemic improvements led to the discontinuation of antidiabetic medications. Unwin et al. [12] further demonstrated that a low-carbohydrate diet could be a practical, primary care-based intervention for achieving drug-free remission, emphasizing the diet's therapeutic potential.

However, concerns regarding safety and adverse effects are also present in the literature. Long et al. [10] noted that in animal models, ketogenic diet could induce hepatic insulin resistance, raising questions about long-term safety. Similarly, Buehler et al. [18] discussed safety considerations in managing type 1 diabetes with ketogenic diets, highlighting the need for careful monitoring. Despite these concerns, the overall evidence suggests that, when properly supervised, ketogenic diets are generally safe and well-tolerated, especially in the short term [13].

In summary, the mechanisms underpinning the benefits of low-carbohydrate and ketogenic diets in weight loss and diabetes remission are multifactorial. They involve metabolic adaptations to ketosis, improved insulin sensitivity, modulation of gut microbiota, alterations in bile acid signaling, and changes in appetite regulation. While the evidence supports their efficacy, especially in the short term, ongoing research is necessary to elucidate long-term safety and sustainability. The current body of literature underscores the potential of these dietary strategies as effective tools in managing obesity and type 2 diabetes, with mechanisms rooted in complex metabolic and microbiome interactions that warrant further exploration

The Primary Metabolic Shift: From Glucose to Ketone Bodies

The fundamental physiological shift that defines the ketogenic diet is the systemic transition from glucose-based to a predominantly fat-based metabolism. In a standard diet, carbohydrates are broken down into glucose, which serves as the body's primary and preferred energy source [19]. This glucose-centric metabolism maintains stable blood sugar levels and supports the high energy demands of the brain and muscles. When dietary carbohydrate intake is drastically reduced, typically to below 50 g per day, this homeostatic balance is disrupted [20]. The body's first response is to utilize stored glucose in the form of glycogen in the liver and muscles. This glycogen depletion occurs rapidly, typically within 24 to 48 h, and is often accompanied by a significant loss of water weight due to the hydration of glycogen molecules [21, 22].

As glycogen stores become depleted, the body can no longer rely on a steady supply of glucose. This scarcity triggers a hormonal cascade, most notably a substantial reduction in circulating insulin levels. Insulin, the primary hormone of energy storage, falls to a low baseline state, signaling the body to switch from storing fat to mobilizing it for energy [23, 24]. The decline in insulin acts as a potent signal for lipolysis, the breakdown of stored triglycerides in adipose tissue into free fatty acids and glycerol. These free fatty acids are released into the bloodstream and become the primary energy substrate for most tissues, including skeletal muscle [25]. However, the brain has a limited capacity to utilize free fatty acids directly due to the blood-brain barrier. To meet the brain's substantial energy demands in the absence of glucose, the liver initiates a critical process called hepatic ketogenesis [26]. Within the liver mitochondria, the influx of free fatty acids is subjected to beta-oxidation, producing acetyl-CoA.

When carbohydrate availability is low, the normal pathway for acetyl-CoA (entry into the citric acid cycle) is overwhelmed. Instead, the liver converts this surplus acetyl-CoA into ketone bodies, primarily beta-hydroxybutyrate and acetoacetate [27, 28]. This process represents a crucial metabolic adaptation, creating an alternative, water-soluble fuel from fat. The production and release of ketone bodies by the liver mark the onset of nutritional ketosis. Beta-hydroxybutyrate, the most abundant ketone in the blood, and acetoacetate are then circulated throughout the body, providing a highly efficient energy source for nearly all tissues [29, 30]. The brain, which typically consumes about 120 g of glucose daily, undergoes a remarkable metabolic adaptation [31]. Over several weeks of sustained ketosis, the brain can derive up to 70% of its energy from ketone bodies, significantly reducing its glucose requirement [32]. This shift preserves muscle protein, as the need for gluconeogenesis from amino acids is greatly diminished.

Beyond the central nervous system, ketone bodies serve as a preferred fuel for other vital organs, including the heart. Cardiac muscle efficiently oxidizes ketones, which may contribute to improved cardiac efficiency, and research suggests they may provide a more energy-yielding substrate than fatty acids under certain conditions [33, 34]. Importantly, the role of ketones extends far beyond that of a mere alternative fuel. Beta-hydroxybutyrate, in particular, functions as a potent signaling molecule with pleiotropic effects [35]. It can inhibit histone deacetylases (HDAC), leading to altered gene expression that enhances oxidative stress resistance and reduces inflammation. Furthermore, ketone bodies have been shown to influence the activity of various receptors and metabolic pathways [36]. For instance, Beta-hydroxybutyrate can activate specific G-protein coupled receptors, such as HCAR2, which may mediate anti-inflammatory effects and modulate lipid metabolism [37]. This signaling function positions ketones as key mediators of the broader metabolic benefits of the diet.

In summary, the primary metabolic shift induced by carbohydrate restriction is a coordinated adaptation from glucose to fat and ketone-based energetics. Driven by glycogen depletion and low insulin, this state is characterized by elevated fatty acid oxidation, robust hepatic ketogenesis, and the systemic utilization of ketone bodies. These molecules not only serve as a crucial energy source for the brain and heart but also act as important signaling molecules that contribute to the improved metabolic and inflammatory profile observed with ketogenic diets.

Hormonal Regulation: The Central Role of Insulin Reduction

The efficacy of low-carbohydrate and ketogenic diets in promoting weight loss and metabolic health is profoundly mediated by a fundamental shift in endocrine physiology, with the reduction of insulin secretion representing a central, orchestrating mechanism (Table 1). Insulin, a peptide hormone secreted by the pancreatic beta cells, is the primary anabolic hormone responsible for nutrient storage in the fed state [38]. Under conditions of a standard carbohydrate-rich diet, the postprandial rise in blood glucose serves as the principal stimulus for insulin release. This hormonal response is both rapid and substantial, with the magnitude of secretion being directly proportional to the glycemic load of the meal consumed [23]. In stark contrast, low-carbohydrate and ketogenic diets fundamentally alter this dynamic by drastically minimizing the dietary intake of carbohydrates, the most potent insulin secretagogue. The removal of high-glycemic carbohydrates leads to a marked attenuation of postprandial glucose excursions, thereby eliminating the primary signal for robust insulin secretion [39, 40].

Consequently, the pancreatic beta cells are relieved of a significant secretory burden, leading to a sustained, low-level baseline of insulin circulation. This state of physiological hypoinsulinemia is a cornerstone of the metabolic effects of low-carbohydrate and ketogenic diets, creating a hormonal environment diametrically opposed to that of chronic energy storage [41]. The impact of this lowered insulin state on adipose tissue is particularly profound and direct. Insulin exerts powerful inhibitory control over hormone-sensitive lipase, the key enzyme responsible for the hydrolysis of stored triglycerides within adipocytes into free fatty acids and glycerol [42]. In a high-insulin environment, hormone-sensitive lipase is suppressed, effectively 'locking' fat in the adipose tissue and promoting a state of continuous fat storage, or lipogenesis [43]. This process is facilitated by insulin's activation of lipoprotein lipase, which cleaves circulating triglycerides for uptake into fat cells [44]. When insulin levels fall, as they do consistently on a low-carbohydrate and ketogenic diet, this inhibitory brake on fat is released. The resultant activation of hormone-sensitive lipase initiates and sustains a continuous process of lipolysis, liberating free fatty acids from adipose tissue stores into the bloodstream for use as fuel by peripheral tissues [45].

Simultaneously, the low-insulin environment leads to a downregulation of lipogenic pathways. With diminished insulin signaling, the processes of de novo lipogenesis-the conversion of carbohydrates into fatty acids in the liver-and the storage of dietary fat in adipocytes are significantly reduced [46]. The combination of these two processes-increased lipolysis and decreased lipogenesis-creates a powerful, hormonally driven shift in energy flux [47]. The body transitions from a state of net fat accumulation to a state of net fat mobilization and oxidation. This hormonally enabled state of continuous fat mobilization is a key differentiator of low-carbohydrate and ketogenic diets from simple caloric restriction. While energy deficit alone can promote weight loss, the specific endocrine milieu of a low-carbohydrate and ketogenic diet ensures that the body is hormonally primed to access and utilize stored fat as its primary energy source. The sustained lipolysis provides a steady stream of free fatty acids, which are not only oxidized directly by muscles and other tissues but also serve as the essential substrate for the liver to produce ketone bodies through the process of hepatic ketogenesis [48], as detailed in the previous section.

Beyond adipose tissue, the reduction in insulin has systemic effects that further contribute to metabolic health. Lower insulin levels reduce sodium reabsorption in the kidneys, often leading to a beneficial diuresis and a reduction in blood pressure, a common comorbidity in metabolic syndrome [49, 50]. Furthermore, chronic hyperinsulinemia is increasingly recognized as a pathophysiological driver of insulin resistance itself, a concept known as 'insulin-induced insulin resistance' [51]. By alleviating the persistent demand for high insulin secretion, low-carbohydrate and ketogenic diets can help break this cycle, allowing for the restoration of insulin sensitivity in peripheral tissues. The role of other counter-regulatory hormones, such as glucagon, is also modulated in this context [52]. While the classic insulin-glucagon ratio is altered, the primary driver of the metabolic shift remains the profound reduction in insulin's inhibitory tone on fat metabolism.

In summary, the dramatic reduction in dietary insulin secretion is a pivotal mechanism of low-carbohydrate and ketogenic diets. By creating a state of physiological hypoinsulinemia, these diets hormonally enable a continuous state of fat mobilization, characterized by activated lipolysis and suppressed lipogenesis. This endocrine reconfiguration not only facilitates the liberation and oxidation of stored fat for energy but also underpins many of the improvements in glycemic control and metabolic syndrome parameters observed in clinical practice.

Metabolic Advantages: The Theory of Increased Energy Expenditure

A compelling, though debated, hypothesis in the field of nutritional science is that low-carbohydrate and ketogenic diets may offer a 'metabolic advantage' by increasing total energy expenditure beyond what would be predicted by their macronutrient composition alone. This concept suggests that, for the same caloric intake, a low-carbohydrate and ketogenic diet could promote greater energy loss as heat, thereby enhancing weight loss efficiency [53, 54]. The theory challenges the conventional energy balance model, which posits that a calorie is a calorie, regardless of its source, and has been the subject

Table 1: Hormonal and metabolic shifts induced by low-carbohydrate and ketogenic diets.

Hormone/factor	Direction of change	Primary trigger	Metabolic consequences
Insulin	↓↓↓ substantial decrease	Drastic reduction in dietary carbohydrate intake	• Disinhibition of hormone-sensitive lipase. • Promotes lipolysis and fat mobilization. • Suppresses de novo lipogenesis. • Reduces renal sodium reabsorption (lowering blood pressure).
Glucagon	↑/→ variable	Reduced insulin and increased amino acid availability	• Stimulates gluconeogenesis and glycogenolysis (initially). • The insulin-glucagon ratio is profoundly lowered.
Free fatty acids	↑↑ increase	Activation of lipolysis due to low insulin	• Become the primary energy substrate for most tissues. • Serve as the essential substrate for hepatic ketogenesis.
Ketone bodies	↑↑↑ substantial increase	Hepatic ketogenesis from acetyl-CoA derived from beta-oxidation of free fatty acids	• Provide an alternative fuel for the brain and heart. • Act as signaling molecules (e.g., anti-inflammatory, HDAC inhibition). • May suppress appetite and proteolysis.

of significant research and discussion. Proponents of the metabolic advantage point to several mechanistic pathways that could contribute to this phenomenon. These include the energetic inefficiency of gluconeogenesis, the high thermic effect of protein, and the potential for low-carbohydrate and ketogenic diets to mitigate the adaptive thermogenesis-or metabolic slowdown that typically accompanies weight loss [55, 56]. Each of these factors represents a potential pathway for increased energy dissipation on a low-carbohydrate and ketogenic diet.

However, literature remains contentious, with studies producing conflicting results. Some well-controlled trials have reported modest but significant increases in total energy expenditure on low-carbohydrate and ketogenic diets, while others have found no such effect. This inconsistency underscores the complexity of human metabolism and the influence of factors such as diet adherence, individual metabolic variability, and study duration. The ongoing debate highlights the need for further rigorous investigation into the potential energetic properties of macronutrients.

The metabolic cost of gluconeogenesis

One proposed contributor to increased energy expenditure on a low-carbohydrate and ketogenic diet is the upregulation and energetic cost of gluconeogenesis. Gluconeogenesis is the metabolic pathway through which the liver (and to a lesser extent, the kidneys) synthesizes new glucose from non-carbohydrate precursors, primarily lactate, glycerol, and glucogenic amino acids [57, 58]. On a carbohydrate-restricted diet, the body must rely more heavily on gluconeogenesis to produce the glucose required by obligate glycolytic tissues, such as certain brain cells and red blood cells. This process is metabolically expensive. While the precise adenosine triphosphate (ATP) cost is subject to debate, estimates suggest that synthesizing one molecule of glucose from pyruvate consumes 6 ATP equivalents, and the process may be even more costly when starting from other substrates [59, 60]. This stands in stark contrast to the minimal energy cost of storing and retrieving glucose from dietary carbohydrates as glycogen. The increased flux through gluconeogenesis on a low-carbohydrate and ketogenic diet could therefore represent a sustained, low-level energy drain.

Critics of this mechanism argue that the overall quantitative contribution of gluconeogenesis to total energy expenditure is likely small. They note that the body's glucose demands from gluconeogenesis are finite and that the process becomes more efficient over time [61]. Nevertheless, when combined with other energy-costly processes, the cumulative effect of a persistently elevated rate of gluconeogenesis may contribute to a meaningful increase in daily energy expenditure, forming one part of the proposed metabolic advantage.

The thermic effect of protein and substrate cycling

The high thermic effect of protein is a less contentious but significant factor in the energy expenditure equation. The thermic effect of protein refers to the energy required to digest, absorb, transport, and store nutrients. Protein has a markedly higher thermic effect of protein (20 to 30%) compared to carbohydrates (5 to 10%) and fat (0 to 3%) [62]. Low-carbohydrate diets are often, though not always, higher in protein content than the high-carbohydrate diets to which they are compared [63]. Therefore, when isocaloric, a diet higher in protein will result in a greater postprandial energy expenditure. A greater proportion of the calories consumed from protein are 'lost' as heat during metabolic processing, making fewer net calories available for storage or other bodily functions [64]. This provides a clear and well-established mechanism for a metabolic advantage in low-carbohydrate and ketogenic diets that are also protein-rich.

Beyond the direct cost of protein metabolism, low-carbohydrate and ketogenic diets may promote increased energy expenditure through enhanced substrate cycling. The simultaneous processes of hepatic ketogenesis (fat burning) and hepatic gluconeogenesis (glucose production), along with the Cori cycle (lactate recycling), are energetically demanding cycles that are particularly active during nutritional ketosis [65, 66]. These futile cycles, where simultaneous synthesis and breakdown pathways occur, consume ATP without performing network, effectively dissipating energy as heat and contributing to total energy expenditure.

Attenuation of metabolic adaptation

A potentially crucial advantage of low-carbohydrate and ketogenic diets may not be a gross increase in total energy expenditure above baseline, but rather a mitigation of the decline in total energy expenditure that typically occurs with weight loss. This phenomenon, known as adaptive thermogenesis or 'metabolic adaptation, involves a reduction in energy expenditure beyond what can be attributed to the loss of metabolically active tissue [67, 68]. It is a physiological defense mechanism that can impede long-term weight loss maintenance. Emerging evidence suggests that low-carbohydrate and ketogenic diets may help preserve energy expenditure and total energy expenditure to a greater extent than low-fat diets during active weight loss [69, 70]. The mechanisms for this are not fully elucidated but may be related to the hormonal milieu. The sustained elevation of circulating free fatty acids and ketone bodies, coupled with lower insulin levels, may provide a metabolic signal that helps maintain a higher metabolic rate compared to the more pronounced energy conservation state induced by other diets.

This attenuation of metabolic adaptation is of profound clinical importance. By blunting the body's propensity to slow metabolism in response to caloric deficit, low-carbohydrate and ketogenic diets could theoretically make sustained weight loss easier to achieve and maintain [71, 72]. This positions the 'metabolic advantage' not solely as a short-term boost in calorie burning, but as a strategic approach to countering the body's innate resistance to long-term fat loss, thereby improving the sustainability of weight management.

Glycemic Control: Direct Mechanisms for Diabetes Remission

The most rapid and clinically significant effects of low-carbohydrate and ketogenic diets are often observed in the realm of glycemic control, particularly for individuals with type 2 diabetes and insulin resistance. The mechanisms through which these diets facilitate improvement and even remission of type 2 diabetes are direct, multi-faceted, and rooted in fundamental physiology (Table 2). By addressing the primary dietary source of blood glucose and reprogramming underlying metabolic dysfunctions, low-carbohydrate and ketogenic diets can induce a rapid therapeutic response. These mechanisms operate on a continuum, from immediate postprandial effects to longer-term adaptations in hepatic and peripheral insulin sensitivity. The direct reduction in dietary carbohydrate load provides instantaneous relief to an overburdened glycemic control system, while subsequent metabolic changes work to reverse the core pathophysiological defects of type 2 diabetes [73, 74]. This combined approach targets both the symptom-hyperglycemia-and its underlying causes.

Table 2: Direct mechanisms of glycemic control and diabetes remission with low-carbohydrate/ketogenic diets.

Mechanism	Physiological action	Clinical outcome
Elimination of dietary glucose load	Removal of primary dietary driver of postprandial hyperglycemia; drastically reduces carbohydrate intake.	• Near-immediate blunting of postprandial glucose spikes. Reduced glycemic variability. • Creates a stable, low-glycemic baseline.
Reduction of hepatic glucose output	Low insulin resensitizes liver to insulin's suppressive signal. Reduced substrate (lactate, glycerol availability for gluconeogenesis.	• Significant decrease in fasting blood glucose. • Addresses a core defect of hepatic insulin resistance in type 2 diabetes.
Medically assisted medication de-escalation	Rapid lowering of plasma glucose eliminates the need for previous pharmacologic doses, especially insulin and secretagogues.	• High risk of iatrogenic hypoglycemia without pre-emptive dose reduction. • Enables rapid reduction or discontinuation of glucose-lowering drugs. • Facilitates 'drug-free remission' as a direct result of improved physiology.

Central to this process is the concept of low-carbohydrate and ketogenic diets as a form of 'medically assisted carbohydrate restriction.' This framing positions the dietary intervention not merely as a lifestyle change, but as a potent therapeutic tool that directly competes with and can often replace pharmacological management of blood glucose. The speed and magnitude of this effect necessitate careful clinical monitoring and medication adjustment to prevent iatrogenic hypoglycemia.

Immediate elimination of dietary glucose load

The most immediate mechanism for improved glycemic control is the direct and substantial reduction of exogenous carbohydrate intake. In individuals with type 2 diabetes, the body's ability to manage the postprandial influx of dietary glucose is severely compromised due to insulin resistance and/or insufficient insulin secretion [75]. Carbohydrates, especially refined sugars and starches, represent the primary dietary driver of postprandial hyperglycemia [76]. By restricting carbohydrates to a minimal level, low-carbohydrate and ketogenic diets effectively remove this primary glycemic challenge. Without a large glucose load entering the bloodstream after a meal, the demand on the dysfunctional insulin signaling pathway is dramatically reduced [77]. This leads to an almost immediate blunting of postprandial glucose spikes, flattening the glycemic variability that is increasingly recognized as an independent contributor to diabetic complications.

This effect is independent of weight loss and can be observed within days of initiating the diet. It provides a foundational stability to the blood glucose profile, creating a predictable and low-glycemic environment. This stability is the first critical step away from the glucotoxic state that characterizes type 2 diabetes, allowing downstream metabolic organs, particularly the liver, to begin recalibrating their glucose metabolism.

Restoration of hepatic insulin sensitivity and suppression of gluconeogenesis

A core defect in type 2 diabetes is hepatic insulin resistance, which manifests as an unsuppressed overproduction of glucose by the liver, known as fasting hepatic glucose output. Even in the fast state, the liver of an individual with type 2 diabetes inappropriately dumps glucose into the bloodstream, contributing significantly to fasting hyperglycemia [78]. Lowering insulin levels via carbohydrate restriction plays a paradoxical but crucial role in addressing this. Chronically elevated insulin levels, a hallmark of the hyperinsulinemic state that precedes and accompanies type 2 diabetes, can induce hepatic insulin resistance through receptor downregulation and post-receptor desensitization [79, 80]. The sustained low insulin levels achieved on a low-carbohydrate and ketogenic diet help to resensitize the liver to insulin's action. As hepatic insulin sensitivity is restored, even a small amount of endogenous insulin can effectively signal the liver to suppress gluconeogenesis and reduce hepatic glucose output.

Furthermore, the reduced substrate availability for gluconeogenesis reinforces this effect. With lower levels of lactate, glycerol from lipolysis, and glucogenic amino acids (due to adequate dietary protein and suppressed proteolysis), the liver has both less signal and less raw material for excessive glucose production [81, 82]. The combination of restored insulin signaling and diminished substrate flux results in a rapid and significant decrease in fasting blood glucose levels, addressing a key contributor to overall hyperglycemia.

Medically assisted medication de-escalation

The profound and rapid reduction in both postprandial and fasting glucose levels creates a therapeutic scenario where the existing pharmacological regimen becomes excessive, posing a significant risk of hypoglycemia. This necessitates the pre-emptive and careful reduction or discontinuation of glucose-lowering medications, a process that is a direct consequence of the diet's efficacy [83]. This is the practical application of 'medically assisted carbohydrate restriction.' Insulin therapy and insulin secretagogues (e.g., sulfonylureas) carry the highest risk of hypoglycemia in this context and often require the most immediate and dramatic dose reduction [84]. For patients on high-dose insulin, reductions of 50% or more at the initiation of the diet are frequently necessary, with many patients able to completely discontinue insulin therapy within days to weeks [85]. This rapid de-escalation is a powerful demonstration of the diet's ability to address the root cause of dysglycemia.

This process transforms the management of type 2 diabetes from a perpetual cycle of treating high blood sugar with drugs to a strategy of removing the dietary cause and subsequently removing the now-redundant pharmacological intervention [86]. It empowers patients, reduces polypharmacy, minimizes side effects and treatment costs, and can serve as a powerful motivator for dietary adherence. The ability to achieve 'drug-free remission' is thus not a separate outcome, but the direct result of these interconnected mechanisms restoring intrinsic metabolic control.

Body Composition and Fat Partitioning

Beyond the number on the scale, the specific composition of weight loss and the location from which fat is lost are critical determinants of metabolic health improvement. Low-carbohydrate and ketogenic diets appear to exert favorable effects on body composition that extend beyond simple fat mass reduction, preferentially targeting the most metabolically detrimental fat depots [87]. This selective mobilization of fat is a key mechanism linking these diets to improved insulin sensitivity and reduced cardiometabolic risk. The 2 most significant fat depots in this context are visceral adipose tissue, located within the abdominal cavity, and ectopic fat, which accumulates in non-adipose organs like

the liver and skeletal muscle [88]. These depots are not inert storage sites; they are metabolically active, producing inflammatory cytokines and free fatty acids that directly contribute to insulin resistance and the pathogenesis of type 2 diabetes [89]. Consequently, the impact of dietary intervention on these specific depots is a more meaningful metric of their efficacy than total weight loss alone. Evidence suggests that low-carbohydrate and ketogenic diets are particularly effective at reducing visceral adipose tissue and ectopic fat, even under conditions of equivalent weight loss compared to other diets, highlighting a potential unique advantage for metabolic syndrome reversal [90, 91].

Preferential reduction of visceral adipose tissue

Visceral adipose tissue, the fat stored around the internal organs, is highly lipolytically active and strongly associated with insulin resistance, dyslipidemia, and systemic inflammation. The hormonal environment created by a low-carbohydrate and ketogenic diet is particularly conducive to the mobilization of this depot [92]. The sustained low insulin levels characteristic of nutritional ketosis releases the brake on hormone-sensitive lipase in all fat cells, but visceral adipose tissue appears to be exceptionally responsive to this signal due to its higher density of beta-adrenergic receptors and greater blood flow compared to subcutaneous fat [93]. Imaging studies, such as those using computed tomography or magnetic resonance imaging, have consistently demonstrated that low-carbohydrate and ketogenic diets studies where total weight loss was similar to that of a low-fat diet, suggesting a preferential targeting of this harmful fat depot [94]. The rapid loss of visceral adipose tissue contributes disproportionately to early improvements in hepatic and peripheral insulin sensitivity, as it directly reduces the flux of inflammatory adipokines and free fatty acids to the liver via the portal circulation.

The reduction of visceral adipose tissue is therefore not merely a cosmetic change but a fundamental therapeutic outcome. By depleting this pathogenic fat store, low-carbohydrate and ketogenic diets directly mitigate a key driver of metabolic disease. This rapid improvement in the core defect of adiposopathy helps to explain the swift glycemic benefits often seen in clinical practice, which can occur before substantial total weight loss is achieved.

Mobilization of ectopic fat in liver and muscle

Ectopic fat accumulation, particularly in the liver (hepatic steatosis) and within skeletal muscle cells (intramyocellular lipids), is a hallmark of severe insulin resistance. The liver and muscle, overwhelmed by a constant influx of fatty acids and dietary carbohydrates that promote de novo lipogenesis, begin storing triglycerides, which interfere with their normal insulin signaling pathways [95, 96]. Low-carbohydrate and ketogenic diets directly address this lipid overflow. In the liver, the combination of low insulin and low substrate for de novo lipogenesis (due to absent dietary carbohydrates) halts the primary drivers of fat accumulation [97]. Simultaneously, the elevated fatty acid oxidation and ketogenic state actively promote the burning and export of existing liver fat as ketone bodies. Magnetic resonance spectroscopy studies have shown that very-low-carbohydrate diets can produce rapid and dramatic reductions in liver fat content, often normalizing it within a matter of weeks, which is crucial for restoring hepatic insulin sensitivity.

Similarly, in skeletal muscle, the shift to fat and ketone body oxidation reduces the reliance on glucose and the subsequent accumulation of lipid intermediates like diacylglycerols and ceramides, which are known to disrupt the insulin signaling cascade [98]. By 'unclogging' the mitochondria with a clean-burning fat-derived fuel (ketones) and reducing the toxic lipid byproducts of incomplete fatty acid oxidation, low-carbohydrate and ketogenic diets help restore insulin-mediated glucose uptake into muscle [99]. This clearance of ectopic fat from key metabolic organs is a central mechanism for reversing the underlying insulin resistance that defines type 2 diabetes.

Preservation of lean mass during weight loss

A primary concern with any weight loss diet is the potential for the loss of lean body mass, which includes skeletal muscle, alongside fat mass. A loss of lean body mass can lower resting metabolic rate and impair physical function, undermining long-term weight maintenance [100]. The evidence suggests that when protein intake is adequate, low-carbohydrate and ketogenic diets are highly effective at preserving lean body mass, often outperforming or matching other dietary approaches [101]. Several factors contribute to this favorable outcome. The elevated ketone bodies, particularly beta-hydroxybutyrate, may have an anti-catabolic effect by suppressing proteolysis (muscle breakdown) [102]. Furthermore, the consistent energy supply from fat and ketones provides a stable substrate for muscle, preventing the body from needing to break down muscle protein for gluconeogenesis to a significant extent, as the brain's energy needs are largely met by ketones [103].

When compared to isocaloric low-fat diets, meta-analyses of controlled trials often show that very-low-carbohydrate ketogenic diets result in a similar or superior fat-to-lean mass loss ratio. The high satiety of protein and fat can lead to a spontaneous reduction in caloric intake without protein deficiency, ensuring the body retains its metabolically active muscle tissue while drawing down energy reserves from adipose tissue, visceral adipose tissue, and ectopic fat stores [104]. This preservation of functional lean mass ensures that the weight loss is primarily pathogenic fat, maximizing the health benefits per pound lost.

Impact on Lipid Metabolism and Cardiovascular Risk Factors

The impact of low-carbohydrate and ketogenic diets on lipid profiles and cardiovascular risk markers is complex and often misunderstood, characterized by both highly consistent, beneficial changes and a variable, potentially concerning response that requires careful interpretation. The classic lipid triad observed on a well-formulated low-carbohydrate and ketogenic diet includes a dramatic reduction in triglycerides, a substantial increase in high-density lipoprotein cholesterol, and a variable response in low-density lipoprotein cholesterol [105]. This pattern represents a significant shift from the atherogenic dyslipidemia commonly associated with insulin resistance. The most rapid and consistent beneficial change is a profound reduction in fasting and postprandial triglycerides. This effect is primarily driven by 2 mechanisms. First, the reduction in dietary carbohydrates decreases the substrate for hepatic de novo lipogenesis and the production of very low-density lipoproteins, the primary carrier of triglycerides in the fasting state [46]. Second, the low-insulin state enhances lipoprotein lipase activity in peripheral tissues, increasing the clearance of triglyceride-rich lipoproteins from the circulation [106].

Concurrently, high-density lipoprotein cholesterol levels typically rise significantly. This increase is mechanistically linked to the reduction in triglycerides. As triglyceride-rich lipoproteins are cleared from the blood, there is less exchange of core lipids between them and high-

density lipoprotein particles via cholesteryl ester transfer protein [107]. With less triglyceride enrichment, high-density lipoprotein particles become larger, more cholesterol-rich, and are catabolized more slowly, leading to higher circulating concentrations. This rise in high-density lipoprotein cholesterol is considered a favorable shift, though its direct causal role in atherosclerosis remains debated. The most variable and clinically debated lipid response is in low-density lipoprotein cholesterol levels. While many individuals experience stable or even decreased low-density lipoprotein cholesterol on a low-carbohydrate and ketogenic diet, a significant minority, often termed 'lean mass hyper-responders,' may exhibit a substantial increase [108]. This rise is thought to be driven by several factors, including the high dietary saturated fat intake in some versions of the diet, which can upregulate low-density lipoprotein receptor activity in a variable manner, and a shift in the body's preferred fuel carrier from triglyceride-rich lipoproteins to cholesterol-rich low-density lipoprotein.

Beyond the concentration of low-density lipoprotein cholesterol, the quality of low-density lipoprotein particles undergoes a significant and generally beneficial transformation. Low-carbohydrate and ketogenic diets consistently promote a shift in low-density lipoprotein subclass distribution from small, dense pattern B particles to large, buoyant pattern A particles [109]. This is a direct consequence of the low triglyceride environment, as cholesterol ester-rich low-density lipoprotein particles are not subjected to high levels of cholesteryl ester transfer protein-mediated triglyceride enrichment and subsequent hepatic lipase-mediated remodeling into small, dense particles. This shift in particle size is metabolically critical. Small, dense low-density lipoprotein particles are more strongly associated with cardiovascular risk because they are more prone to oxidation, have greater arterial wall permeability, and have lower affinity for the low-density lipoprotein receptor, leading to a longer circulation time. In contrast, the large, buoyant low-density lipoprotein particles that predominate on a low-carbohydrate and ketogenic diet are less atherogenic. Therefore, even in the context of a rising total low-density lipoprotein cholesterol, a shift towards a less atherogenic particle phenotype may modify the associated risk [110].

A more comprehensive assessment of atherogenic risk involves apolipoprotein B, which is a single molecule on each low-density lipoprotein, very-low-density lipoproteins, and intermediate-density lipoprotein particle. Since there is one apolipoprotein B per atherogenic particle, it is considered a superior marker of cardiovascular risk than low-density lipoprotein cholesterol alone [111]. On a low-carbohydrate and ketogenic diet, the dramatic reduction in very-low-density lipoproteins (a major contributor to the apolipoprotein B count) often leads to a less pronounced increase in apolipoprotein B than in low-density lipoprotein cholesterol, and in many cases, apolipoprotein B may remain stable or even decrease, suggesting the total number of atherogenic particles may not rise proportionally to the low-density lipoprotein cholesterol concentration [112]. Beyond the standard lipid panel, low-carbohydrate and ketogenic diets exert positive effects on other cardiovascular risk factors [113]. A common and rapid effect is a reduction in blood pressure, attributable to several factors, including enhanced sodium and water excretion due to lower insulin levels (insulin promotes sodium reabsorption in the kidneys), weight loss, and reduced inflammation. This can lead to significant improvements in hypertension, a major component of metabolic syndrome.

Furthermore, the overall metabolic context of a successful low-carbohydrate and ketogenic diet intervention must be considered. The diet often leads to powerful improvements in core drivers of cardiovascular disease, including reduced insulin resistance, lower glucose levels, decreased visceral and ectopic fat, and attenuated postprandial lipemia [114]. These systemic improvements create a metabolic environment that is fundamentally less pro-inflammatory and less pro-atherogenic, which may counterbalance concerns about an isolated rise in low-density lipoprotein cholesterol in some individuals.

In summary, the impact of low-carbohydrate and ketogenic diets on cardiovascular risk is multifaceted. The consistent improvements in triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein particle size, blood pressure, and underlying insulin resistance represent a potent anti-atherogenic package. The highly variable low-density lipoprotein cholesterol response, however, necessitates a personalized approach. Clinicians should consider advanced lipid testing (including low-density lipoprotein particle number and size or apolipoprotein B) and view lipid changes within the broader context of the patient's overall metabolic health improvement when evaluating the net cardiovascular benefit.

Clinical Trials

A randomized controlled trial by Yancy et al. [115] comparing a low-carbohydrate, ketogenic diet with a low-fat diet for treating obesity and hyperlipidemia which yielded several significant findings over 24 weeks (Figure 1). The low-carbohydrate diet group showed better participant retention compared to the low-fat diet group. Specifically,

Variable	Low-Fat Diet Group (n = 60)				Low-Carbohydrate, Ketogenic Diet Group (n = 59)				*P* Value for Between-Group Comparison
	Week 0	Week 24	Change	*P* Value	Week 0	Week 24	Change	*P* Value	
Total cholesterol level, *mmol/L (mg/dL)*	6.20 (239.9)	5.85 (226.2)	−0.35 (−13.7)	0.008	6.32 (244.5)	6.11 (236.4)	−0.21 (−8.1)	0.08	>0.2
Triglyceride level, *mmol/L (mg/dL)*	2.15 (190.7)	1.84 (162.7)	−0.31 (−27.9)	0.02	1.78 (157.8)	0.94 (83.6)	−0.84 (−74.2)	<0.001	0.004
LDL cholesterol level, *mmol/L (mg/dL)*	3.83 (148.0)	3.64 (140.6)	−0.19 (−7.4)	0.2	4.07 (157.2)	4.11 (158.8)	0.04 (1.6)	>0.2	0.2
HDL cholesterol level, *mmol/L (mg/dL)*	1.40 (54.1)	1.36 (52.5)	−0.04 (−1.6)	>0.2	1.43 (55.4)	1.57 (60.9)	0.14 (5.5)	<0.001	<0.001
Ratio of total cholesterol to HDL cholesterol	4.7	4.4	−0.3	0.09	4.7	4.1	−0.6	<0.001	0.09
Ratio of triglyceride to HDL cholesterol	4.1	3.4	−0.6	0.02	3.2	1.6	−1.6	<0.001	0.02

* Values are expected means by linear mixed-effects model analysis. HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Figure 1: Effect of diet programs on fasting lipid profiles [115].

76% of participants in the low-carbohydrate group completed the study, whereas only 57% of those in the low-fat group did, a statistically significant difference ($p = 0.02$). During the 24 weeks, the low-carbohydrate diet group experienced significantly greater weight loss than the low-fat diet group. The mean change in weight was -12.9% for the low-carbohydrate group versus -6.7% for the low-fat group ($p < 0.001$). Both groups lost substantial fat mass. The low-carbohydrate diet led to a -9.4 kg reduction in fat mass, while the low-fat diet resulted in a -4.8 kg reduction. Fat-free mass also decreased in both groups, with changes of -3.3 kg for the low-carbohydrate diet and -2.4 kg for the low-fat diet. Participants on the low-carbohydrate diet had significantly greater decreases in serum triglyceride levels compared to those on the low-fat diet (change of -0.84 mmol/L (-74.2 mg/Dl) vs. -0.31 mmol/L (-27.9 mg/dL); $p = 0.004$). The low-carbohydrate diet group experienced greater increases in high-density lipoprotein cholesterol levels (0.14 mmol/L (5.5 mg/dL)) compared to a decrease in the low-fat diet group (-0.04 mmol/L (-1.6 mg/dL); $p < 0.001$). There was no statistically significant difference in the changes in low-density lipoprotein cholesterol levels between the two groups. The low-carbohydrate diet showed a change of 0.04 mmol/L (1.6 mg/dL), and the low-fat diet showed a change of -0.19 mmol/L (-7.4 mg/dL) ($p = 0.2$). Minor adverse effects were more frequently reported in the low-carbohydrate diet group. The study noted limitations, including the inability to definitively distinguish the effects of the low-carbohydrate diet from those of nutritional supplements provided exclusively to that group. Additionally, participants were healthy, and the follow-up period was limited to 24 weeks, which restricts the generalizability of the findings. In summary, the study concluded that the low-carbohydrate diet program demonstrated better participant retention and greater weight loss than the low-fat diet. During the active weight loss phase, the low-carbohydrate diet also led to more significant reductions in serum triglyceride levels and greater increases in high-density lipoprotein cholesterol levels.

A study by Cicero et al. [116] investigated the middle and long-term impact of a very low-carbohydrate ketogenic diet on cardiometabolic factors in a general practice setting. The key findings demonstrate significant improvements across various health markers, which were largely maintained over the observation period (Figure 2). Patients experienced a substantial reduction in body weight. From baseline to 4 weeks, there was a decrease of -7 ± 5 kg ($p < 0.001$), followed by an additional -5 ± 3 kg ($p < 0.001$) from 4 to 12 weeks. After one year, the mean total body weight loss was 14 ± 10 kg. Body mass index also significantly improved, with a reduction of -3 ± 2 kg/m^2 ($p < 0.001$) from baseline to 4 weeks, and a further -2 ± 2 kg/m^2 ($p < 0.001$) from 4 to 12 weeks. The total mean body mass index loss after one year was 5 ± 3 kg/m^2. Waist circumference showed significant improvement, decreasing by -7 ± 4 cm ($p < 0.001$) from baseline to 4 weeks, and an additional -5 ± 7 cm ($p < 0.001$) from 4 to 12 weeks. The total mean reduction after one year was 13 ± 7 cm. The estimated percentage of body fat significantly improved by $-3.8 \pm 3.8\%$ ($p < 0.001$) from baseline to 4 weeks, and $-3.4 \pm 3.5\%$ ($p < 0.001$) from 4 to 12 weeks. After one year, the mean total body fat loss was $8.1 \pm 5.9\%$. Systolic blood pressure significantly improved by -10.5 ± 6.4 mmHg ($p < 0.001$) from baseline to 3 months, with no further changes observed after one year. Diastolic blood pressure and pulse pressure showed similar trends. Fasting plasma glucose significantly improved by -8.7 ± 15.3 mg/dL ($p < 0.001$) from baseline to 4 weeks, with stability thereafter. Glycated hemoglobin (HbA1c) also improved by -0.3 ± 0.7 mg/dL ($p < 0.001$) from baseline to 3 months and remained steady. Low-density lipoprotein cholesterol

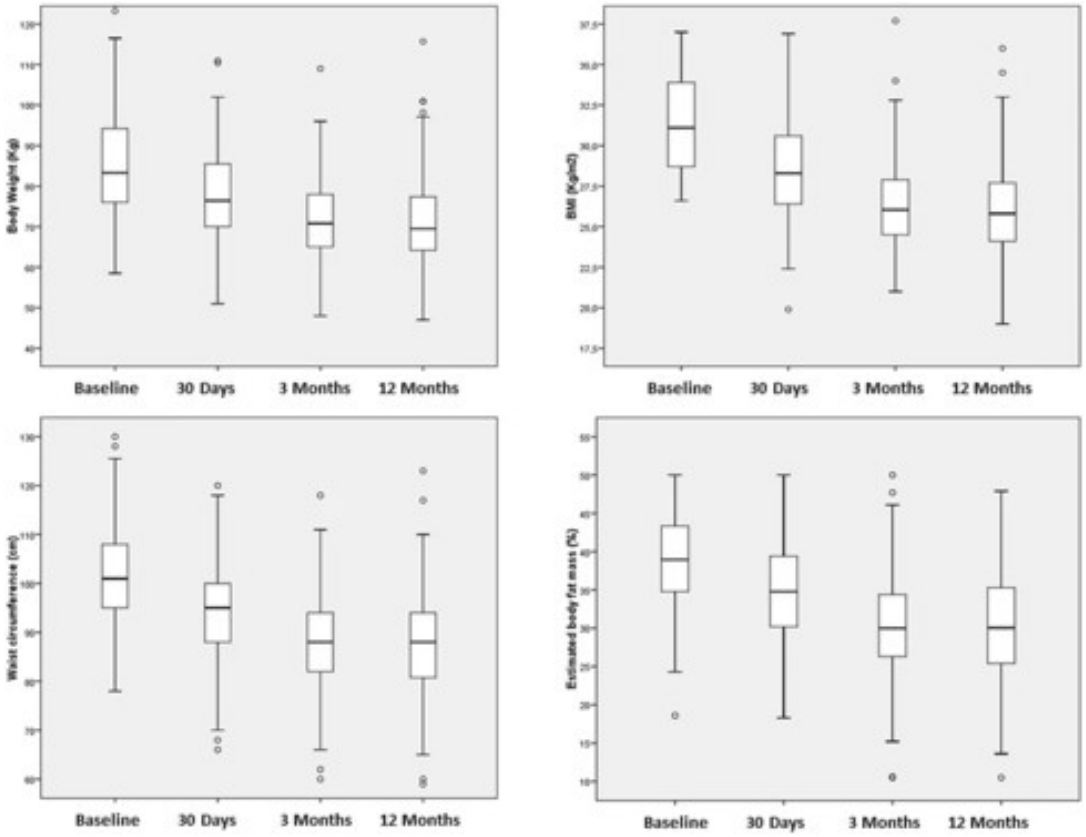

Figure 2: Body weight, body mass index, waist circumference, and estimated body fat mass changes during the different study phases [116].

significantly improved by -19.5 ± 16.9 mg/dL ($p < 0.001$) from baseline to 3 months. Triglycerides also improved by -23.4 ± 30.2 mg/dL ($p < 0.001$). High-density lipoprotein cholesterol improved by +1.8 ± 5.6 mg/dL ($p = 0.038$) from baseline to 4 weeks and further improved by +3.5 ± 3.3 mg/dL ($p < 0.001$) after 12 months. Liver transaminases (AST and ALT) significantly improved from 1 to 3 months, with gamma-GT improving from baseline to 4 weeks. These improvements were sustained over the observation period. Estimated glomerular filtration rate, creatinine, and microalbuminuria were not significantly modified. Uricemia showed a mild but significant improvement of -0.4 ± 1.5 mg/dL ($p = 0.048$) from the 3rd month to the end of the study. The study concluded that the very low-carbohydrate ketogenic diet, when managed by trained general physicians in a clinical practice setting, significantly improves a range of anthropometric, hemodynamic, and metabolic parameters related to cardiovascular disease risk in the middle term, with these improvements largely maintained on the long-term, and an overall good tolerability.

An open-label pilot study by Tzenios et al. [113] (NCT04195594) investigated the efficacy of a very-low-carbohydrate ketogenic diet over 140 days on cardiometabolic markers in healthy adults with mildly elevated low-density lipoprotein cholesterol (Figure 3). The study found several significant changes in body composition and cardiometabolic markers, indicating potential benefits and safety of the diet. Participants experienced a significant decrease in body fat percentage, specifically a 2.25% reduction by day 70 and a 4.41% reduction by day 140. This reduction was also observed in android and gynoid fat percentages, leading to a decrease in the android/gynoid fat ratio. Muscle mass increased by 2.24% on day 70 and 4.38% on day 140. This suggests that weight loss was primarily due to fat loss rather than muscle loss. A significant reduction in body weight was noted on day 28, maintained until day 140, resulting in a 10.65% reduction from baseline. Consequently, the mean body mass index decreased by 6.2% on day 70 and 10.6% on day 140, changing from an overweight to a normal weight category. Total cholesterol and low-density lipoprotein cholesterol levels increased from baseline across all study visits, including day 140. However, these levels generally remained within acceptable laboratory ranges for the study population and were not considered clinically relevant. A significant 12.8% increase in high-density lipoprotein cholesterol was observed, with 73% of participants showing increased high-density lipoprotein cholesterol by day 140. This increase is considered clinically relevant, as a 1% increase in high-density lipoprotein cholesterol is associated with a 2

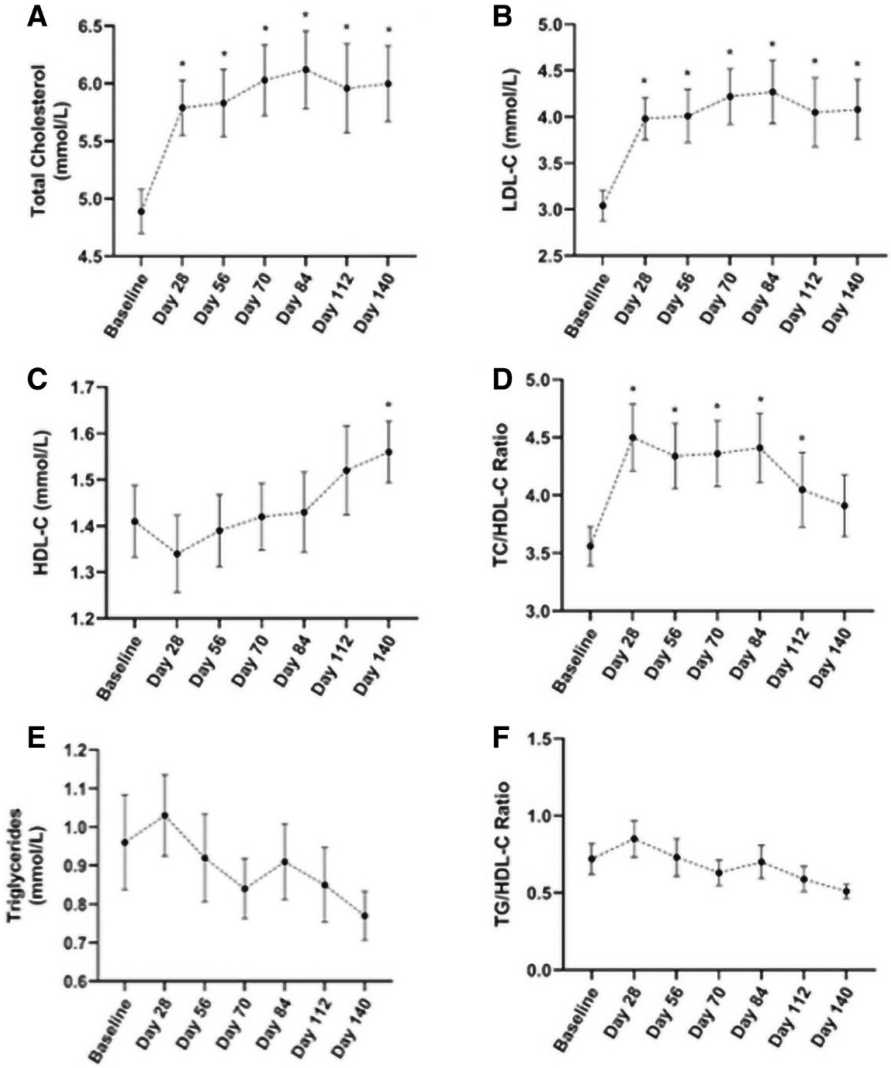

Figure 3: Mean total cholesterol **(A)**, low-density lipoprotein cholesterol **(B)**, high-density lipoprotein cholesterol **(C)**, total cholesterol/high-density lipoprotein cholesterol ratio **(D)**, triglycerides **(E)**, and triglyceride/high-density lipoprotein cholesterol ratio **(F)** from baseline to day 140 of participants following a very-low-carbohydrate ketogenic diet [113].

to 3% reduction in cardiovascular disease risk. No significant change was observed in triglycerides levels or the triglycerides/high-density lipoprotein cholesterol ratio during the study. Systolic blood pressure decreased by 5.3% from baseline by day 140. A reduction in glycated hemoglobin was observed by day 140. Free triiodothyronine (T3) levels also decreased by day 140. Other markers: no significant changes were found in fasting glucose, erythrocyte sedimentation rate, or C-reactive protein. Participants significantly reduced daily calorie intake by 594 kcal and showed a significant reduction in carbohydrate intake, with a corresponding increase in fat intake. The macronutrient composition aligned with the very low-carbohydrate ketogenic diet requirements (5% carbohydrates, 70% fat, and 25% protein), confirming participant compliance. Mean ketone concentrations increased from 0.52 mmol/L at pre-intervention to 0.81 mmol/L on day 140, and the glucose ketone index improved. A total of 44 post-emergent adverse events were reported, with 13 possibly related to the diet, primarily gastrointestinal issues such as constipation, diarrhea, heartburn, nausea, and vomiting. All adverse events were resolved by day 140. Hematology, clinical chemistry, electrolytes, and liver and kidney function markers remained within healthy clinical reference ranges, and no clinically relevant electrocardiogram or heart rate findings were observed. The diet was found to be safe and well-tolerated. In summary, the study indicates that the very-low-carbohydrate ketogenic diet led to beneficial changes in body composition, including significant fat loss and muscle gain, and improvements in several cardiometabolic markers such as systolic blood pressure, glycated hemoglobin, and high-density lipoprotein cholesterol, while being generally well-tolerated. The observed increases in total cholesterol and low-density lipoprotein cholesterol were deemed not clinically relevant given the context of the study population. These findings suggest a potential role for very-low-carbohydrate ketogenic diet in managing cardiovascular disease risk, warranting further research with larger, randomized controlled trials

Comparative Efficacy: Low-carbohydrate and Ketogenic Diets vs Other Dietary Patterns

When evaluating the efficacy of any dietary strategy, it is essential to compare its outcomes against other established dietary patterns, such as low-fat and Mediterranean diets, within the rigorous context of randomized controlled trials. These comparisons reveal a nuanced picture of the relative strengths of low-carbohydrate and ketogenic diets, particularly concerning the outcomes of weight loss and glycemic control, and underscore the critical role of long-term adherence.

In the short term (typically defined as 6 months or less), low-carbohydrate and ketogenic diets consistently demonstrate superior efficacy for weight loss and improvements in glycemic parameters compared to low-fat diets [117]. Randomized controlled trials often show significantly greater reductions in body weight, body fat percentage, and fasting insulin levels in the low-carbohydrate and ketogenic diet groups [118]. This early advantage is also pronounced in glycemic control, with low-carbohydrate and ketogenic diets leading to greater reductions in hemoglobin A1c and a higher likelihood of reducing or discontinuing glucose-lowering medications in individuals with type 2 diabetes. This short-term superiority can be attributed to the potent physiological mechanisms previously discussed. The rapid initial weight loss is driven by glycogen depletion and associated water loss, heightened satiety from protein and fat leading to spontaneous caloric reduction, and the metabolic effects of ketosis [117]. The dramatic improvement in glycemia is a direct result of removing dietary carbohydrates, the primary driver of postprandial hyperglycemia.

However, a common finding in the literature is that this significant advantage tends to be attenuated over longer follow-up periods (1 to 2 years). In many long-term randomized controlled trials, the difference in weight loss between low-carbohydrate and ketogenic diets and low-fat diets narrows and often ceases to be statistically significant [119]. Similarly, while glycemic benefits often persist, the magnitude of difference between dietary groups may decrease over time. This convergence of outcomes highlights the challenge of sustained dietary adherence. This phenomenon points to a fundamental principle in nutritional science: the long-term success of a diet is less about its macronutrient composition per se and more about an individual's ability to adhere to it consistently. All dietary interventions face the challenge of declining compliance over time [120]. The initial rapid results and high satiety of a low-carbohydrate and ketogenic diet may boost motivation early on, but long-term sustainability can be challenged by factors such as dietary restrictiveness, social pressures, and monotony.

When compared to the Mediterranean diet, which emphasizes fruits, vegetables, whole grains, legumes, and olive oil, the comparative outcomes become even more nuanced [121]. Some studies show similar efficacy between low-carbohydrate and ketogenic diets and Mediterranean diets for weight loss and glycemic control, while others show context-dependent advantages. The Mediterranean diet is well-established for primary and secondary prevention of cardiovascular events, an outcome for which long-term data on low-carbohydrate and ketogenic diets is still maturing [122]. A key differentiator that often emerges from these comparative trials is not just the degree of weight loss, but the quality of metabolic improvements. Even in studies where total weight loss converges, low-carbohydrate and ketogenic diets often maintain a more favorable impact on specific metabolic markers, such as producing greater increases in high-density lipoprotein cholesterol and greater reductions in triglycerides compared to isocaloric low-fat diets [123]. This suggests a unique cardiometabolic benefit independent of the weight loss itself. The choice between dietary patterns, therefore, is not a matter of identifying a single 'best' diet for all. Instead, the evidence supports a patient-centered or personalized medicine approach [124]. For some individuals, particularly those with insulin resistance, prediabetes, or type 2 diabetes, the potent early glycemic benefits of a low-carbohydrate and ketogenic diet can be transformative and provide the motivation needed for sustained lifestyle change. The ability to see rapid results can be a powerful catalyst.

Ultimately, the comparative efficacy of low-carbohydrate and ketogenic diets is robust in the short term and remains significant for specific metabolic parameters in the long term. The tendency for weight loss convergence in long-term studies across all dietary types underscores that no diet is a passive cure; all require ongoing behavioral commitment. The 'best' diet is ultimately the one that is medically appropriate, nutritionally adequate, and that an individual can adhere to over the long term, making dietary adherence the ultimate mediator of comparative efficacy.

Conclusion

In conclusion, low-carbohydrate and ketogenic diets function as potent therapeutic tools for weight loss and type 2 diabetes remission through a coordinated series of metabolic and hormonal adaptations. The evidence robustly demonstrates that the mechanisms extend far beyond simple caloric restriction, encompassing a fundamental shift in fuel metabolism, a hormonally enabled state of fat mobilization, direct improvements in glycemic control, and beneficial partitioning of body

composition. These diets effectively target the core pathophysiological defects of metabolic syndrome, including hyperinsulinemia, insulin resistance, and ectopic fat accumulation, offering a viable pathway to drug-free remission for a substantial proportion of patients.

Looking ahead, the future of these dietary strategies lies in refining their application through personalized medicine and resolving outstanding questions of long-term sustainability. Future research must prioritize large-scale, long-term trials to definitively establish cardiovascular safety outcomes and durability of remission. Furthermore, investigation into the molecular roles of ketone bodies as signaling molecules, the interplay with the gut microbiome, and the identification of genetic or phenotypic predictors of response will be crucial. This evolving evidence base will empower clinicians to more precisely identify which patients will benefit most, ultimately integrating low-carbohydrate and ketogenic diets as powerful, mechanism-driven options within the broader spectrum of nutritional therapeutics.

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None.

Conflict of Interest

None.

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