

Hypothesis

Carnivore Diet as Regenerative Immunotherapy for Treating Inflammatory Bowel Disease: Literature Review, A Novel Hypothesis and Experimental Design

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Abstract: The purpose of this paper is to evaluate the possible application of a therapeutic carnivore diet regimen in the treatment of chronic inflammatory bowel disease (IBD). Based on current research and anecdotal reports, we hypothesized that the diet might potentially exhibit both anti-inflammatory and microbiome-modulating properties salutary to the IBD patient population. Our hypothesis demands comprehensive clinical validation. Therefore, in this paper, we review theories on ketogenic and carnivore diets, discussing their immunomodulatory effects and propose an experimental study to test the feasibility, safety, and clinical efficacy of the carnivore diet for IBD treatment.

Keywords: carnivore diet, ketogenic diet, inflammatory bowel disease, meat

1. Introduction

A carnivore diet consists of only animal-based products: meat, fish, eggs, and animal fats. It has been anecdotally attributed to a number of health benefits, including improved digestion, weight loss, and reduced inflammation. Preliminary evidence and personal testimony show that it may be effective in managing the symptoms of chronic IBDs. It is hypothesized that the carnivorous diet might have regenerative immunotherapeutic effects with the potential of inducing the resolution of IBD, having modes of action shared with, but not being exclusive to, the ketogenic diets. Our goal is to present best available evidence, formulate a hypothesis and provide an experimental framework for its clinical validation.

1.1. Ketogenic diet as regenerative immunotherapy

The ketogenic diet (KD) is a high-fat, very low-carbohydrate diet (VLCKD) that has been shown to induce a metabolic state similar to that of fasting, which stimulates the synthesis of ketone bodies in the liver. It has shown clinical efficacy in drug-resistant epilepsy [1–3] and displays promising potential in the treatment of psychiatric [4] and neurodegenerative diseases [5]; it is now being studied with respect to metabolic and inflammatory conditions [6]. Interestingly, KD regulates the immune response by virtue of lowered pro-inflammatory cytokine levels, Th1/Th2 balance, and pathways like the NLRP3 inflammasome [7].

In an interesting manner, KD promotes the growth of colonic short-chain fatty acid-producing bacteria with an eventual effect on modulating gene expressions that regulate tissue inflammation. Of particular importance is this finding in the context of dysbiosis, which is highly prevalent in IBD patients [8]. Ketone bodies were even able to directly regulate stem cell activity and control gene expression post-transcriptionally leading to improved intestinal regenerative capacity (See Figure 1) [9,10].

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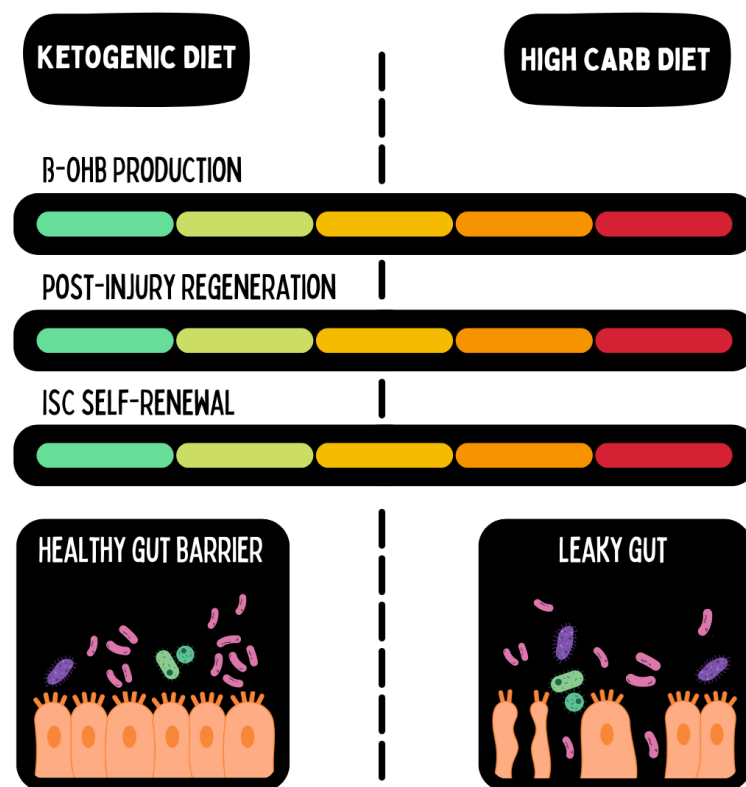


Figure 1. Ketone bodies directly interact with gene expression and post-translational modifications on the level of intestinal stem cells. This strengthens the regenerative capacity of the intestinal wall. Adapted from Cheng et al., 2019. Graphics with kind permission from the MOJO Institute.

1.2. Carnivore Diet as a regenerative Immunotherapy

The carnivore diet has recently gained recognition as a potential paradigm-shifting therapeutic modality for complex chronic diseases. Possibly, the effects are mediated by this diet being closest to the evolutionary origins of our species, as homo sapiens were most likely an apex predator with a carnivorous diet in higher, rather rigid trophic levels up to the late pleistocene [11].

The carnivore diet expands on principles of the VLCKD by excluding all plant-based foods and relying only on animal-derived nutrients. Advocates claim that it enhances gut health by removing plant toxins and anti-nutrients such as solanines, saponins, and lectins [12–15].

Furthermore, increased micronutrient availability in the carnivore diet due to lower phytate content and increased mineral density of animal based foods (see Figure 2) may contribute to higher regenerative capacity and better immune regulation during carnivore diets [16,17].

The relatively low dietary fiber content is a promoted benefit for some conditions of the gastrointestinal tract since soluble dietary fiber may interfere with the activities of pancreatic enzymes and digestion of protein, whereas insoluble fiber could provoke bloating and distension [18,19]. Casual observations and self-claimed benefits are weight loss, improved glucose control, reduced medication needs, and improvements in gut health [20]. However, scientific confirmation under tight regulation is still needed.

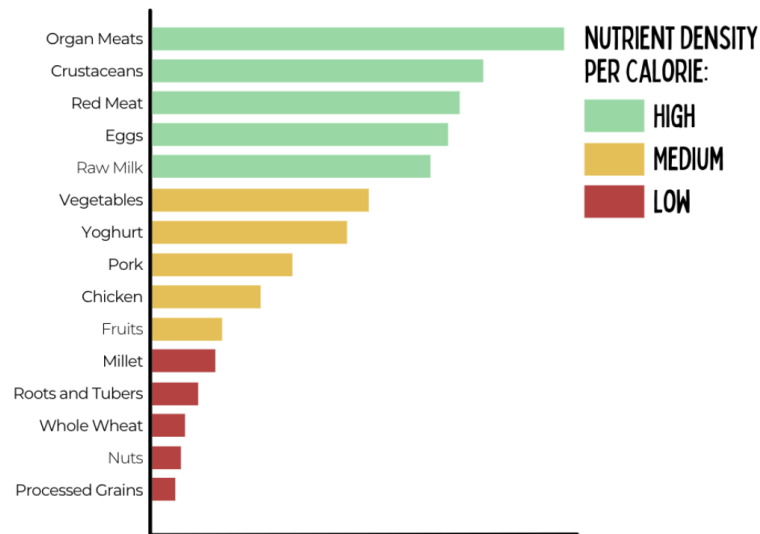


Figure 2. Mineral and vitamin density per calorie is significantly higher in animal-based foods compared to plant-based foods, and especially grains, which exhibit the lowest bioavailable nutrient density. Adapted from Beal et al., 2022, with permission from the MOJO Institute.

2. Hypothesized Mechanisms of the Carnivore Diet

The carnivore diet may offer some advantages over the VLCKD, particularly for patients with IBD. These are:

1. **Decreased Plant Toxins:** Plants contain various toxins. Lectins, solanines, and saponins are associated with autoimmunity and inflammation [12,13,15];
2. **Direct SCFA Supply:** With the direct provision of SCFAs and the growth stimulation of SCFA-producing bacteria (see Figure 3), the carnivore diet may bypass pre-existing dysbiosis, which is highly prevalent in the IBD population. [8,21,22];
3. **Reduced Omega-6 (Linoleic Acid) consumption:** Linoleic Acid may directly induce inflammation in the intestinal epithelium via formation of oxidative linoleic acid metabolites (OXLAMs) and consequent dysregulation of the Endocannabinoid System [23]. Carnivore diets more closely resemble the pre-modern consumption of <2g/day linoleic acid vs. the modern consumption of 29g/day [24];
4. **Higher Micronutrient Density:** Animal Foods are more dense in most micronutrients (vitamins and minerals) relevant to ATP synthesis (see Figure 4) compared with plant foods and lack anti-nutrients such as phytates [16,17], which may improve immune regulation and regenerative capacity of intestinal epithelial cells;
5. **Reduced Dietary Fiber:** Soluble fiber inhibits activity of pancreatic enzymes and protein sequestration while insoluble fiber increases bloating and tension (see Figure 5) possibly contributing to intestinal pathologies [18,19].

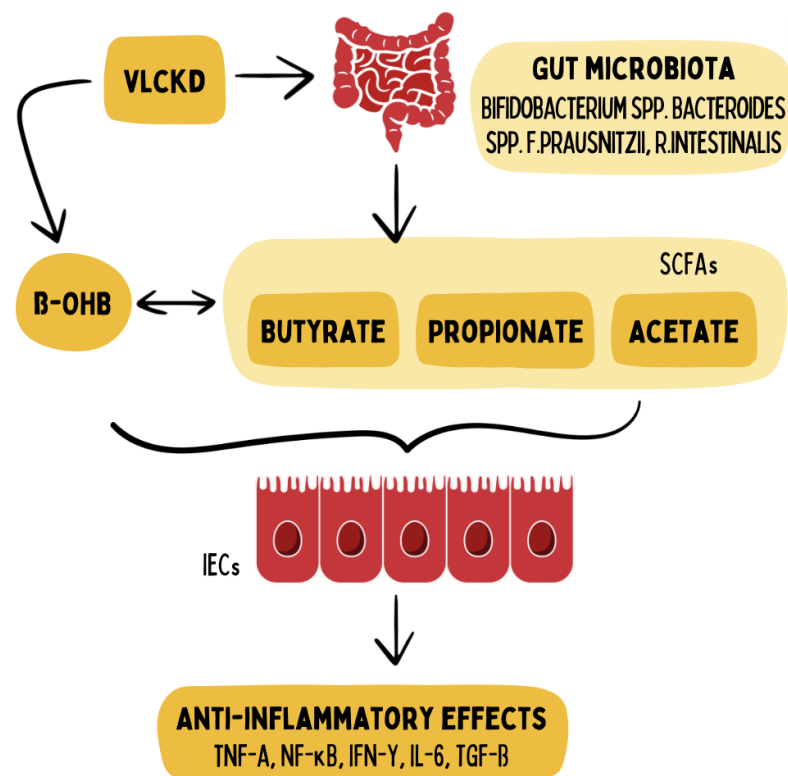


Figure 3. A ketogenic diet supports the proliferation of SCFA-producing bacteria and increases supply of ketone bodies like β -hydroxybutyrate (β -OHB), in turn modifying epigenetic control of gene expression in intestinal epithelial cells (IECs) and thus regulating inflammatory cytokines in IBD. Adapted from Alsharairi et al., 2021. Graphic provided with the permission of the MOJO Institute, Hennef, Germany

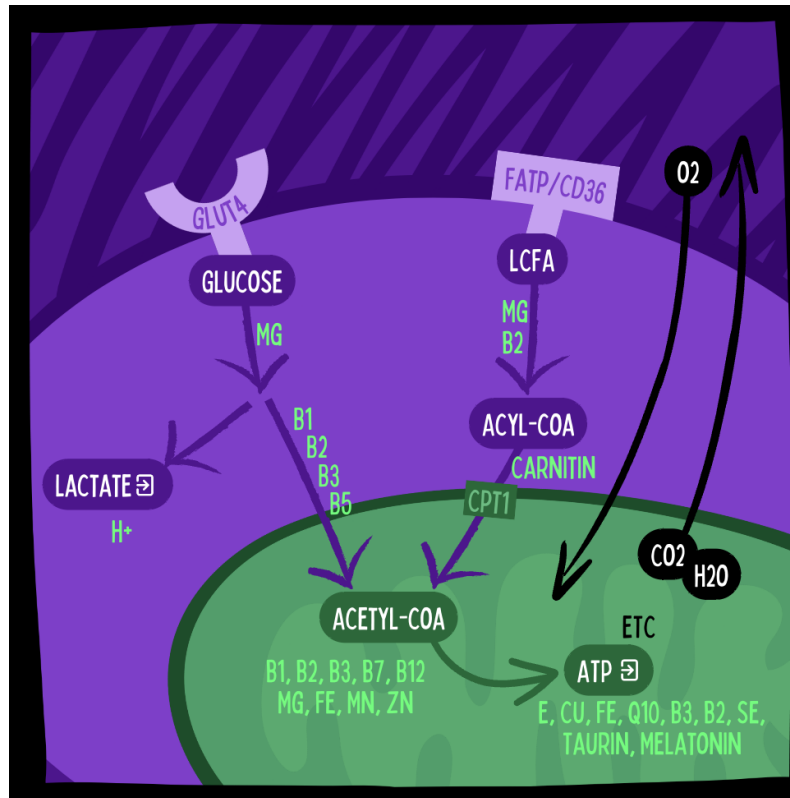


Figure 4. The Oxidative Metabolism of Glucose and Fatty Acids into ATP in Mitochondria and the Electron Transport Chain (ETC) Requires Multiple Micronutrients Including Vitamins and Minerals. These micronutrients are more concentrated in animal products than in plant based foods. Illustration by MOJO Institute, Hennef/Germany.

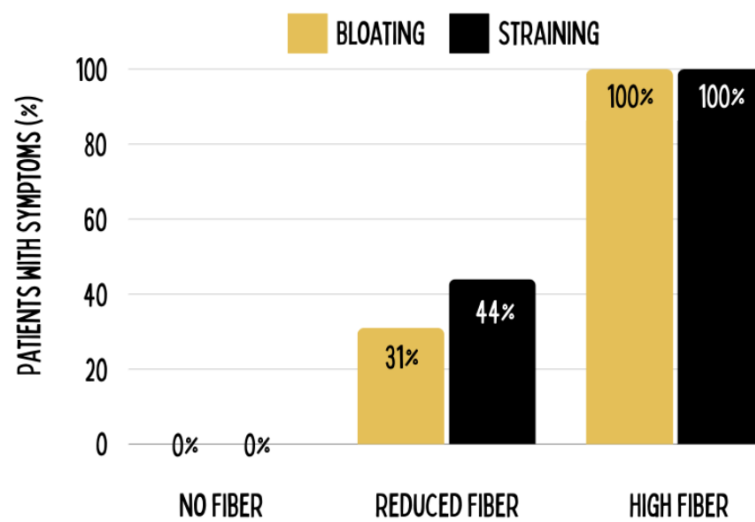


Figure 5. Dietary fiber can contribute to bloating and straining, as was revealed by an experimental study in which 63 patients were subjected to three levels of fiber intake: no fiber restriction, medium fiber restriction, and complete fiber restriction over six months. Results indicated that while all patients on the high-fiber diet remained symptomatic, none of the patients on the zero-fiber diet exhibited symptoms after six months. Figure adapted from Tan et al., 2012, courtesy of the MOJO Institute, Hennef, Germany.

3. Possible Concerns

A carnivore diet has been subject to some stringent criticisms in terms of potential individual health risks:

- Gout Risks:** The supersaturation of uric acid can -under the wrong circumstances- lead to the deposition of monosodium urate monohydrate crystals in the tissues, with resultant gout arthritis. Gout can be manifested by the elevation of serum urate, acute gouty arthritic attacks, the formation of tophi, gouty nephropathy, and uric acid stones. Meat itself has not been established as a causative agent, but the high amount of purine within it can serve as a triggering factor in causing episodes of gout arthritis in a pre-existing metabolic dysregulation. Our own clinical experience shows that a ketogenic/carnivore diet can even alleviate gout medium term. Hypothetically, this could be due to reduced oxidative stress since uric acid acts as an antioxidant, reduced availability of dietary monosodium (glutamate), or perhaps increased exercise in our patient population since muscle activity induces myokine secretion, hence helping in the conversion of uric acid to allantoin for excretion through the kidneys [25]. Indeed, recent reviews have confirmed our observation of reduced uric acid in very low carbohydrate ketogenic diets [26].
- Carcinogenicity:** The World Health Organization's (WHO) International Agency for the Research of Cancer (IARC) has classified Processed Meat as carcinogenic (Class I), and unprocessed Red Meat as possibly carcinogenic (Class IIa). No causal relationships have been established and no causal agents in red meat have been identified to date. By the classification standards of IARC, the classification is to be based on an associative relationship and does not establish the magnitude of risk. Recent systematic reviews have argued that evidence even for the proposed associative relationship between unprocessed red meat and negative health outcomes (including cancer) is lacking, and recommendations for reduced consumption of unprocessed red meat are currently not backed by scientific data [14,27].
- Dyslipidemia and Cardiovascular Risks:** For a given population on a standard diet, increased serum total LDL Lipoprotein molecular mass (measured in mg/dl) has been considered causal in the progression of atherosclerosis (Libby 2021). On ketogenic diets, total serum LDL lipoprotein mass can and most likely will increase; however, the size of the LDL particle becomes larger, thereby reducing the number of atherogenic particles [28–31]. A reduction in the number of the atherogenic small and dense LDL lipoproteins and concurrent increase in the lipoprotein size is associated with improved cardiovascular risk markers such as reduced BMI, body weight, inflammatory markers, sdLDL, Triglycerides, Lipoprotein A, Apolipoprotein B, Blood Glucose, HbA1c, Insulin, and Blood Pressure, and increased HDL. During ketogenic diets LDL Lipoproteins serve other functions as in standard diets and are not to be interpreted as signs of metabolic dysfunction [32]. Therefore, increased serum LDL on a ketogenic diet has to be evaluated differently than increased serum LDL on a standard diet and statin therapy is usually not warranted in a low-carbohydrate ketogenic diet [33].

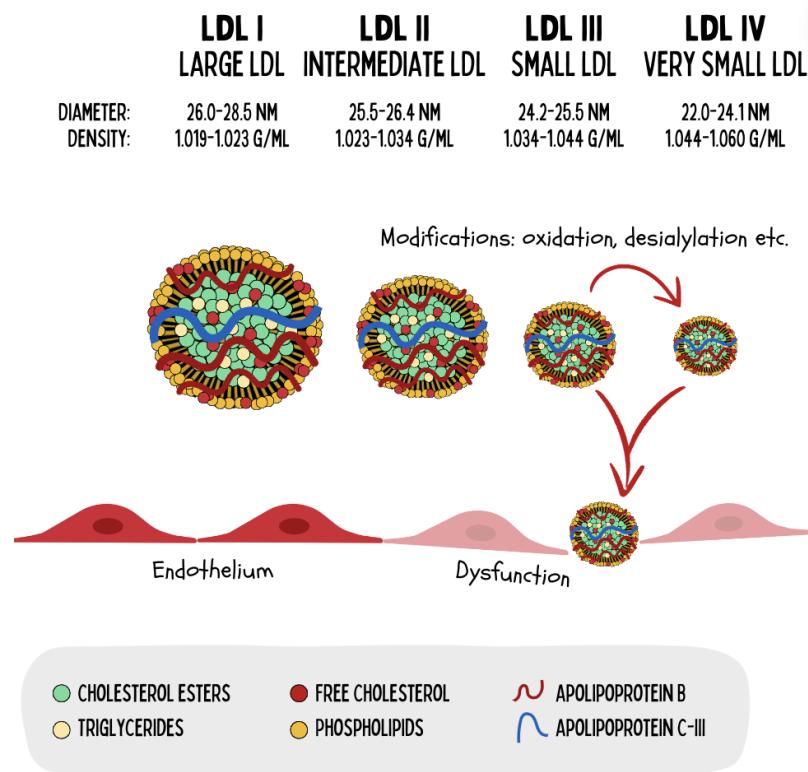


Figure 6. Low Density Lipoproteins (LDL) vary by size. Smaller Lipoproteins have a higher propensity to oxidize and paracellularly pass the endothelium to assist in the progression of atherosclerosis. Under ketogenic diets lipoproteins tend to increase in size without increasing the particle number, resulting in higher serum weights (measured in mg/dl). According to best available evidence this increase in mass, while at the same time increasing size with stable or even decreased particle numbers (as measured by reduced apolipoprotein B under ketogenic conditions) does not constitute an increased cardiovascular risk and does not warrant statin therapy. Adapted from Qiao et al., 2022, courtesy of the MOJO Institute, Hennef, Germany.

None of the proposed risks have so far been conclusively confirmed nor denied. Small associations have been spotted between intake of meat and gout, cancers, and cardiovascular events absent identification of causal relationships or conclusive causal agents. On the other hand, there are also no conclusive trials to indicate the long-term safety of a carnivore or meat-intensive diet. Hence further research is warranted.

4. Testing the Hypothesis – Study Design and Methodology

The hypothesis can be tested in a 12-week clinical study, investigating safety, feasibility, and clinical efficacy of a carnivore diet in a cohort of IBD patients.

4.1. Study Objectives

The primary objective is to establish the feasibility and safety of a carnivore diet in a cohort of IBD patients. Secondary objectives will assess clinical and functional outcomes at 1, 6, and 12 weeks with the IBDQ-32, SCCI, and CDAI. Other measures will include heart rate variability, bioimpedance, blood pressure, body measurements, body temperature, breath analysis, gut microbiota, inflammation markers, urea and electrolyte levels, liver function, fasting insulin, HbA1c, vitamin and mineral status, and lipid profile. Appendix A provides a detailed listing of the lab parameters to be measured, which include, but are not limited to, inflammation markers, lipid profile, vitamins, mineral levels, and other biomarkers as needed. Participants will keep a food diary daily and monitor their blood ketone levels.

4.2. Study Design 134

This prospective study should enroll a minimum of 12 IBD patients in a 12-week non-randomized, single-arm pilot study. All participants will be taken through written informed consent. 135
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4.3. Participant Criteria 138

4.3.1. Inclusion Criteria 139

- Diagnosis of IBD as per Montreal classification, 140
- Aged 18-70 years. 141

4.3.2. Exclusion Criteria: General 142

- Pregnant or intending to become pregnant within the next 3 months, 143
- Currently abusing substances, 144
- On ketogenic or carnivore diet in last 6 months, 145
- Currently Vegan or vegetarian diet and unwilling to switch to carnivore diet, 146
- Hospitalization during the last 3 months, 147
- Participation in another research project, 148
- Inability to fill out the initial questionnaires, 149
- Active liver, kidney, or cardiovascular diseases, kidney stones, severe hyperlipidemia. 150

4.3.3. Exclusion Criteria: Metabolic Disorders 151

- Glycogen storage disease type 1 (von Gierke disease), 152
- Carnitine palmitoyltransferase deficiencies (CPT I/II), 153
- Primary carnitine deficiency, 154
- Carnitine-acylcarnitine translocase deficiency, 155
- Pyruvate carboxylase deficiency, 156
- Succinyl-CoA acetoacetate transferase deficiency, 157
- Various fatty acid oxidation disorders, 158
- Acute intermittent porphyria. 159

4.4. Implementation and Follow-Up 160

4.4.1. Participant Training 161

The participants will be trained once in an educational workshop, given at the Kick-off event of the study, about: 162
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- Nutritional science behind the ketogenic and carnivore diets, 164
- Appropriate foods and sample recipes, 165
- Targeted ketone and glucose levels, 166
- Food measurement-grams, 167
- Preparation for diet initiation across environments, 168
- Overcoming obstacles-quality, procurement, and preparation, 169
- Dining out, traveling, and illness guidelines, 170
- Medication guidelines, 171
- Prevention/management of potential side effects; for example hypoglycemia or hyperketosis, 172
173
- Why diets may fail, 174
- Modifications for illness-more water, no concern for ketone level, 175
- Fitting the diet into larger ecological, spiritual, and economic contexts. 176

4.4.2. Ketone Monitoring 177

The nutritional and socio-medical history will be obtained through digital intake interviews with the participants. Continuous monitoring of glucose/ketones will be done with monitoring devices, the data of which is managed daily by the specialist. The participants will have digital access to a community platform, where they can find recipes 178
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and instructions. Group exchanges in this online format should also be possible. Once a week, video calls with the specialist and mentor will be used to discuss practical and emotional problems arising from dietary adherence.

5. Discussion

Chronic complex illnesses such as IBD can be frustrating for both patients and therapists, because of a lack of promising treatment options that resemble full reconstitution/regeneration. The need to advance medical knowledge and care for patients afflicted by these diseases is rising. The carnivore diet -a possible new regenerative immunotherapy- seems promising. Yet, for patients with IBD, being put on a radical carnivorous diet would require multifaceted consideration of ethical, ecological, economic concerns and individual health needs.

Fully informed consent -as in all medical therapies- is needed, where all possible benefits and risks should be presented. Ecologically, a diet with a high intake of animal products has sustainability concerns, which are yet unclear; hence, this too will require discussion in light of finding ethical and sustainable ways of sourcing animal products. Economically, dietary cost and food access need consideration to ensure that it will place no undue burden on the patients or that it will not further exacerbate health disparities.

From the point of view of individual health, even if there is plenty of anecdotal evidence, in particular, as to the benefits, the adverse effects should be carefully and intensively investigated. High animal product consumption entails risks for diseases such as gout, cardiovascular diseases, and particular types of cancer. These risks should be assessed and followed closely for therapeutic carnivore diets in order to attend to the subjects' long-term safety and vitality.

The following monitoring protocols are necessary:

- for gout risk, check uric acid levels on a regular basis.
- for cancer risk, perform long-term monitoring of biomarkers for cancer.
- for cardiovascular risk, evaluate lipid profiles including Apolipoprotein B as a measure of particle number, blood pressure, visceral body fat and markers of systemic inflammation such as hsCRP.

6. Conclusions

Academia and clinical medicine needs a multi-disciplinary approach, which has to integrate nutrition, behavioral psychology, immunology, gastroenterology, and bioethics. By balancing and reviewing all aspects, we want to explore the healing potential of a carnivore diet while ensuring the safety of the patient and also regarding the possible ethical, ecological as well as economic issues.

We hereby summarize the current best available evidence for a therapeutic carnivore diet as a regenerative immunotherapy and hypothesize that it could make a significant difference in the management of IBD and perhaps bring relief to patients unresponsive to current treatments. Such a therapeutic carnivore diet requires very considered planning, transparent reporting, and dedication to responsible and comprehensive patient care. An experimental design to test our hypothesis was proposed. This review, hypothesis, and experimental design guarantee a comprehensive framework for investigating the carnivore diet as a novel regenerative immunotherapy in IBD, which can have a clinical application based on such findings. Insights from this would extend beyond the specific focus to wider applications in other chronic inflammatory diseases.

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Appendix A. Suggested Lab Analysis

Appendix A.1. Standard Labs

Alkaline Phosphatase (Serum), Calcium (Serum), Chloride (Serum), Cholesterol (Serum), HDL (Serum), LDL (Serum), CK (Serum), CK-MB (Serum), Iron (Serum), Protein Electrophoresis (Serum), Total Protein (Serum), GOT (Serum), GPT (Serum), Uric Acid (Serum), Urea (Serum), HbA1 (EDTA), Potassium (Serum), Creatinine (Serum), LDH (Serum), Sodium (Serum), Inorganic Phosphate (Serum), Transferrin (Serum), Triglycerides (Serum), Full Blood Count (EDTA), Reticulocytes (EDTA), Quick/INR (Citrate), PTT (Citrate), Thrombin Time (Citrate), Indirect Bilirubin (Serum), hsCRP (Serum), Ferritin (Serum), TSH Basal (Serum)

Appendix A.2. Specialized Labs

Whole Blood Minerals 11+4 (Heparin), TNF-alpha (Serum), Vitamin B1 bioactive (Serum), Vitamin B2 bioactive (Serum), Vitamin B6 bioactive (Serum), Vitamin B9 bioactive (EDTA), Vitamin B12 bioactive (Serum), 25-OH-Vitamin D (Serum), Amino Acids Metabolism (EDTA Plasma), Amino Acids Neuro (EDTA Plasma), Lactate/Pyruvate (Fluoride 3x), Nitrotyrosine (Serum), Carnitine (Serum), Fatty Acids of Erythrocyte Membrane (EDTA), Lipoprotein (a) (Serum), Apo-Lipoprotein B (Serum), Homocysteine (Serum centrifuged), SCFA (Short-Chain Fatty Acids) (Serum), MDA-LDL (Serum), AGE (Serum), IL-6 (Serum), BDNF (Serum), Lipopolysaccharide Binding Protein (LBP) (Serum centrifuged), IFABP (Serum)

Appendix A.3. Stool and Saliva Labs

Cortisol Awake Response (Saliva), Molecular Genetic Profile Microbiota (Stool) SCFA (Short-Chain Fatty Acids) (Stool), Pancreatic Elastase (Stool), Bile Acids (Stool), Alpha-1-Antitrypsin (Stool), Zonulin (Stool), Calprotectin (Stool)

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