

Exploring the Therapeutic Potential of the Ketogenic Diet in Autoimmune Disorders: A Comprehensive Review

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Abstract: Autoimmune diseases, marked by the immune system erroneously targeting healthy cells, pose significant health challenges. The ketogenic diet, characterised by high fat, low carbohydrate, and moderate protein intake, has garnered attention for its anti-inflammatory, and thus autoimmune mediating, effects. Additionally, the diet shows promise in improving metabolic markers, suggesting potential benefits for autoimmune conditions with metabolic components. The paper focuses on specific autoimmune disorders, namely multiple sclerosis and rheumatoid arthritis, delving into existing studies to discern the impact of ketogenic diets. By examining the current scientific literature, the paper aims to illuminate the potential role of the ketogenic diet in the management of autoimmune disorders. The focus on specific conditions provides a nuanced understanding of the diet's implications. The findings underscore the need for more robust research efforts in this domain, advocating for further exploration of the diet's efficacy and safety. As our understanding of the intricate interplay between diet and autoimmune responses evolves, this research serves as a stepping-stone toward establishing the ketogenic diet as a credible and viable therapeutic strategy for autoimmune disorders.

Keywords: Ketogenic Diet, Autoimmune Disorders, Multiple Sclerosis, Rheumatoid Arthritis, Therapeutic Strategy

1. Introduction

Although autoimmune disorders were once thought to be an uncommon possibility, they are today recognised as some of the most common noncommunicable diseases worldwide. The field of autoimmunity has greatly advanced in understanding. Today, we have a solid understanding of the macro structural and micro molecular mechanisms underlying autoimmunity (Chandrashekar 2012, 665). The theories of causality which studied such molecular mechanisms have expanded now to include how a disease spreads through novel mechanisms like clones which break down immunity at various points. (Chandrashekar 2012, 665). The way we currently understand immunology in autoimmune diseases and their spread has consequently evolved dramatically.

Within this framework of immunity, autoimmune diseases can best be understood by first understanding the concept of the immune system. A robust immune system protects the body against illness and infection. However, when the immune system isn't working properly, it starts attacking healthy tissues, cells, and organs. These attacks, which form the basis of autoimmune diseases, can impact every area of the body, impairing physiological function and even posing a threat to life (National Institute of Environmental Health Sciences, n. d.).

There are around 80 autoimmune illnesses that are known to scientists like lupus, rheumatoid arthritis, multiple sclerosis, and type 1 diabetes (National Institute of Environmental Health Sciences n. d.). Patients with uncommon autoimmune illnesses may endure years of suffering prior to receiving an accurate diagnosis. While there is typically no treatment for autoimmune illnesses, they can often be managed. Historically, the following have been used as treatments – anti-inflammatory drugs, corticosteroids, painkilling medications, immunosuppressant drugs, physical therapy

and so on. (National Institute of Environmental Health Sciences n. d.) However, scientists have been actively exploring better and more effective cures for autoimmune diseases (Better Health Channel n. d.).

This paper seeks to add to the ongoing research about the treatment of autoimmune diseases. It focuses on the impact ketogenic diets can have on autoimmune diseases – particularly, rheumatoid arthritis and multiple sclerosis. The first part of the paper is devoted to describing the ketogenic diet and molecular mechanisms of the ketogenic diet that aid in autoimmunity. This section also notes the need for further research in this area. The next part of the paper examines the effect of ketogenic diet on anti-inflammatory molecular mechanisms with a special focus on multiple sclerosis and rheumatoid arthritis. It describes the molecular mechanisms involved in the inflammatory processes of multiple sclerosis and rheumatoid arthritis. It concludes by summarising the state of research in the field and suggesting pathways for future research and policy action.

2. The Ketogenic Diet

In 1921, Russell Wilder utilised the ketogenic diet for the first time to treat epilepsy. Additionally, he created the term "ketogenic diet" (Masood et al, 2023). The ketogenic diet is a nutritional strategy designed to promote energy, improve mental clarity, and aid in weight loss (Masood et al, 2023). The main components of a ketogenic diet are low carbohydrate intake, moderate protein intake, and high fat intake. Generally speaking, the distribution of macronutrients is as follows:

Macronutrient Name	Percentage Range
Fat	55% - 60%
Protein	30% - 35%
Carbohydrates	5% - 10%

Volume 13 Issue 2, February 2024

Fully Refereed | Open Access | Double Blind Peer Reviewed Journal

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The daily carbohydrate limit on a diet of 2000 kilocalories would be about 20 to 50 grammes (Masood et al, 2023). This significant restriction on carbohydrates, causes the body to use ketones and fatty acids instead of glucose as its main energy source. These can be produced from dietary fats and proteins as well as from endogenous sources such as glycogen and adipose reserves through lipolysis. The process of ketogenesis involves the conversion of acetyl - CoA into ketone bodies due to the faster mobilisation rate of fatty acids from adipose tissue (Ciaffi et al.2021, 2 - 3). The liver is the primary site of ketogenesis, and it has two mechanisms to make ketone bodies. The first mechanism involves the direct conversion of amino acids into ketone bodies or the oxidation of fatty acids to acetyl - CoA, the building blocks of the ketone bodies. This results in the synthesis of beta - hydroxybutyrate, acetoacetate, and acetone (Ciaffi et al.2021, 3 - 4). However, because succinyl CoA: 3 - ketoacid CoA transferase is absent, the liver is unable to use ketone bodies. Consequently, extrahepatic tissues use ketone bodies as fuel, sparing glucose metabolism. Under these conditions, most of the glucose needed by the brain is replaced by ketone bodies, while the limited amount of energy necessary by glucose - dependent tissues is provided by liver gluconeogenesis (Ciaffi et al.2021, 4). The balance between ketone body synthesis (ketogenesis) and breakdown (ketolysis), which is primarily regulated by insulin and glucagon release, determines the amount of ketone bodies in circulation (Ciaffi et al.2021, 2).

1) Autoimmunity and the Ketogenic Diet: Molecular Mechanisms

To understand how ketogenic diets can help in cases of autoimmunity, we need to understand how inflammation and autoimmunity are connected. Inflammation is a normal physiological defence against pathogen infection and tissue damage and quickly subsides in normal circumstances. Pro - inflammatory and anti - inflammatory cytokine production regulates systemic inflammation. Systemic inflammation is then either reduced or increased because of changes in the balance of these mediators. The three primary factors which are associated with the effects of ketogenic diet on systemic inflammation are: (1) decreased insulin, (2) increased glucagon, and (3) reduced betahydroxybutyrate production (Ciaffi et al.2021, 3). Ketogenic diets aid in insulin reduction and that has shown health benefits in various studies of weight loss, seizure reduction, cognitive function, and so on. Insulin and chronic hyperinsulinemia are associated with an increase of the pro - inflammatory cytokines TNF - α , IL - 1 α , IL - 1 β , IL - 6, and leptin. (Ciaffi et al.2021, 3). Moreover, reduced betahydroxybutyrate leads to an effect on the NLRP3 inflammasome complex which itself is involved in monocyte - induced inflammation. When activated, the complex induces caspase 1 which suppresses, through a complex mechanism, pro - inflammatory cytokine production, including TNF - α , IL - 6, IL - 12, and IL - 1 (Ciaffi et al.2021, 4). Finally, glucagon increase is directly related to the decrease in insulin. Glucagon is an important hormone that can affect the working of many systems – including the immune system. It activates the cyclic adenosine monophosphate pathway which suppresses the release of pro - inflammatory mediators including TNF - α , IL - 17, IFN - γ (Ciaffi et al.2021, 4 - 5).

Following a ketogenic diet has some potential to be a therapeutic option as it works against inflammation through multiple mechanisms. One key mechanism involves suppressing the synthesis of the IL - 2 element in macrophages and neutrophils (Ciaffi et al.2021, 5 - 6). This happens through the action of beta - hydroxybutyrate, one of the key ketone bodies utilized for energy generation. It works by inhibiting nicotinamide adenine dinucleotide (NAD⁺) induced inflammation, and thus reducing tumour necrosis factor - alpha (Ciaffi et al.2021, 5 - 6). Two distinct receptors attach themselves to TNF - α , initiating signal transduction pathways. Numerous biological reactions, such as cell survival, differentiation, and proliferation, are triggered by these pathways (Jang et al.2021, 1). Autoimmune disorders are linked to the incorrect or overactivation of TNF - α signalling. Presently, TNF - α inhibitors that have been approved for clinical use have demonstrated significant effectiveness in treating several autoimmune disorders, and new TNF - α signalling inhibitors are undergoing clinical trials (Jang et al.2021, 1). BHB ketone body also suppresses the action of inflammatory IL - 1, IL - 12, and IL - 6 and IL - 18 through the activation of hydroxycarboxylic acid receptor (HCAr) and through its effect on NOD - like receptor protein 3 (NLRP3), and thus contributes to decreased inflammation (Ciaffi et al.2021, 5).

Additionally, a well - formulated ketogenic diet is usually achieved with the inclusion of enough sources of fibre from foods like avocado, seeds, nuts, coconut, spinach, broccoli, cauliflower, and berries. When combined, these high - nutrient prebiotic foods would raise the numbers of *Bacteroides* and *Bifidobacterium* while lowering the numbers of *Firmicutes*, thus having a beneficial effect on the gut microbiome and subsequently overall health (DOWIS ET AL.2021, 20 - 21).

An understanding of the molecular mechanisms that spur autoimmunity can also aid in responding to autoimmune conditions. The next section examines and builds on how ketogenic diets can prove to be a therapeutic intervention for multiple sclerosis and rheumatoid arthritis.

2) Discussion on Rheumatoid Arthritis and Multiple Sclerosis

This section is divided into two sub - parts: the first one describes what rheumatoid arthritis is and the impact of a ketogenic diet on rheumatoid arthritis, and the second sub - part describes what multiple sclerosis is and the impact of a ketogenic diet on multiple sclerosis.

3) Rheumatoid Arthritis and Ketogenic Diet

Rheumatoid arthritis results from the immune system unintentionally attacking healthy cells in the body, which in turn causes inflammation (painful swelling) in the affected body parts (Centers for Disease Control and Prevention, 2022). Although the precise origins of rheumatoid arthritis are unknown, a number of variables can raise one's risk of getting the illness (Centers for Disease Control and Prevention, 2022). It mostly targets the knees, wrists, and joints and as such, results in inflammation of the joint lining, which damages the tissue within the joint (Centers for Disease Control and Prevention, 2022). This tissue injury

can result in deformity (misshapeness), unsteadiness (loss of balance), and chronic or persistent pain. It can also have an impact on other body areas and lead to issues with organs like the heart, lungs, and eyes (Centers for Disease Control and Prevention, 2022).

Interestingly, a recent study was done exploring the impact of inducing the state of ketosis through the supplementation of medium - chain fatty acids (MCFAs) in a group of 61 patients with rheumatoid arthritis over a period of several weeks. The preliminary findings of the study implied that, according to the Simplified Disease Activity Index used, there had been a significant decrease in the amount of disease activity in the patients (Heidt et al.2019, 10 - 11). An increased amount of β - hydroxybutyrate was also noted. Though the mechanisms by which this effect may take place are unclear, the researchers hypothesise that this may be due to effects on the gut barrier or on autoimmune mechanisms (Heidt et al.2019, 10 - 11). The study's findings suggest a potential link between MCT - induced ketosis and improved rheumatoid arthritis symptoms – thereby, providing support to the idea that a ketogenic diet, with an emphasise on MCTs, may be helpful in controlling the symptoms of rheumatoid arthritis (Heidt et al.2019, 11).

4) Multiple Sclerosis and Ketogenic Diet

The most prevalent neurological condition that disables young adults is multiple sclerosis, which often manifests as symptoms between the ages of 20 and 40 (National Institute of Neurological Disorders and Stroke n. d.). In multiple sclerosis, myelin in the central nervous system (brain, optic nerves, and spinal cord) is inadvertently attacked by immune system cells that should be defending one against viruses, germs, and harmful cells. The material that covers nerve

fibres (axons) as a protective sheath is called myelin (National Institute of Neurological Disorders and Stroke n. d.). Multiple sclerosis then is a persistent illness that has varying effects on individuals. A tiny percentage of patients suffering from multiple sclerosis will experience a mild course with little to no disability, whereas the majority will experience a condition that gradually worsens and causes increasing disability over time (National Institute of Neurological Disorders and Stroke n. d.).

A positive impact of ketogenic diets on anti - inflammatory molecular mechanisms has also been observed in the case of multiple sclerosis. In a study, 65 patients with relapsing multiple sclerosis were put on the ketogenic diet for a period of 6 months. Their symptoms were assessed with metrics for multiple sclerosis such as the Expanded Disability Status Scale scores, 6 - minute walk and Nine - Hole Peg Test as well as fatigue and quality of life scores (Nicholas Brenton et al.2022). The ketogenic diet led to an almost 50% decrease in fatigue and depression scores as reported by the patients. An improvement in neurological ability, walking capacity, and finger dexterity can also be observed from the improvement in the clinical metric scores. It was observed that in addition to the immunomodulatory properties that ketogenic diets have – which anyways help with multiple sclerosis – a strict adherence to a ketogenic diet can lead to an impact on adipokines, pro - inflammatory cytokines, nuclear factor - erythroid - 2 - related factor 2 and nuclear factor - κ B pathway. This suggests that ketogenic diets are associated with positive outcomes in individuals with relapsing multiple sclerosis (Nicholas Brenton et al.2022).

An apt tabular summary of this section would be as follows:

Rheumatoid Arthritis		
Mode of Study	Results	Underlying Mechanisms Observed
Sample study of 61 patients.	Decrease in inflammation and an increase in β - hydroxybutyrate.	Macronutrients in the ketogenic diet affect the gut barrier and induce ketosis. This research needs further study.
Multiple Sclerosis		
Mode of Study	Results	Underlying Mechanisms Observed
Sample study of 65 patients.	Improvement in neurological ability coupled with a 50% decrease in fatigue and depression scores.	Immunomodulatory properties of the ketogenic diet enhanced through an adherence to the diet leading to an impact on nuclear pathways and cytokines.

3. Conclusion

The ketogenic diet shows promising results in mediating inflammation and in managing the mechanisms underlying autoimmunity. Thus, for patients who suffer from autoimmune diseases, it seems to be a potential therapeutic option. There is evidence, particularly in the cases of rheumatoid arthritis and multiple sclerosis, pointing to potential benefits. However, there still needs to be more robust research efforts that account for the unknown variables that might be at play. It is important to explore the ketogenic diet's efficacy and safety and in order to establish it as a credible and viable therapeutic strategy for autoimmune disorders. Additionally, it is important to note that the adoption of a ketogenic diet should be done under the supervision of an expert as results of anti - inflammatory effects of the diet are still far from conclusive. Furthermore, there is a need for wider policy changes to facilitate the widespread adoption of ketogenic diets by patients who are

afflicted by autoimmune disorders. This could include mass awareness programmes and subsidies on essential commodities that constitute the diet. Thus, exploring the role of the ketogenic diet as a therapeutic option for autoimmune conditions serves to pave the way for a better management of these complex disorders.

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