

KETOGENIC METABOLIC THERAPY RESEARCH

by Metabolic Health Initiative

An overview of research and advances in ketogenic metabolic therapy.

TABLE OF CONTENTS

- 3** Ketogenic Metabolic Therapy in 2021
- 4** Neurological Health
- 13** Cancer
- 20** Metabolic Dysfunction
- 30** Human Optimization & Aging
- 39** Clinical Application
- 43** Where Keto Science Meets Society

» *Ketogenic Metabolic Therapy Pushes Forward in 2021*

As throughout the decade that preceded it, the field of ketogenic metabolic therapy (KMT) continued to move forward in leaps and bounds in 2021.

Consider this Year in Review eBook as a user-friendly guide to help you uncover some of the newest discoveries in this rapidly evolving field. Use the links within these pages as a jumping off point into a sea of new information, research, topics, and ideas. You may become acquainted with new aspects and advances in KMT for which you were not yet aware. Or you may use this as a tool to get updated on areas of work that you've been following for years.

As you read, keep in mind that the studies listed here are not comprehensive. Mentioning every KMT research study published in 2021 would require a novel-sized eBook! Rather, this publication is but an overview of some of the exciting and far-reaching work that came out in 2021. For the over 100 primary research articles mentioned here, you'll find a quick reference to selected key findings and conclusions. Please follow the link to each study for the full citation, abstract with a more complete description of study results and analysis, and options for accessing the article. In each content section, you'll also see lists of review articles published in 2021 that will serve as great resources to acquire a more comprehensive overview of specific topics.

We hope that you enjoy reading through the exciting findings highlighted in our 2021 Ketogenic Metabolic Therapy Research Year in Review eBook. We loved taking a close look at the hundreds of new research studies that help expand our understanding and application of these tools. We know that 2022 will continue to bring more illuminating findings, and we promise to be here helping spread the word about this new data as it comes to light. Here's to revolutionizing health through nutrition!



Metabolic Health Initiative

Dr. Angela Poff & Victoria Field

info@metabolichealthsummit.com

www.metabolichealthsummit.com



NEUROLOGICAL HEALTH

The history of the ketogenic diet begins, and is to this day the most impressive, in the field of neurological health. 2021 marked the centennial anniversary of the creation of the therapeutic ketogenic diet for epilepsy, a condition for which it remains standard of care to this day. One hundred years later, research into ketogenic therapy for neurological health has exploded, and now reaches into even the most obscure corners of the field. In 2021, advances in our understanding of the mechanisms of efficacy and clinical utility of ketogenic metabolic therapy were made in some of the most common, and most rare, neurological conditions.



A KETOGENIC DRINK IMPROVES COGNITION IN MILD COGNITIVE IMPAIRMENT: RESULTS OF A 6-MONTH RCT; FORTIER ET AL.

DIFFERENTIAL KETOGENIC DIET-INDUCED SHIFT IN CSF LIPID/CARBOHYDRATE METABOLOME OF PEDIATRIC EPILEPSY PATIENTS WITH OPTIMAL VS. NO ANTICONVULSANT RESPONSE: A PILOT STUDY; MASINO ET AL.

KETOGENIC DIET-MEDIATED STEROID METABOLISM REPROGRAMMING IMPROVES THE IMMUNE MICROENVIRONMENT AND MYELIN GROWTH IN SCI RATS ACCORDING TO GENE AND CO-EXPRESSION NETWORK ANALYSES; ZENG ET AL.

EFFECTIVENESS OF KETOGENIC DIET IN TREATMENT OF PATIENTS WITH REFRACTORY CHRONIC MIGRAINE; BONGIOVANNI ET AL.

- Supplementing a normal diet with 30g/day of a ketogenic drink containing medium-chain triglycerides for 6 months increased blood ketone levels and significantly improved mild cognitive impairment in the areas of executive function, memory, and language.
 - Plasma metabolic profiles and ketone responses were unchanged throughout the study.
 - Age, sex, and ApoE status did not have an effect on improving mild cognitive impairment.
-
- Pediatric patients with epilepsy who have a stronger metabolic response to the ketogenic diet therapy also have a more effective anticonvulsant response.
 - Early response to KD treatment may predict the ultimate anticonvulsant outcome.
-
- Prior research demonstrated KD promotes functional recovery after spinal cord injury in rats, but mechanism of action was unknown.
 - In this follow up, a short-term KD altered gene expression, modulated steroid metabolism pathways, and improved the immune microenvironment, contributing to myelin growth after spinal cord injury.
-
- 3 months of ketogenic diet greatly reduced the length, frequency, and intensity of pain symptoms in a cohort of 50 patients with drug refractory chronic migraine.
 - Median days with symptoms decreased from 30 to 7.5, median duration of symptoms decreased from 24 to 5.5 hrs, median number of monthly doses of medication decreased from 30 to 6, and pain level improved in >50% of patients.

THE KETOGENIC DIET RAISES BRAIN OXYGEN LEVELS, ATTENUATES POSTICTAL HYPOXIA, AND PROTECTS AGAINST LEARNING IMPAIRMENTS; GOM ET AL

- Ketogenic diet increased hippocampal oxygen, and reduced post-seizure hypoxia and learning impairments in rats with electrically elicited (kindled) seizures.
- Beta-hydroxybutyrate administration did not alter oxygen levels, suggesting the effect of ketogenic diet on this phenomenon is likely independent from its induction of ketosis.

CHRONIC KETOSIS MODULATES HIF1 ALPHA-MEDIATED INFLAMMATORY RESPONSE IN RAT BRAIN; SETHURAMAN ET AL

- Chronic ketosis correlated with neuroprotection in both aged rodents and in rodents who have experienced ischemic stroke.
- The brain of ketogenic diet-fed rats showed significantly higher levels of HIF-1a and anti-inflammatory marker Interleukin-10 (IL10), while pro-inflammatory TNF α pathway and Interleukin-6 levels were reduced.
- Stabilization of HIF-1a through ketosis is associated with neuroprotection following a restriction in blood supply and oxygen to the brain (ischemic injury).

ADJUNCTIVE USE OF THE KETOGENIC DIET IN A YOUNG ADULT WITH UBE2A DEFICIENCY SYNDROME AND SUPER-REFRACTORY STATUS EPILEPTICUS; ALLEN ET AL

- A case study of a 19-year old male with UBE2A deficient syndrome, drug-resistant generalized epilepsy, and severe intellectual disability reported that once ketosis was reached, his super-refractory status epilepticus was resolved, and recovered to his normal cognitive state.

THE KETOGENIC DIET INCREASES NEUREGULIN 1 EXPRESSION VIA ELEVATING HISTONE ACETYLATION AND ITS ANTI-SEIZURE EFFECT REQUIRES ERBB4 KINASE ACTIVITY; WANG ET AL

- The ketogenic diet increased Type 1 Neurogeulin 1 (NRG1) expression in the hippocampus, activating Erb4, and decreasing seizure activity in a kainic acid-induced mouse seizure model. Erb4 kinase appears to play an essential role in the ketogenic diet's role in inhibiting seizures in this model.
- Both pharmacological and genetic inhibitors of Erb4 kinase were effective at decreasing seizures, indicating a potential novel therapeutic intervention for epilepsy.
- Inhibition of NRG1/Erb4 decreased the synaptic activity of the calming neurotransmitter GABA, preventing the ketogenic diet from being able to control seizure activity, and highlighting the importance of this pathway in ketosis-mediated seizure reduction.

A KETOGENIC DIET REDUCES MECHANICAL ALLODYNIA AND IMPROVES EPIDERMAL INNERVATION IN DIABETIC MICE; ENDERS ET AL

- Ketogenic diet normalized weight gain, reduced blood glucose, induced ketosis, and lowered HbA1c in a mouse model of Type 1 diabetes, both when used as a preventative (3 weeks prior to streptozotocin administration to induce diabetes) or therapeutic (9 weeks post diabetes induction).
- Diabetic mice developed hind paw mechanical allodynia (pain) and loss of thermal sensation, both of which were improved by KD.
- KD-treated diabetic mice also exhibited normalized epidermal innervation compared to standard rodent chow controls.

THE EFFECT OF KETOGENIC DIET ON SERUM LIPID CONCENTRATIONS IN CHILDREN WITH MEDICATION RESISTANT EPILEPSY; YILMAZ ET AL

- This study concluded that the ketogenic diet can be safely used for children with medication-resistant epilepsy, even in cases of pre-existing dyslipidemia (elevation of total cholesterol, LDL cholesterol, triglycerides, or decreased HDL cholesterol). The ketogenic diet does not appear to lead to long-term complications associated with hyperlipidemia in this patient group.
- The general trend of serum lipid levels for children with medication-resistant epilepsy on a ketogenic diet is as follows:
 - Month 1: significant increase in cholesterol and triglyceride levels
 - Months 2-24: gradual decreasing trend in cholesterol and triglyceride levels
 - Months 24 and beyond: return to normal baseline cholesterol and triglycerides levels
- Children with pre-existing dyslipidemia did not experience a further exacerbation of serum lipid levels on ketogenic diet therapy for medication resistant epilepsy.

EFFECT OF KETOGENIC DIET VERSUS REGULAR DIET ON VOICE QUALITY OF PATIENTS WITH PARKINSON'S DISEASE; KOYUNCU ET AL

- 3 months of ketogenic diet therapy improved all mean Voice Handicap Index (VHI) parameters in patients with Parkinson's disease compared to a regular diet control group.
- A larger trial is warranted to determine the potential use of KD on voice quality in PD patients.

EXPERIENCE OF PARTICIPANTS WITH CHRONIC PAIN IN A PILOT RANDOMIZED CLINICAL TRIAL USING A KETOGENIC DIET; FIELD ET AL



- The experience of chronic pain patients consuming either a well-formulated ketogenic diet (WFKD) or whole-food diet (WFD) was assessed using surveys.
- Both diets were deemed feasible in this patient group. Adherence was 82% for the WFKD and 87% for the WFD, while enjoyment was rated at 66% (WFKD) and 81% (WFD).
- Reports on the ease of diet adherence varied more in the WFKD than WFD group, with notable barriers listed as knowledge integration, time management, social food environment, and emotional attachment to eliminated foods.

KETOGENIC DIET FOR KARS-RELATED MITOCHONDRIAL DYSFUNCTION AND PROGRESSIVE LEUKODYSTROPHY; MUROFUSHI ET AL



- A 5 year old patient with asymmetrical leukodystrophy and mitochondrial dysfunction treated with ketogenic diet and vitamin supplementation showed improvements in psychomotor function and partial restoration of abilities within 4 months of therapy. No appreciable adverse effects were reported.

A KETOGENIC DIET AFFECTS BRAIN VOLUME AND METABOLOME IN JUVENILE MICE; MAYENGBAM ET AL



- Juvenile mice fed a 6.3 : 1 ketogenic diet resulted in an approximate 10% reduction in the volume, but a similar relative volume between regions, of most brain structures compared to those on standard diet. The affected areas included different brain regions, ventricles, and white matter.
- Global metabolomics profiling revealed significant alterations between KD and SD fed mice in different brain regions and pathways.
- These anatomical and metabolic changes did not seem to correlate to overt functional consequences, as spontaneous EEG to measure brain network activity revealed limited alterations between the groups. Furthermore, BDNF levels were not altered.
- The implications of these volumetric and metabolic differences during neurodevelopment are unclear, and warrant investigation to determine if similar changes occur in children on ketogenic therapy, and what effects they may have, positive, negative, or neutral.

INCREASED BETA-HYDROXYBUTYRATE LEVEL IS NOT SUFFICIENT FOR THE NEUROPROTECTIVE EFFECT OF LONG-TERM KETOGENIC DIET IN AN ANIMAL MODEL OF EARLY PARKINSON'S DISEASE. EXPLORATION OF BRAIN AND LIVER ENERGY METABOLISM MARKERS; KUTER ET AL

A KETOGENIC DIET PROTECTS DBA/1 AND SCN1A R1407X/+ MICE AGAINST SEIZURE-INDUCED RESPIRATORY ARREST INDEPENDENT OF KETOSIS; CROTTS ET AL

CAN KETOGENIC DIET THERAPY IMPROVE MIGRAINE FREQUENCY, SEVERITY AND DURATION? HASLAM ET AL

KETOGENIC DIET REDUCES EARLY MORTALITY FOLLOWING TRAUMATIC BRAIN INJURY IN DROSOPHILA VIA THE PPAR-G ORTHOLOG EIP75B; BLOMER ET AL

- Ketogenic diet improved locomotor activity and normalized DA turnover in the striatum in a rat 6-OHDA injection based model of Parkinson's disease, but did not protect against 6-OHDA induced dopaminergic neuron lesions.
- This data suggests KD may be a helpful therapeutic to support late compensatory mechanisms in PD, but may not counteract early oxidative stress-induced neurodegeneration itself. Additional research is warranted.
- Ketogenic diet decreased seizure induced mortality in Dravet Syndrome mice, and delayed latency to onset of seizure-induced respiratory arrest in DBA/1 mice, compared to control diet.
- The therapeutic effects were maintained despite a glucose-induced reduction in beta-hydroxybutyrate levels, suggesting the effect may be independent on ketone generation.
- A trend towards lower migraine duration was observed in chronic migrainers undergoing ketogenic diet therapy, though differences in migraine frequency, severity, or duration between KD and control groups were not statistically significant.
- The most commonly reported side effect of KD was fatigue.
- Fruit flies fed a ketogenic diet following TBI were protected from early and late mortality.
- Flies with mutant Eip75B (the fly ortholog of the mammalian PPAR γ transcription factor) did not retain the same level of therapeutic benefit from KD, suggesting this pathway may be important mechanistically.

KETOGENIC DIET-MEDIATED SEIZURE REDUCTION PRESERVES CA1 CELL NUMBERS IN EPILEPTIC KCNA1-NULL MICE: AN UNBIASED STEREOLOGICAL ASSESSMENT; SIMEONE ET AL

- Both ketogenic diet (KD) and the widely used antiepileptic drug phenobarbital (PB) reduced seizure activity to similar degrees in epileptic *Kcna1*-null mice; however, only KD protected against CA1 neuron loss in the hippocampus. Cell numbers in KD-treated mice were not significantly different than wild type mice, while PB-treated mice exhibited 23-31% less neurons in this region than wild type mice.
- This data suggests that KD and PB elicit distinct anti-seizure mechanisms, and KD may uniquely engage protective mechanism to protect neuron integrity in ways that PB does not.

DIFFERENTIAL RESPONSE OF HIPPOCAMPAL AND CEREBROCORTICAL AUTOPHAGY AND KETONE BODY METABOLISM TO THE KETOGENIC DIET; LISKIEWICZ ET AL

- Autophagy and ketone metabolism markers were markedly altered in the brains of mice fed either an animal-based or plant-based ketogenic diet for 4 weeks.
- Notably, the hippocampus showed robust changes in the markers assessed, with more subtle changes in the frontal cortex.
- Changes in these pathways were more profound in the plant-based KD group, suggesting the potential for a more profound regulation of of autophagy and ketone metabolism compared to the animal-based KD tested in this study.

SYSTEMATIC REVIEW - NEUROPROTECTION OF KETOSIS IN ACUTE INJURY OF THE MAMMALIAN CENTRAL NERVOUS SYSTEM: A META-ANALYSIS; GAMBARDELLA ET AL

- In this systematic review and meta-analysis of animal experiments on the mitigating effects of ketosis on acute CNS damage, ketogenic therapy was shown to reduce mortality, neuronal damage, and dysfunction.
- Protection against mortality was particularly pronounced in adult animals, while the aggregated advantage of ketosis was most pronounced in young animals and those with ischemic insult.
- The degree of ketosis was a predictor of neuroprotection, with greater protection observed higher increases in blood ketone levels.

RESCUE OF HISTONE HYPOACETYLATION AND SOCIAL DEFICITS BY KETOGENIC DIET IN A SHANK3 MOUSE MODEL OF AUTISM; QIN ET AL

- 4 weeks of ketogenic diet reversed the diminished histone acetylation in the prefrontal cortex of a mouse model of autism while also increasing expression of HDAC target genes known to be reduced in humans with autism.
- KD treatment also improved social preference deficits in the mice, suggesting ketogenic therapy may provide benefit in autism disorder by restoring epigenetic regulation and gene expression in the brain.

A KETOGENIC SUPPLEMENT IMPROVES WHITE MATTER ENERGY SUPPLY AND PROCESSING SPEED IN MILD COGNITIVE IMPAIRMENT; ROY ET AL

- Neurocognitive battery testing and brain imaging pre- and post- 6 months of ketogenic medium chain triglyceride drink revealed significant ketone uptake in all white matter fascicles of interest in patients with mild cognitive impairment.
- White matter ketone uptake was associated with an improvement in processing speed, suggesting ketones may support myelin integrity in MCI patients.

EFFICACY AND SAFETY OF KETOGENIC DIETARY THERAPIES IN INFANCY. A SINGLE-CENTER EXPERIENCE IN 42 INFANTS LESS THAN TWO YEARS OF AGE; RUIZ-HERRERO ET AL

- In this retrospective, descriptive, and observational study of 42 infants on ketogenic diet therapy for epilepsy, most experienced >50% seizure reduction compared to baseline, and some experienced >90% seizure reduction from baseline, though efficacy declined with time.
- Early adverse effects observed included asymptomatic hypoglycemia and gastrointestinal disturbances, while late-onset adverse effects included hypercalciuria and dyslipidemia.

CLINICAL AND MAGNETIC RESONANCE STUDY OF A CASE OF SUBACUTE SCLEROSING PANENCEPHALITIS TREATED WITH KETOGENIC DIET; VALENTE ET AL

- Ketogenic diet dramatically improved neurological and other clinical conditions and stopped the progression of demyelination in a 17-year old patient with subacute sclerosing panencephalitis.
- This case report supports further investigation into KD therapy for this rare yet often fatal disease that lacks effective treatments.

IMPACT OF DIETARY INTERVENTION ON SERUM NEUROFILAMENT LIGHT CHAIN IN MULTIPLE SCLEROSIS; BOCK ET AL



- Adapted ketogenic diet reduced serum neurofilament light chain levels in patients with relapsing-remitting multiple sclerosis, suggesting a potential protective effect on neuroaxonal damage.

ADENOSINE RECEPTORS MODULATE THE EXOGENOUS KETOGENIC SUPPLEMENT-EVOKED ALLEVIATING EFFECT ON LIPOPOLYSACCHARIDE-GENERATED INCREASE IN ABSENCE EPILEPTIC ACTIVITY IN WAG/RIJ RATS; BRUNNER ET AL



- Inhibition of A1R but not A2AR adenosine receptors blocked the therapeutic effects of exogenous ketogenic supplements (ketone salt + ketone ester) on spike-wave discharge in rats challenged with LPS.
- This data suggests the neuromodulatory benefits of exogenous ketosis in this model may rely specifically on this receptor signaling pathway.

EXOGENOUS KETONE ESTER DELAYS CNS OXYGEN TOXICITY WITHOUT IMPAIRING COGNITIVE AND MOTOR PERFORMANCE IN MALE SPRAGUE-DAWLEY RATS; STAVITZSKI ET AL

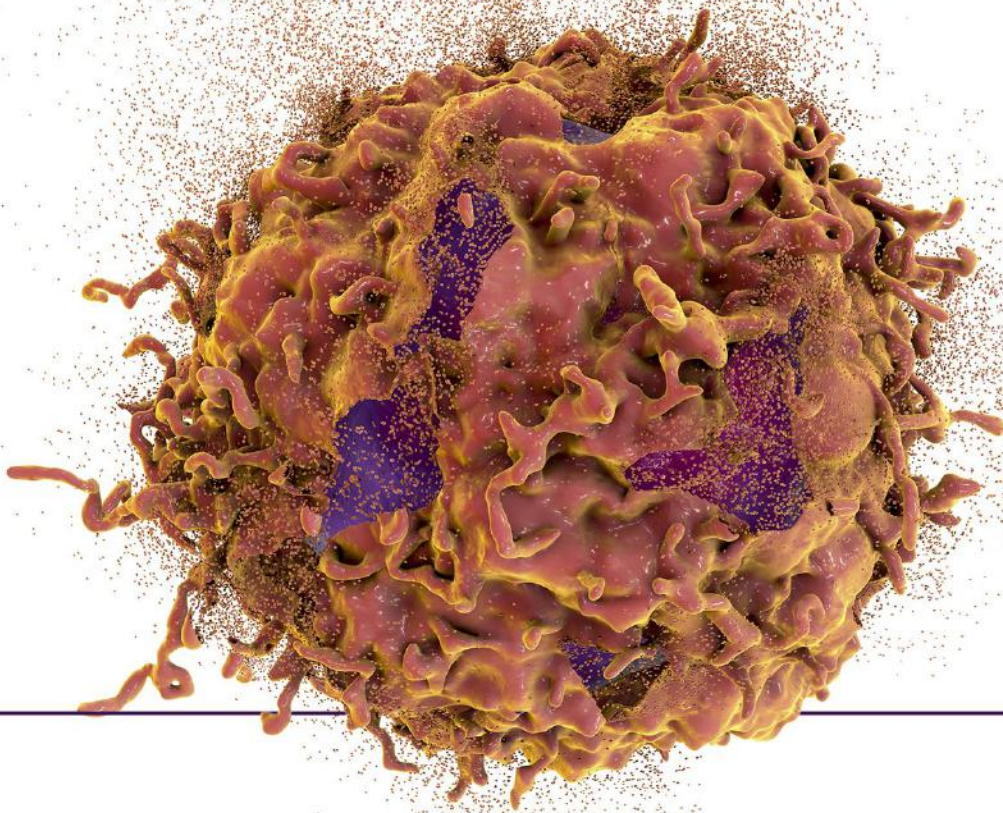


- Ketone ester delayed central nervous system oxygen toxicity onset by 307%, and prevented seizure onset in some animals, in a rat model of the condition.
- No adverse effects on cognitive or motor performance were noted. Rather, ketone ester reduced anxiety in the rats per Open Field and Light-Dark testing.

DIVE DEEPER: Literature Reviews on Neurological Health from 2021

- Ketogenic diet for depression: A potential dietary regimen to maintain euthymia? Wlodarczyk et al
- Ketogenic diet therapy in Alzheimer's disease: an updated review; Lilamand et al
- Ketogenic regimens for acute neurotraumatic events; Yazar-Fisher et al
- Can Ketogenic Diet Improve Alzheimer's Disease? Association With Anxiety, Depression, and Glutamate System; Enrique de la Rubia Orti et al
- Nutritional Ketosis in Parkinson's Disease - a Review of Remaining Questions and Insights; Choi et al
- Exogenous ketosis, a nutritional strategy to preserve brain health? Robberechts et al
- The Efficacy of Ketogenic Therapies in the Clinical Management of People with Neurodegenerative Disease: A Systematic Review; Dewsbury et al
- Ketogenic diet, seizure control, & cardiometabolic risk in adult patients with pharmaco-resistant epilepsy: a review; Neves et al

CANCER



Oncology may represent one of the most recent fields of research for ketogenic therapy, but it is perhaps also one of the most rapidly progressing. Though still in its infancy, research on ketogenic metabolic therapy for cancer is advancing quickly as scientists and clinicians from around the world probe its use in a variety of pre-clinical and clinical studies. In 2021, fascinating research was performed using ketogenic metabolic therapy in brain, breast, prostate, colorectal, head and neck, kidney cancer, and more – each study contributing to the foundation of knowledge necessary to propel this field of study further.

METABOLIC CHANGES AND ANTI-TUMOR EFFECTS OF A KETOGENIC DIET COMBINED WITH ANTI-ANGIOGENIC THERAPY IN A GLIOBLASTOMA MOUSE MODEL; MAEYAMA ET AL

- In a glioblastoma mouse model, the combination of a ketogenic diet and Bevacizumab (Bev) decreased the rate of tumor growth and increased the survival time.
- The ketogenic diet alone did not have a survival benefit, however it enhanced the anti-tumor effect of Bev, a VEGF inhibitor, by further depriving the tumor of glucose.
- A reduction of amino acids threonine valine, isoleucine, and leucine was observed in the Bev and Bev+KD groups.
- The KD group also experienced a significant increase in aspartic acid in the glioma tissue, but not in normal brain tissue.

IMPLEMENTATION OF A LOW-CARBOHYDRATE DIET IMPROVES THE QUALITY OF LIFE OF CANCER PATIENTS - AN ONLINE SURVEY; TULIPAN ET AL

- An online questionnaire was provided to cancer patients on a KD or low carbohydrate diet at the time of participating in the study or when undergoing cancer treatment.
- Nearly half of subjects received their initial diet information from the internet, and 69% reported a perceived improvement in quality of life due to the diet.
- Lean participants did not lose weight while weight loss due to the diet correlated to extent of overweight for an individual subject. Nearly 80% of subjects found long-term adherence to the diet to be easy or very easy.
- Subjects reported a notable gap in professional dietary advice from their cancer care teams, highlighting a significant need for nutrition expert counseling availability to newly diagnosed cancer patients.

KETOGENIC DIET WITH CONCURRENT CHEMORADIATION IN HEAD AND NECK SQUAMOUS CELL CARCINOMA: PRECLINICAL AND PHASE 1 TRIAL RESULTS; MA ET AL

- Mice with head and neck cancer xenografts fed KD and treated with radiation therapy exhibited a slight improvement in tumor growth rate and survival time over controls (SD+Rad).
- In a Phase I trial of patients with locally advanced head and neck cancer, 12 subjects consumed KD while undergoing radiotherapy and cisplatin chemotherapy, but 5 removed from the trial due to poor tolerability and 3 were removed for toxicity (hyperuricemia & acute pancreatitis).
- While mouse data is encouraging in this cancer type, safety and tolerability in this patient population was difficult in the current trial.

KETOGENIC DIET PREVENTS PACLITAXEL-INDUCED NEUROPATHIC NOCICEPTION THROUGH ACTIVATION OF PPAR-G SIGNALLING PATHWAY AND INHIBITION OF NEUROINFLAMMATION IN RAT DORSAL ROOT GANGLION; ZHONG ET AL



KETOGENIC METABOLIC THERAPY, WITHOUT CHEMO OR RADIATION, FOR THE LONG-TERM MANAGEMENT OF IDH1-MUTANT GLIOBLASTOMA: AN 80-MONTH FOLLOW-UP CASE REPORT; SEYFRIED ET AL



METABOLICALLY SUPPORTED CHEMOTHERAPY FOR MANAGING END-STAGE BREAST CANCER: A COMPLETE AND DURABLE RESPONSE; IYIKESICI ET AL



THE MEDIUM-CHAIN FATTY ACID DECANOIC ACID REDUCES OXIDATIVE STRESS LEVELS IN NEUROBLASTOMA CELLS; MÜLLER ET AL



- Ketogenic diet prevented chemotherapy induced neuropathic pain and reduced expression of pro-inflammatory cytokines and NF-kB activity in an animal model of the disorder.
- Differences in genes related to the PPAR pathway and oxidative phosphorylation signaling were notable, both known to be activated by ketone metabolism, hinting towards a potential mechanism.
- Rat primary dorsal root ganglion neurons treated with a PPAR γ agonist exhibited less cell death and ROS production, further supporting this potential mechanism in the neuroprotective effects of KD.

- This case report details a 32-year-old male glioblastoma patient with IDH1 mutation who continues to follow a ketogenic diet as metabolic therapy at 80 months of life after diagnosis. He reports a good quality of life aside from an occasional seizure.
- The patient's glioblastoma grew slowly until 2017 when he decided to undergo a debulking surgery to remove as much of the tumor as possible. Since then, he continues to use ketogenic metabolic therapy to manage symptoms with the goal of preventing progression.

- A 47-year-old premenopausal woman with end-stage breast cancer (stage IV grade 3, ER+, PR+, HERR2-) metastasized to brain, lungs liver, abdomen, and bones was treated for 6 months with metabolically supported chemotherapy, ketogenic diet, hyperthermia, and hyperbaric oxygen therapy.
- All detectable lesions were eliminated, and her therapeutic response continues to be maintained beyond 2 years using a ketogenic diet, dietary supplements, and repurposed medication.

- Phosphatidylcholine (PC) containing medium-chain fatty acid (MCFAs) decanoic acid (10:0) reduces cellular levels of hydrogen peroxide thereby significantly decreasing reactive oxygen species (ROS) accumulation in neuroblastoma cells when compared to solvent l- α -Glycerophosphorylcholine and PC-containing long-chain fatty acid arachidic acid (20:0).
- Decanoic acid and other MCFAs may directly reduce oxidative stress independent of ketone levels, thereby promoting neuronal health.

A KETOGENIC DIET CONSUMED DURING RADIOTHERAPY IMPROVES SEVERAL ASPECTS OF QUALITY OF LIFE AND METABOLIC HEALTH IN WOMEN WITH BREAST CANCER; KLEMENT ET AL

- Women with breast cancer receiving radiotherapy and on the ketogenic diet fared better than those on a standard diet in breast symptoms, emotional functioning, and sleep quality.
- While both the ketogenic and standard diet groups experienced a worsening of subjective breast symptoms, the ketogenic diet group's symptoms trended better overall than those of the standard diet.
- The ketogenic diet was deemed safe, did not affect liver or kidney function, and may improve quality of life and metabolic health for women with breast cancer undergoing radiotherapy.

KETOGENIC DIET AND KETONE BODIES ENHANCE THE ANTICANCER EFFECTS OF PD-1 BLOCKADE; FERRERE ET AL

- The stress induced by a ketogenic-diet on energy pathways provokes an anti-tumor response from the immune system in a mouse tumor model.
- The ketogenic diet was found to significantly improve the efficacy of anti-CTLA-4 immunotherapy by decreasing PD-L1 levels while also increasing type-1 interferon and antigen-presenting genes.
- Combined, these effects display the key role of AMPK in regulating the immune system and resulted in a significant improvement in overall survival rate in the mice.

B-HYDROXYBUTYRATE DOES NOT ALTER THE EFFECTS OF GLUCOSE DEPRIVATION ON BREAST CANCER CELLS; MALDONADO ET AL

- *In vitro* experiments performed demonstrate that cells from two different breast cancer cell lines (MCF-7 and T47D) have reduced growth when deprived of glucose, and proliferation is not increased when beta-hydroxybutyrate (BHB), a ketone, levels increase.
- Under glucose deprivation in the presence of BHB, there are significant changes in the expression of multiple genes, but no significant changes in the metabolic pathways investigated.
- The authors warn that a subgroup of patients whose cancers show an increased expression of certain ketone catabolic enzymes may experience a detrimental effect on the KD.

THE INFLUENCE OF LOW-CARBOHYDRATE DIETS ON THE METABOLIC RESPONSE TO ANDROGEN-DEPRIVATION THERAPY IN PROSTATE CANCER; CHI ET AL

- A low-carbohydrate diet was found to significantly reverse many metabolic abnormalities induced by Androgen Deprivation Therapy (ADT) for prostate cancer while also further reducing androgens in the blood.
- The authors suggest that this state of decreased androgens may aid in delaying prostate cancer progression as well as mitigate other ADT-linked metabolic imbalances.

IMPACT OF A KETOGENIC DIET INTERVENTION DURING RADIOTHERAPY ON BODY COMPOSITION: IV. FINAL RESULTS OF THE KETOCOMP STUDY FOR RECTAL CANCER PATIENTS; KLEMENT ET AL

- A whole-foods-based ketogenic diet improved body composition and tumor response to radiotherapy in patients with non-metastasized rectal cancer.
- Patients on a ketogenic diet significantly reduced body weight and fat mass while preserving skeletal muscle mass, which is associated with longer and higher quality disease-free survival.

LOW CARB AND KETOGENIC DIETS INCREASE QUALITY OF LIFE, PHYSICAL PERFORMANCE, BODY COMPOSITION, AND METABOLIC HEALTH OF WOMEN WITH BREAST CANCER; KÄMMERER ET AL

- Among breast cancer patients in the rehabilitation phase, a healthy standard diet, a low carb diet (LCD) and a ketogenic diet all enhanced quality of life, body composition, and physical performance, though LCD patients experienced the greatest improvements in QoL.
- The ketogenic diet group did experience an increase in cholesterol levels, however they also had the best triglyceride/ high-density lipoprotein ratio, the best insulin sensitivity score, and very good physical performance and muscle-to-fat ratio compared to the other groups.

KETOGENIC DIET TREATMENT IN DIFFUSE INTRINSIC PONTINE GLIOMA IN CHILDREN: RETROSPECTIVE ANALYSIS OF FEASIBILITY, SAFETY, AND SURVIVAL DATA; PEREZ ET AL

- In five diffuse intrinsic pontine glioma (DIPG) patients aged 2.5 to 14 years, it was found to be safe and feasible to follow the ketogenic diet for more than 3 months with no adverse side effects.
- The ketogenic diet appeared to improve DIPG symptoms overall and promote participation in daily life activities.
- The median overall survival in the cases investigated was 18.7 months, a potential improvement over the expected 11-month prognosis, although this study was not powered to determine statistical significance between the groups.

IMPACT OF A KETOGENIC DIET INTERVENTION DURING RADIOTHERAPY ON BODY COMPOSITION: IV. FINAL RESULTS OF THE KETOCOMP STUDY FOR RECTAL CANCER PATIENTS; KLEMENT ET AL

- Patients with non-metastatic rectal cancer were treated with either KD or an unspecified standard diet while undergoing radiation therapy.
- While SD patients did not experience any changes in body composition, KD patients lost significant body weight and fat mass while preserving lean muscle mass.
- KD patients also experienced a trend towards larger Dworak regression grade and a larger percentage of near-complete responses that nearly met statistical significance in intention-to-treat analysis. Larger trials are strongly warranted.

SHORT-TERM FASTING IN GLIOMA PATIENTS: ANALYSIS OF DIET DIARIES AND METABOLIC PARAMETERS OF THE ERGO2 TRIAL; VOSS ET AL

- 50 patients undergoing re-irradiation for recurrent brain tumors were treated with either SD or KD + intermittent fasting.
- Though the study failed to meet its primary endpoint of improved progression-free survival and neither quality of life nor cognition were affected by the diet, KD-IF treated patients had significant decreases in leptin and insulin.
- Furthermore, low glucose was observed to be a significant prognostic parameter in a best responder analysis.

EPIGENETIC INACTIVATION OF ACETYL-COA ACETYLTRANSFERASE 1 PROMOTES THE PROLIFERATION AND METASTASIS IN NASOPHARYNGEAL CARCINOMA BY BLOCKING KETOGENESIS; LU ET AL

- Previously, this team reported that ketone metabolism enzymes act as tumor suppressor genes in nasopharyngeal carcinoma (NPC) through effects on epigenetic signaling.
- Here the same researchers showed that ACAT1, another ketone metabolism enzyme, is transcriptionally inactivated in NPC due to promoter hypermethylation. However, overexpression of ACAT1 suppressed proliferation, colony formation, and migratory and invasive capacity of NPC *in vitro*.
- *In vivo*, ACAT1 overexpressing cells had reduced tumorigenic capacity and modulated epithelial-mesenchymal transition (EMT) in an anti-cancer fashion. Furthermore, exogenously supplied ketones inhibited the growth of NPC cells in a dose-dependent fashion.
- Together, ketone metabolism elicits anti-cancer effects in NPC and may serve as a promising therapeutic target in this cancer type.

FEASIBILITY AND BIOLOGICAL ACTIVITY OF A KETOGENIC/INTERMITTENT-FASTING DIET IN PATIENTS WITH GLIOMA; SHRECK ET AL



- 25 astrocytoma patients with stable disease after chemotherapy underwent an 8 week Glioma Atkins-Based Diet, inclusive of a weekly protocol of 2 days of fasting followed by 5 days of modified Atkins diet.
- The diet was well tolerated, and a 80% of patients reached ketosis. Ketone uptake increased in both the tumor and contralateral healthy brain relative to urine ketone levels. And HbA1c, insulin, and fat body mass decreased while lean body mass increased in the patients.

EPIGENETIC INACTIVATION OF HYDROXYMETHYLGLUTARYL COA SYNTHASE REDUCES KETOGENESIS AND FACILITATES TUMOR CELL MOTILITY IN CLEAR CELL RENAL CARCINOMA; HAN ET AL



- Expression of HMGCS2, a key enzyme in ketone synthesis, is reduced by promoter region hypermethylation in clear cell renal cell carcinoma (ccRCC) cells. Greater suppression of HMGCS2 is associated with poorer clinical outcome.
- Restoration of HMGCS2 expression was possible via pharmacological manipulation and provision of exogenous BHB, and led to reduced migration and invasion of ccRCC in vitro.
- Ketone metabolism may represent a valuable therapeutic target for ccRCC, and HMGCS2 expression a valid prognostic biomarker for disease therapy and therapeutic efficacy.

DIVE DEEPER: Literature Reviews on Metabolic Therapy for Cancer from 2021

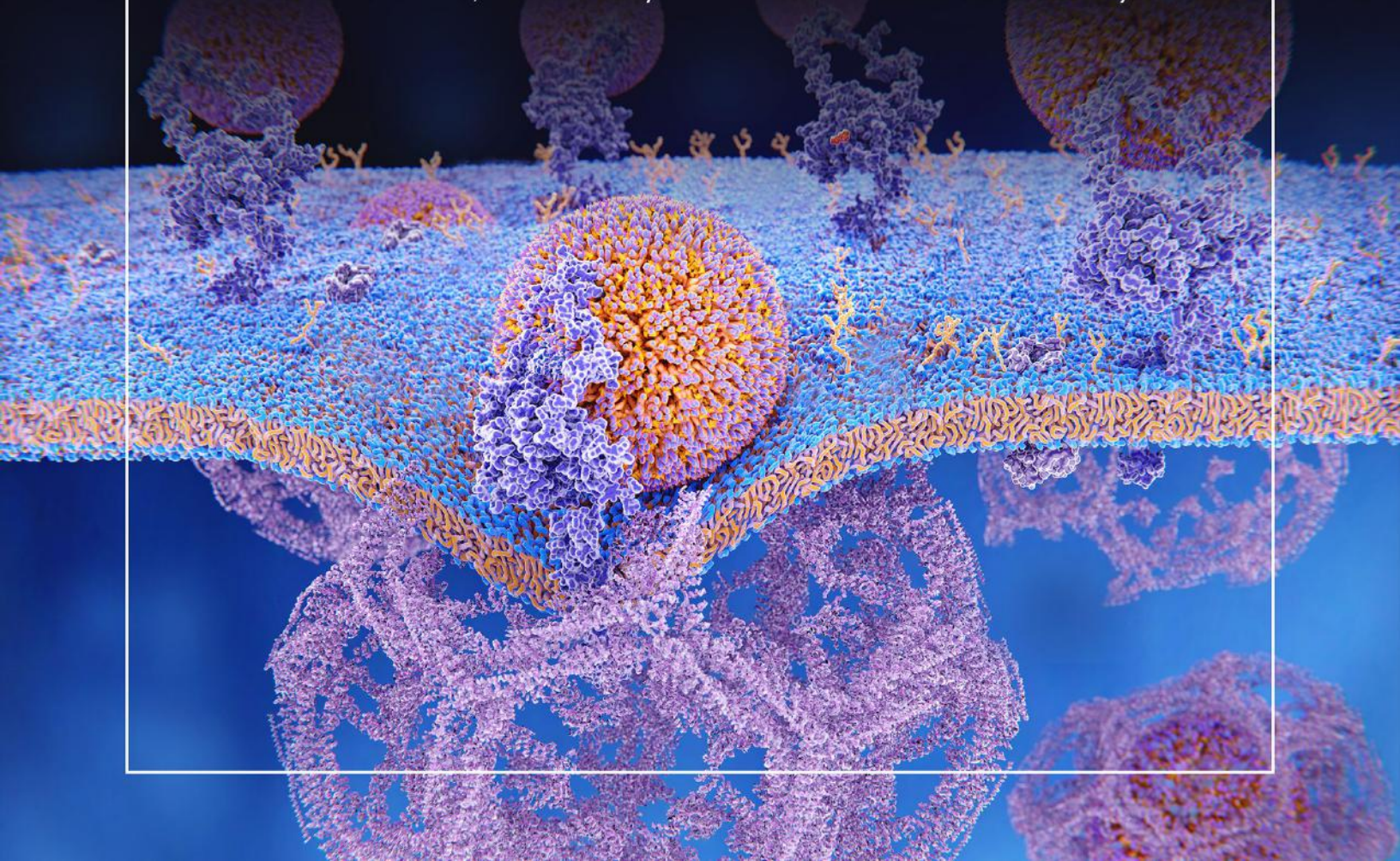
- Ketogenic Diet for Cancer: Critical Assessment and Research Recommendations; Lane et al
- A Root in Synapsis and the Other One in the Gut Microbiome-Brain Axis: Are the Two Poles of Ketogenic Diet Enough to Challenge Glioblastoma? Montella et al
- The use of ketogenic diets in cancer patients: a systematic review; Romer et al
- Ketogenic Diets in Pancreatic Cancer and Associated Cachexia: Cellular Mechanisms and Clinical Perspectives; Cortez et al



METABOLIC DYSFUNCTION

Ketogenic metabolic therapy induces a dramatic shift in physiological and cellular signaling, hormonal, and metabolic pathways, all of which come into play in the context of an individual with dysfunctional metabolism.

Though this dizzying array of effects can seem complicated, this multifaceted targeting is likely one major reason why such therapy can be a powerful therapeutic tool in tackling metabolic dysfunction. In 2021, an impressive number of studies were published evaluating the use and mechanisms underlying ketogenic metabolic therapy in a variety of metabolic disorders, from obesity and diabetes to heart failure & beyond.



SEVEN-DAY FASTING AS A MULTIMODAL COMPLEX INTERVENTION FOR ADULTS WITH TYPE 1 DIABETES: FEASIBILITY, BENEFIT AND SAFETY IN A CONTROLLED PILOT STUDY; BERGER ET AL

- A 7-day liquid-based fast was found to be a safe and feasible in type-1 diabetic patients with stable blood sugar values and did not cause diabetic ketoacidosis. Risk factors for metabolic syndrome such as weight, blood pressure, and cholesterol levels improved significantly during the fast.
- Ketone body levels increased while glucose levels were maintained throughout the fast.
- The authors note that patients with type-1 diabetes should only perform a fasting regimen under medical supervision.

AGE- AND SEX-DEPENDENT MODULATION OF EXOGENOUS KETONE SUPPLEMENT-EVOKED EFFECTS ON BLOOD GLUCOSE AND KETONE BODY LEVELS IN WISTAR ALBINO GLAXO RIJSWIJK RATS; KOVÁCS ET AL

- Rodent data suggests that the different responses to exogenous ketone supplements (EKS) on blood beta-hydroxybutyrate and glucose concentrations can, at least in part, be attributed to age and sex. These differences may play a role in how men and women respond differently to metabolic therapies.
- Female rats given a daily dose of a 1:1 mix of ketone ester and medium-chain triglyceride had higher levels of blood BHB but followed a similar decreasing trend to the controls as they aged. However, males receiving the EKS experienced a higher level of blood BHB that continued to increase as they aged, unlike the controls.
- For blood glucose concentrations, both males and females followed similar trends, albeit at lower glucose levels, as the controls. Females tended to stay around the same level as they aged, with a slight increase at the end of life whereas the glucose level for males continuously declined with age.

LOW-CARBOHYDRATE HIGH-FAT DIET AND EXERCISE: EFFECT OF A 10-WEEK INTERVENTION ON BODY COMPOSITION AND CVD RISK FACTORS IN OVERWEIGHT AND OBESE WOMEN—A RANDOMIZED CONTROLLED TRIAL; VALSDOTTIR ET AL

- 10 weeks of standard diet or a low-carbohydrate high-fat diet, both with or without exercise, were tested in overweight and obese women.
- All four groups achieved a weight loss of over 5% of initial body weight, however there were no differences between the groups 6 weeks post intervention.
- The low-carbohydrate-high-fat diet did not have a superior effect on body composition, aerobic endurance, (VO₂ peak), or cardiovascular risk factors in this study.
- Regardless of diet, exercise elicited beneficial effects on cardiorespiratory fitness.

VERY-LOW-CALORIE KETOGENIC DIET AS A SAFE AND VALUABLE TOOL FOR LONG-TERM GLYCEMIC MANAGEMENT IN PATIENTS WITH OBESITY AND TYPE 2 DIABETES; MORICONI ET AL

- In Type-2 diabetes patients, a very-low-calorie ketogenic diet (VLCKD) promoted significant weight loss and improved quality of life scores, whereas no significant changes were observed in the low-calorie diet (LCD) group.
- At the end of the year-long study, 26.6% of patients in the VLCKD group had stopped all antidiabetic medications, and 73.3% were taking only metformin, whereas 46.6% of LCD patients had to increase antidiabetic medications.

NUTRITIONAL KETOSIS TO TREAT PULMONARY HYPERTENSION ASSOCIATED WITH OBESITY AND METABOLIC SYNDROME: A CASE REPORT; KIM ET AL

- A 62-year-old woman with morbid obesity, pulmonary hypertension, and metabolic syndrome successfully followed a ketogenic diet through telehealth remote care for one year, resulting in the reversal of metabolic syndrome, weight loss, and hemodynamic improvement.

KETOGENIC DIET IN WOMEN WITH POLYCYSTIC OVARY SYNDROME AND LIVER DYSFUNCTION WHO ARE OBESE: A RANDOMIZED, OPEN-LABEL, PARALLEL-GROUP, CONTROLLED PILOT TRIAL; BAI ET AL

- Women with polycystic ovary syndrome and liver dysfunction who are obese and followed a ketogenic diet for 12 weeks experienced an improvement in the menstrual cycle, reduced blood glucose, reduced body weight, and improved liver function compared to a parallel group that received traditional pharmacological treatment.

INGESTED KETONE ESTER LEADS TO A RAPID RISE OF ACETYL-COA AND COMPETES WITH GLUCOSE METABOLISM IN THE BRAIN OF NON-FASTED MICE; SUISSA ET AL

- Exogenous ketone ester (R)-3-hydroxybutyl (R)-3-hydroxybutyrate) rapidly increases plasma BHB in non-fasted mice. Brain BHB uptake strongly correlated with circulating levels and was preferentially taken into the neocortex.
- Brain acetyl-CoA and citric acid cycle intermediaries rose, while glycolysis was inhibited.
- The authors suggest these metabolic effects could be therapeutic in diverse neurological diseases.

A KETOGENIC LOW-CARBOHYDRATE HIGH-FAT DIET INCREASES LDL CHOLESTEROL IN HEALTHY, YOUNG, NORMAL-WEIGHT WOMEN: A RANDOMIZED CONTROLLED FEEDING TRIAL; BUREN ET AL

- A four-week ketogenic low-carbohydrate high-fat (LCHF) diet rich in saturated fatty acids increased overall low-density lipoprotein (LDL) cholesterol, apolipoprotein B-100, small, dense LDL cholesterol, and large, buoyant LDL cholesterol in young, healthy normal-weight women.

KETOGENIC DIET ALLEVIATES COLITIS BY REDUCTION OF COLONIC GROUP 3 INNATE LYMPHOID CELLS THROUGH ALTERING GUT MICROBIOME; KONG ET AL

- A ketogenic diet (KD) alleviated inflammatory colitis in an animal model by altering the gut microbiota and metabolites. Amelioration of colitis was dependent on the KD's effects on the gut microbiome. This improvement was not found in the low-carbohydrate diet group.
- The KD promoted the protection of the intestinal barrier, reduced production of group 3 innate lymphoid cells (ILCs), and reduced inflammatory interleukin cytokines.

OBESITY AND CIRCULATING LEVELS OF VITAMIN D BEFORE AND AFTER WEIGHT LOSS INDUCED BY A VERY LOW-CALORIE KETOGENIC DIET; BUSCEMI ET AL

- Patients with obesity on a very-low-calorie ketogenic diet had significant fat loss associated with a normalization in serum Vitamin D levels and parathyroid blood levels.
- Adipose tissue plays a prominent role in the storage of Vitamin D, which is released through the breakdown of adipose cells during weight loss facilitated by a VLCKD.

KETOGENIC DIET EFFECTS ON INFLAMMATORY ALLODYNIA AND ONGOING PAIN IN RODENTS; RUSKIN ET AL

- 3-4 weeks on a ketogenic diet significantly improved induced inflammatory pain in rodents, with more of an effect on rats than on mice.
- The KD reduced pro-inflammatory cytokines and eicosanoids while elevating anti-inflammatory cytokines.

LOW-CARBOHYDRATE DIETS LEAD TO GREATER WEIGHT LOSS AND BETTER GLUCOSE HOMEOSTASIS THAN EXERCISE: A RANDOMIZED CLINICAL TRIAL

- A pilot study of obese and overweight adults on a low-carbohydrate diet (LCD) experienced greater weight loss, fat loss, and waist reduction than those in the exercise (EX) group.
- Both the LCD and EX groups reduced visceral and subcutaneous fat, improved liver steatosis, and improved insulin resistance.
- Triglycerides decreased in both groups, while low-density lipoprotein cholesterol increased in the LCD group while decreasing in the EX group.

ASSOCIATION BETWEEN KETOSIS AND METABOLIC ADAPTATION AT THE LEVEL OF RESTING METABOLIC RATE; MARTINS ET AL

- Significant metabolic adaptation was observed in obese patients on a low-calorie ketogenic diet for 8 weeks. BHB may be part of a starvation signal and likely a modulator of metabolic adaptation. The greater the BHB concentration, the greater the reduction in resting metabolic rate, potentially aiming to slow down the metabolism and conserve energy stores in response to starvation.
- Women on ketogenic diets with high BHB plasma concentration may be at increased risk of metabolic adaptation of reduced resting metabolic rate, and may experience resistance to weight loss due to the starvation signaling pathway.
- There was no significant correlation between BHB levels and metabolic adaptation of males.

KETOGENIC DIET AGGRAVATES COLITIS, IMPAIRS INTESTINAL BARRIER AND ALTERS GUT MICROBIOTA AND METABOLISM IN DSS-INDUCED MICE; LI ET AL

- In this mouse chemical-induced model of inflammatory bowel disease, a ketogenic diet worsened colitis as noted by increased body weight loss, DAI (disease activity index) scores, and histological scores, and worse colon shortening.
- The KD also increased the expression of several serum and colon inflammatory cytokines and chemokines in this model, as well as increased intestinal permeability and reduced markers of intestinal epithelial barrier function.
- Pre-treatment with KD also negatively influenced the gut microbiota, increasing prevalence of pathogenic taxa and reducing that of beneficial microbes.
- More data is needed, but KD may worsen symptoms of individuals with inflammatory bowel disease.

KETOGENIC DIET AS AN ADVANCED OPTION FOR THE MANAGEMENT OF PEDIATRIC OBESITY; FAVRET ET AL



- A low-carbohydrate high-fat ketogenic dietary eating plan was safe and feasible in pediatric patients with obesity enrolled in the Staged Transitional Eating Plan at the Duke Healthy Lifestyles Program.
- STEP's goal is to achieve weight loss with careful attention to optimal food choices. They found this ketogenic protocol is particularly ideal for those interested in LC nutrition who have good vegetable acceptance and a family willing to participate in the same eating plan.

NOVEL KETOGENIC DIET FORMULATION IMPROVES SUCROSE-INDUCED INSULIN RESISTANCE IN CANTON STRAIN DROSOPHILA MELANOGASTER; KAYODE ET AL



- Fruit flies treated with a KD experienced an improvement in markers of sucrose-induced insulin resistance, including weight gain, glucose concentration, triglycerides, antioxidant status, lipid peroxidation compared to those on a standard control diet or high-sucrose diet alone.

A MULTIPHASE DIETETIC PROTOCOL INCORPORATING AN IMPROVED KETOGENIC DIET ENHANCES WEIGHT LOSS AND ALTERS THE GUT MICROBIOME OF OBESE PEOPLE; YUAN ET AL



- A 12-week multiphase dietetic protocol inclusive of a ketogenic diet modulated the gut microbiome of obese subjects by decreasing abundance of the Lachnospiraceae ND3007 group, the Eubacterium hallii group, and Pseudomonas and Blautia.
- The intervention also enhanced weight loss and subjects exhibited a more healthy gut microbiota co-occurrence network post-intervention.
- The authors suggest that the super weight loss outcomes may be associated with the dietary-induced changes in the gut microbiota.

EFFECTS OF COMBINED EXERCISE AND LOW CARBOHYDRATE KETOGENIC DIET INTERVENTIONS ON WAIST CIRCUMFERENCE AND TRIGLYCERIDES IN OVERWEIGHT AND OBESE INDIVIDUALS: A SYSTEMATIC REVIEW AND META-ANALYSIS



- A meta-analysis investigating combined exercise and low carbohydrate ketogenic diet interventions (CELCKD) had a beneficial effect on obese and overweight individuals.
- CELCKD was found to be an effective intervention in increasing metabolic health, decreasing waist circumference, and improving triglyceride levels. Body composition, fasting glucose, and other lipid profiles were not statistically different post-intervention. No adverse side effects were reported.

EFFECT OF A VERY LOW-CARBOHYDRATE KETOGENIC DIET VS RECOMMENDED DIETS IN PATIENTS WITH TYPE 2 DIABETES: A META-ANALYSIS; RAFIULLAH ET AL

- A meta-analysis of randomized controlled trials comparing a very low carbohydrate KD to any other recommended diet in type 2 diabetics found that VLCKDs result in superior weight loss, and HbA1c for 6 months, and in greater improvements in triglycerides, HDL, and anti-diabetic medication requirements for 12 months.
- The major observed limitation was patient adherence to carbohydrate restriction.

THE EFFECT OF KETOGENIC DIET ON SERUM LIPID CONCENTRATIONS IN CHILDREN WITH MEDICATION RESISTANT EPILEPSY; YILMAZ ET AL

- In this clinical trial of 73 children with drug-resistant epilepsy treated with KD, triglycerides and total cholesterol increased over the first month, but stabilized over time. By 24 months, total cholesterol was not significantly higher than baseline, and triglycerides exhibited a downward trend that neared normal levels.
- Notably, the rise in TG and TC did not occur in patients with pre-existing dyslipidemia.

CASE REPORT: KETOGENIC DIET IS ASSOCIATED WITH IMPROVEMENTS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE; NORWITZ ET AL

- After adapting a KD, a 54-yr old patient with Chronic Obstructive Pulmonary Disease (COPD) experienced marked improvements in inflammation and lung function. Inflammatory markers returned to a normal range, and his forced expiratory volume increased by 37.5%.
- These promising results strongly support further study of KD for COPD, which is typically considered progressive and incurable.

EFFECTIVENESS AND SAFETY OF A VERY LOW-CALORIE KETOGENIC DIET ON WEIGHT REGAIN FOLLOWING BARIATRIC SURGERY; LUGARINHO CORREA ET AL

- 11 patients post-gastric bypass surgery without >50% body weight reduction or weight regain underwent a very low calorie KD (600-800 kcal/d).
- Weight, BMI, abdominal circumference, and HbA1c were significantly reduced and no serious adverse effects were reported.

KETOGENIC DIET AS ELECTIVE TREATMENT IN PATIENTS WITH DRUG-UNRESPONSIVE HYPERINSULINEMIC HYPOGLYCEMIA CAUSED BY GLUCOKINASE MUTATIONS; MAIORANA ET AL

- Ketogenic diet resolved symptoms, improved alertness, stopped seizures, and increased IQ in three children with diffuse drug-unresponsive hyperinsulinemic hypoglycemia, averting the need for a pancreatectomy.
- Caregivers reported substantial improvements in physical and psychosocial well-being and quality of life.
- This case series suggests that KMT is safe and very effective and may represent an invaluable therapeutic strategy to improve outcomes in this patient population.

DIETARY CARBOHYDRATES RESTRICTION INHIBITS THE DEVELOPMENT OF CARDIAC HYPERTROPHY AND HEART FAILURE; NAKAMURA ET AL

- Mice were fed either control diet, or a low-carbohydrate diet with either high fat (LCHF) or high protein (LCHP) following transverse aortic constriction, a model system for chronic hypertensive cardiac remodeling.
- Both LC groups exhibited reduced hypertrophy and systolic dysfunction compared to control.
- Both LC groups re-activated GSK-3B, an anti-hypertrophic serine/threonine kinase, hinting at the potential mechanism of action. However, only LCHF, but not LCHP, was cardioprotective in GSK-3B cardiac-specific knockout mice. This appeared to be related to LCHF's unique elevation in B-hydroxybutyrate.

LOW-CALORIE KETOGENIC DIET WITH CONTINUOUS POSITIVE AIRWAY PRESSURE TO ALLEVIATE SEVERE OBSTRUCTIVE SLEEP APNEA SYNDROME IN PATIENTS WITH OBESITY SCHEDULED FOR BARIATRIC/METABOLIC SURGERY: A PILOT, PROSPECTIVE, RANDOMIZED MULTICENTER COMPARATIVE STUDY

- Obese patients with obstructive sleep apnea syndrome treated with a low calorie ketogenic diet during pre-bariatric surgery preoperative continuous positive airway pressure (CPAP) reduced body weight, CRP, blood pressure, total cholesterol, LDL, and triglycerides, but the effects were not greater than CPAP alone.
- CRP was lower in the LCKD + CPAP group compared to CPAP alone, suggesting a possible benefit on chronic inflammatory status.
- While both groups improved on the apnea-hypopnea index (AHI), there was no observed advantage of adding LCKD.

EFFECT OF VERY LOW-CALORIE KETOGENIC DIET IN COMBINATION WITH OMEGA-3 ON INFLAMMATION, SATIETY HORMONES, BODY COMPOSITION, AND METABOLIC MARKERS. A PILOT STUDY IN CLASS I OBESE SUBJECTS; RONDANELLI ET AL



- In a pilot open label study, 12 women with class I obesity consumed a very low-calorie ketogenic diet with omega-3 supplementation followed by a non-ketogenic low carbohydrate diet for a period of 90 days.
- Body weight, waist circumference, fat mass, and visceral adipose all decreased, without effects observed on fat free mass, while ghrelin increased over the study period.

THE ROLE OF VERY LOW CALORIE KETOGENIC DIET IN SYMPATHETIC ACTIVATION THROUGH CORTISOL SECRETION IN MALE OBESE POPULATION; POLITO ET AL



- Salivary cortisol levels and galvanic skin response (GSR) decreased in a group of 30 obese patients undergoing 8 weeks of very low calorie ketogenic diet, suggesting a potential benefit on the sympathetic nervous system and HPA axis.
- Weight, BMI, total cholesterol, triglycerides, AST, ALT, GGT, and CRP all decreased as well, while adiponectin increased.

EFFICACY OF KETOGENIC DIETS ON TYPE 2 DIABETES: A SYSTEMATIC REVIEW; TINGUELY ET AL



- In this systematic review, HbA1c of Type 2 Diabetic patients improves within 3 weeks of adaptation to ketogenic diet, with effects persisting for at least 1 year.
- Weight loss and a reduction in glucose-lowering medication is also observed and appears to be maintained with long-term adherence.
- Support in the form of psychological counseling, enhancing positive affectivity, and reinforcing mindful eating improved outcomes and adherence.

EFFECT OF B-HYDROXYBUTYRATE MONOESTER ON MARKERS OF IRON METABOLISM IN NEW-ONSET PREDIABETES: FINDINGS FROM A RANDOMISED PLACEBO-CONTROLLED TRIAL; KIMITA ET AL



- In this randomized controlled cross-over trial, exogenous ketone monoester induced ketosis but did not affect circulating levels of hepcidin or ferritin (markers of iron metabolism) in 18 prediabetic patients following acute pancreatitis.

3-HYDROXYBUTYRATE ADMINISTRATION ELEVATES PLASMA PARATHYROID HORMONE IN A PILOT HUMAN RANDOMIZED, CONTROLLED, CROSS OVER TRIAL; SVART ET AL

- In this randomized, controlled, cross-over study, continuous intravenous infusion of BHB for 390 minutes increased parathyroid hormone by 25%, reduced phosphate by 30%, and increased CTX by 5%, without affecting PINP or albumin-corrected calcium levels.
- The authors conclude that BHB may increase markers of bone resorption and this potential negative effect on bone health warrants additional investigation.

EFFECT OF A KETOGENIC DIET ON THE NUTRITIONAL PARAMETERS OF OBESE PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS; LOPEZ-ESPINOZA ET AL

- A systematic review and random-effects meta-analysis of randomized controlled trials comparing the metabolic effects of KD versus standard diet reported significant heterogeneity and failed to identify statistically significant differences between the groups for BMI, total cholesterol, HDL, LDL, or triglycerides.

EXOGENOUS KETOSIS IN PATIENTS WITH TYPE 2 DIABETES: SAFETY, TOLERABILITY AND EFFECT ON GLYCAEMIC CONTROL; SOTO-MOTA ET AL

- Exogenous ketone monoester consumption in a group of 21 insulin-independent type 2 diabetic patients significantly improved all measured markers of glycemic control including fructosamine, HbA1c, mean daily glucose, and time in range.
- Only mild and infrequent adverse reactions were observed, and electrolyte, acid-base status, and renal function was normal throughout the study.
- The authors suggest that exogenous ketone ester consumption may provide a safe and feasible novel intervention to improve glycemic control in this patient population, and additional research is warranted.

DIVE DEEPER: Literature Reviews on Metabolic Dysfunction from 2021

- Ketogenic diet as a potential intervention for lipedema; Keith et al
- Ketogenic Diet, Physical Activity, and Hypertension-A Narrative Review; Di Raimondo et al
- The ketogenic diet as a therapeutic intervention strategy in mitochondrial disease; Qu et al
- Very-low-calorie ketogenic diet: An alternative to a pharmacological approach to improve glycometabolic and gonadal profile in men with obesity; Mongioi et al
- Ketogenic diets in the management of type 1 diabetes: Safe or safety concern? Buehler et al
- Dietary Interventions: A Promising Treatment for Polycystic Ovary Syndrome; Che et al

HUMAN OPTIMIZATION & AGING

The pursuit of health optimization as we age may represent one of the most valuable goals of healthcare. Understanding the nutritional and metabolic approaches that support our body's needs throughout the phases of life is critical to preventing or reversing the slew of chronic diseases plaguing humans today. In 2021, a number of studies investigated the heart of this question, and asked if nutritional ketosis impacts relevant aspects of our physiology and metabolism. Slowly, the insight gained from these lines of research will help formulate a more accurate and actionable picture of the best methods for optimizing health and longevity.



COMBINED EFFECTS OF A KETOGENIC DIET AND EXERCISE TRAINING ALTER MITOCHONDRIAL AND PEROXISOMAL SUBSTRATE OXIDATIVE CAPACITY IN SKELETAL MUSCLE; HUANG ET AL

A KETOGENIC DIET IMPACTS MARKERS OF MITOCHONDRIAL MASS IN A TISSUE SPECIFIC MANNER IN AGED MICE; ZHOU ET AL

THE KETOGENIC DIET PRESERVES SKELETAL MUSCLE WITH AGING IN MICE; WALLACE ET AL

BICARBONATE UNLOCKS THE ERGOGENIC ACTION OF KETONE MONOESTER INTAKE IN ENDURANCE EXERCISE; POFFÉ ET AL

- A normal-protein ketogenic diet combined with treadmill training in mice increased body weight and fat mass, increased intramuscular triglyceride storage, and upregulated protein metabolism.
- The combination of a normal-protein ketogenic diet with exercise synergistically activated mitochondrial genes related to increasing skeletal muscle oxidative capacity.

- A ketogenic diet stimulated mitochondrial enzymes and prevented age-related decrease in enzyme activity in the brain of C57BL/6JN male mice. No consistent changes were observed in the mitochondria of the liver or kidneys. The KD's effect on mitochondrial activity and structure appears specific to tissue type.

- Skeletal muscle mass was significantly greater in 26-month-old mice who had been on a ketogenic diet for the previous year, suggesting that a long-term ketogenic diet may be effective at preventing sarcopenia.
- The skeletal muscle fibers in the aging mice shifted from type IIb to type IIa fibers, increased mitochondrial biogenesis, oxidative metabolism, and anti-oxidant stress, while decreasing endoplasmic reticulum stress, protein synthesis, and proteasome activity.

- Ingesting bicarbonate (NaHCO_3) along with ketone ester (KE) enhanced high-intensity performance without additional gastrointestinal effects in a group of 9 well-trained cyclists. Neither chemical alone improved performance.
- KE ingestion alone transiently elevated blood ketone levels during the first 2 hours of a simulated cycling race, but resulted in a blood pH drop. Co-ingestion of bicarbonate prevented KE-induced acidosis and improved performance.

EXOGENOUS KETOSIS IMPAIRS 30-MIN TIME-TRIAL PERFORMANCE INDEPENDENT OF BICARBONATE SUPPLEMENTATION; POFFÉ ET AL

- Ketone ester (KE) ingestion increased blood ketone body levels, dropped blood pH, and impaired exercise performance in a group of 14 well-trained male cyclists undergoing high intensity exercise.
- Bicarbonate co-ingestion blocked the acidotic effect but did not sufficiently counteract the performance impairment of KE in this trial unlike previous reports by the same authors in another study.
- The authors suggest that acute exogenous ketosis may not be an optimal nutritional approach for short, high-intensity endurance exercise performance, even when bicarbonate is co-ingested.

A MODIFIED MCT-BASED KETOGENIC DIET INCREASES PLASMA B-HYDROXYBUTYRATE BUT HAS LESS EFFECT ON FATIGUE AND QUALITY OF LIFE IN PEOPLE WITH MULTIPLE SCLEROSIS COMPARED TO A MODIFIED PALEOLITHIC DIET: A WAITLIST-CONTROLLED, RANDOMIZED PILOT STUDY; LEE ET AL

- When comparing the Paleolithic diet to a 1:1 MCT-based ketogenic diet in Multiple Sclerosis (MS) patients in a small randomized, controlled trial, those on a paleo diet experienced greater clinical improvements.
- The Paleo group had significant improvements in fatigue scores and maintained cognitive function while the KD group did not experience notable changes.
- The KD induced a mild level of nutritional ketosis and significantly reduced fasting glucose and insulin compared to baseline.

KETOGENIC DIET INDUCES AUTOPHAGY TO ALLEVIATE BLEOMYCIN-INDUCED PULMONARY FIBROSIS IN MURINE MODELS; MU ET AL

- A ketogenic diet significantly restored pulmonary function in mice with bleomycin-induced lung damage. The ketogenic diet upregulated autophagic cell death by activating the PI3k/AKT/mTOR signaling pathway, renewing alveolar structure, and increasing the survival rate of mice with pulmonary fibrosis.

MURINE NEONATAL KETOGENESIS PRESERVES MITOCHONDRIAL ENERGETICS BY PREVENTING PROTEIN HYPERACETYLATION; ARIMA ET AL



- Neonatal ketogenesis plays a protective role in mitochondrial function by preventing hyperacetylation of mitochondrial proteins in a mouse model.
- Mice without the ability to enter ketosis due to a mutation in hydroxymethylglutaryl-CoA synthase 2 develop microvesicular steatosis (fatty liver) within a few days of birth.

THE EFFECT OF BLOOD KETONE CONCENTRATION AND EXERCISE INTENSITY ON EXOGENOUS KETONE OXIDATION RATES IN ATHLETES; DEARLOVE ET AL



- In this single-blind, random-order controlled, crossover study, six athletes completed a cycling exercise after consuming a low dose of beta-hydroxybutyrate (BHB), a high dose BHB, or bitter water (control). In the high dose group, blood BHB levels doubled that of the low-dose group, however, BHB oxidation rates were similar at rest and throughout exercise.
- Exercise efficiency was significantly improved when blood BHB concentration was raised to ~2mM, however, exercise efficiency and BHB oxidation rates are not further increased with higher blood BHB levels.

KETOGENIC DIET WITH MEDIUM-CHAIN TRIGLYCERIDES RESTORES SKELETAL MUSCLE FUNCTION AND PATHOLOGY IN A RAT MODEL OF DUCHENNE MUSCULAR DYSTROPHY; FUJIKURA ET AL



- An MCT based ketogenic diet increased muscle strength, increased muscle fiber diameter, reduced muscle necrosis, suppressed inflammation, and lessened fibrosis in rats with Duchenne muscular dystrophy.
- These effects were associated with a promotion of satellite cell proliferation which is related to muscle cell regeneration.

EFFECTS OF A LOW-CARBOHYDRATE KETOGENIC DIET ON HEALTH PARAMETERS IN RESISTANCE-TRAINED WOMEN; VARGAS-MOLINA ET AL



- Improvements in systolic blood pressure and bone mineral density were observed in a group of resistance trained women undergoing a training program eating a ketogenic diet, but not in the group consuming a non-ketogenic diet.

A 1-MONTH KETOGENIC DIET INCREASED MITOCHONDRIAL MASS IN RED GASTROCNEMIUS MUSCLE, BUT NOT IN THE BRAIN OR LIVER OF MIDDLE-AGED MICE; ZHOU ET AL

- Increased mitochondrial content was observed in red gastrocnemius muscle, but not the liver, prefrontal cortex, or hippocampus, of healthy middle-aged mice after 1 month of ketogenic diet.
- This data suggests changes in mitochondrial content in response to ketosis is tissue-specific.

EFFECTS OF 30 DAYS OF KETOGENIC DIET ON BODY COMPOSITION, MUSCLE STRENGTH, MUSCLE AREA, METABOLISM, AND PERFORMANCE IN SEMI-PROFESSIONAL SOCCER PLAYERS; PAOLI ET AL

- An isoprotein ketogenic diet induced a greater decrease of body fat, visceral adipose tissue, waist circumference, and extra-cellular water than a western diet in a group of semi-professional soccer players.
- No effects on strength, power, or muscle mass were observed.

ALTERED CYTOKINE LEVELS IN CEREBROSPINAL FLUID FOLLOWING KETOGENIC DIET OF CHILDREN WITH REFRACTORY EPILEPSY; WICKSTROM ET AL

- Three months of ketogenic diet reduced multiple cytokines in the cerebrospinal fluid of pediatric epilepsy patients, supporting theories of an immunomodulatory and potential anti-inflammatory effect of the diet.

THE EFFECT OF A KETOGENIC LOW-CARBOHYDRATE, HIGH-FAT DIET ON AEROBIC CAPACITY AND EXERCISE PERFORMANCE IN ENDURANCE ATHLETES: A SYSTEMATIC REVIEW AND META-ANALYSIS; CAO ET AL

- Low carbohydrate ketogenic diets did not affect VO₂ max, time to exhaustion, HR max, or rating of perceived exhaustion, but did alter substrate oxidation response to respiratory exchange rate, in this systematic review and meta-analysis of 10 studies on endurance athletes.
- This data suggests LCHF KDs do not affect aerobic capacity or exercise performance in this population.

EFFECTS OF TWO MONTHS OF VERY LOW CARBOHYDRATE KETOGENIC DIET ON BODY COMPOSITION, MUSCLE STRENGTH, MUSCLE AREA, AND BLOOD PARAMETERS IN COMPETITIVE NATURAL BODY BUILDERS; PAOLI ET AL

- The ketogenic diet was adequate and beneficial for health and leaning purposes in bodybuilders. Body fat significantly decreased in bodybuilders on KD while lean mass was maintained. Lean mass increased significantly in bodybuilders on a Western diet (WD).
- After an 8-week diet adherence, the KD decreased blood triglycerides, glucose, insulin, and inflammatory cytokines compared to the WD group.
- Brain-derived neurotrophic factor, which is related to neuroplasticity, memory, and glucose metabolism, increased in both the KD and WD group with a greater increase in the KD group.

BODY COMPOSITION CHANGES IN PHYSICALLY ACTIVE INDIVIDUALS CONSUMING KETOGENIC DIETS: A SYSTEMATIC REVIEW; COLEMAN ET AL

- A systematic review of thirteen studies concluded that a ketogenic diet can promote mobilization of fat stores to reduce fat mass, while maintaining fat-free mass in healthy, physically active populations.
- On a ketogenic diet, body mass decreased by 2.7kg (increased 0.3kg in control), fat mass decreased by 2.3kg (0.3kg in control), and fat-free mass decreased by 0.3kg (increased 0.7kg in control).
- The authors note some biases and limitations in the literature including self-selection of diet intervention, lack of controlled feeding, and use of bio-electrical impedance analysis (BIA) to measure body composition.

PERCEPTIONS OF APPETITE DO NOT MATCH HORMONAL MEASURES OF APPETITE IN TRAINED COMPETITIVE CYCLISTS AND TRIATHLETES FOLLOWING A KETOGENIC DIET COMPARED TO A HIGH-CARBOHYDRATE OR HABITUAL DIET: A RANDOMIZED CROSSOVER TRIAL; GRAYBEAL ET AL

- Objective and subjective measures of appetite was measured in athletes eating ketogenic diet (KD), high carbohydrate diet (HCD), or habitual diet (HD).
- Fasting ghrelin was lower and and GLP-1 was higher in the KD group compared to HCD and HD, with no differences in fasting insulin.
- Post-meal ghrelin and insulin were lower, and GLP-1 was higher, in the KD group compared to HCD and HD.
- Despite changes in these objective measures, post-meal subjective appetite ratings did not differ between the groups.

OBESOGENIC AND KETOGENIC DIETS DISTINCTLY REGULATE THE SARS-COV-2 ENTRY PROTEINS ACE2 AND TMPRSS2 AND THE RENIN-ANGIOTENSIN SYSTEM IN RAT LUNG AND HEART TISSUES; DA EIRA ET AL

- An obesogenic high-fat sucrose-enriched diet (HFS) induced obesity and increased angiotensin converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) in the lungs of rats compared to standard rodent chow.
- In contrast, ketogenic diet lowered ACE2, TMPRSS2, toll-like receptor 4, and IL-6 receptor in the lungs in comparison to HFS.
- These pathways represent SARS-CoV2 entry protein pathways and thus the authors conclude that while obesogenic diets may increase viral entry to the lungs, KDs potentially dampen these associated pathways and therefore may reduce viral entry and less severity of infection in COVID-19.

VERY-LOW-CARBOHYDRATE DIET ENHANCES HUMAN T-CELL IMMUNITY THROUGH IMMUNOMETABOLIC REPROGRAMMING; HIRSCHBERGER ET AL

- In a cell-based study on primary human T cells, ketone bodies enhanced CD4+, CD8+, and regulatory T cell capacity, and increased T cell memory formation.
- Gene expression & functional metabolomic analysis revealed an enhancement of mitochondrial oxidative metabolism and substantial immunometabolic reprogramming.
- The authors conclude very low carbohydrate KDs may serve as a novel nutritional intervention and clinical tool to improve T-cell immunity in humans that deserves additional attention and investigation.

ALTERED CHOLESTEROL HOMEOSTASIS IN CRITICAL ILLNESS-INDUCED MUSCLE WEAKNESS: EFFECT OF EXOGENOUS 3-HYDROXYBUTYRATE; GOOSSENS ET AL

- Reduced circulating cholesterol was associated with muscle weakness in both critically ill patients and septic mice.
- In the mice, exogenous beta-hydroxybutyrate increased plasma cholesterol and also the expression of cholesterol synthesis genes in the muscle but not the liver. Tracer studies also revealed that the muscle of the septic mice preferentially took up BHB in comparison to other TCA intermediates.
- Taken together, ketosis may support muscle health in part through its effects on cholesterol homeostasis.

UPREGULATION OF HEPATIC AUTOPHAGY UNDER NUTRITIONAL KETOSIS; LISKIEWICZ ET AL

- Short term (48 hour) animal- or plant-based ketogenic diet exposure induced autophagy in the liver of healthy male mice, though more prominently in mice fed a plant-based KD.
- The mechanisms at play appear to involve activation of SIRT1 and downregulation of FOXO3 and p53.

CHRONIC EXOGENOUS KETONE SUPPLEMENTATION BLUNTS THE DECLINE OF CARDIAC FUNCTION IN THE FAILING HEART; TAKAHARA ET AL

- Chronic (2 weeks) of ketone monoester treatment induced ketosis and attenuated the development of heart failure and cardiomyocyte hypertrophy in a mouse model of the condition compared to control animals.

EXOGENOUS D-B-HYDROXYBUTYRATE LOWERS BLOOD GLUCOSE IN PART BY DECREASING THE AVAILABILITY OF L-ALANINE FOR GLUCONEOGENESIS; SOTO-MOTA ET AL

- Ketone ester elevated blood beta-hydroxybutyrate and reduced glucose and L-alanine in fasted 10 healthy human volunteers.
- Alanine supplementation blunted the ketosis-induced drop in glucose, suggesting that this effect may be elicited in part by a reduced availability of L-alanine for gluconeogenesis during exogenous ketosis.

EXOGENOUS KETOSIS INCREASES BLOOD AND MUSCLE OXYGENATION BUT NOT PERFORMANCE DURING EXERCISE IN HYPOXIA; POFFÉ ET AL

- Ketone ester was administered to a group of highly trained male cyclists prior to a simulated cycling race during which fraction of inspired oxygen was gradually decreased.
- KE prevented the hypoxia-induced reduction in blood and muscle oxygen levels by approximately 3% with no effect on exercise performance.

INCREASED CARDIORESPIRATORY STRESS DURING SUBMAXIMAL CYCLING AFTER KETONE MONOESTER INGESTION IN ENDURANCE-TRAINED ADULTS; MCCARTHY ET AL



- Acute ingestion of ketone monoester prior to a 30-minute cycling test at ventilatory threshold intensity induced ketosis and increased ventilation, heart rate, and perceived exertion compared to placebo during the trial, but did not affect performance.

DIVE DEEPER: Literature Reviews on Human Optimization & Aging from 2021

- Chronobiology and Metabolism: Is Ketogenic Diet Able to Influence Circadian Rhythm?; Gangitano et al
- The therapeutic properties of ketogenic diets, slow-wave sleep, and circadian synchrony; O'Hearn et al
- On the nutritional and therapeutic effects of ketone body D- β -hydroxybutyrate; Yao et al
- β -hydroxybutyrate as an Anti-Aging Metabolite; Wang et al
- Why the diabetic heart is energy inefficient: a ketogenesis and ketolysis perspective; Kumar Mishra et al



CLINICAL APPLICATION

For any new field of medicine, unanswered questions about the optimal implementation of novel therapies are of utmost importance. For ketogenic metabolic therapies, healthcare providers around the world are learning and sharing these clinical insights at breakneck speed. In 2021, several findings were published that help contribute to a more comprehensive understanding of the dos and don'ts of practicing ketogenic medicine.



INTERNATIONAL PATIENT GROUP HARNESSES SOCIAL MEDIA TO HELP INFORM RARE DISEASE RESEARCH: USE OF A LOW CARBOHYDRATE KETOGENIC DIET IN MCARDLE DISEASE; REASON ET AL

- Anecdotal reports from patients with McArdle disease benefitting by KD therapy prompted the International Association for Muscle Glycogen Storage Disease to use the power of social media and explore this potential therapy.
- Efforts led to the development of patient-centered research priorities with clinical researchers.
- Partnerships between patient advocacy organizations and clinical researchers can foster advancements for rare diseases.

METABOLIC ACIDOSIS IN A LACTATING WOMAN INDUCED BY A DELIBERATE KETOGENIC DIET; HONG ET AL

- A nursing mother eating a KD experienced nausea, vomiting, postural dizziness, elevated lipase, and significant metabolic acidosis. She was diagnosed with lactation ketoacidosis.
- The authors suggest such complications could arise in anyone with high metabolic demands adhering to a strict KD.

RECURRENT ACUTE PANCREATITIS DURING A KETOGENIC DIET-A CASE REPORT AND LITERATURE REVIEW; CHOI ET AL

- A 35-year old man typically following a calorie-restricted KD experienced acute pancreatitis following "cheat days".
- He had no other risk factors, and a slow reintroduction of a standard diet resolved the issue.
- The authors suggest that KD may lower the threshold for acute pancreatitis in some individuals.

DIETARY-INDUCED KETOGENESIS: ADULTS ARE NOT CHILDREN; PORPER ET AL

- Ketone levels were measured in children and adults treated with very low carbohydrate KDs of similar ketogenic ratios.
- While ketone levels correlated to ketogenic ratio in both groups, adult ketone levels were approximately 1/4 the level observed in children.
- Children are able to achieve much higher levels of ketosis for comparable ketogenic ratios than adults.

CLINICAL EFFICACY OF EUCALORIC KETOGENIC NUTRITION IN THE COVID-19 CYTOKINE STORM: A RETROSPECTIVE ANALYSIS OF MORTALITY AND INTENSIVE CARE UNIT ADMISSION; SUKKAR ET AL

- Mortality, admission to the intensive care unit, need for non-invasive ventilation, and inflammatory makers were retrospectively compared between hospitalized COVID-19 patients consuming either a eucaloric KD (N=34) or SD (N=68).
- Preliminary analysis suggests an improvement in survival and less need for ICU care in EKD patients. There was also a non-significant ($p=0.062$) trends towards decreased pro-inflammatory IL-6 in the group.
- This promising potential therapeutic strategy is being investigated in an ongoing prospective clinical trial.

INCREASE OF HUMAN MILK FAT INDUCING NUTRITIONAL KETOSIS IN EXCLUSIVELY BREASTFED INFANT, BROUGHT ABOUT BY TREATING THE MOTHER WITH KETOGENIC DIETARY THERAPY; TAN-SMITH ET AL

- A breastfeeding mother was placed on a less stringent KD (61% fat) with the goal of inducing ketosis in her infant who was requiring KD therapy for seizures.
- The mother's milk content increased in caloric content by an additional 134%. Ketosis was established in the infant, and visible seizures ceased.
- This case report highlights a potential alternative method of administering medical ketogenic therapy to infants that does not require cessation of breastfeeding.

ACUTE ECHOCARDIOGRAPHIC EFFECTS OF EXOGENOUS KETONE ADMINISTRATION IN HEALTHY PARTICIPANTS; SELVARAJ ET AL

- Comprehensive echocardiography was performed on 20 healthy subjects before and 30-minutes after oral ketone ester administration.
- Ketones raised from 0.1mM to >3mM. Systolic blood pressure, heart rate, biventricular function, left ventricular global longitudinal strain, and left atrial strain all augmented while systemic vascular resistance decreased.
- The authors suggest that these findings may account for the proposed ergogenic effects of exogenous ketones, and may represent relevant and potentially therapeutic effects for varied health applications.

KETO-SLEUTHS - AN UNUSUAL CAUSE OF LOSS OF KETOSIS?

- An infant being treated with KD for seizures experienced a sudden and unexpected loss of ketosis that resulted in a return of seizure activity.
- Upon close investigation, it was determined that the infant's loss of ketosis was attributed to exposure to starch-containing drywall dust from ongoing home renovation.
- The infant was removed from the home until construction was complete, and both ketosis and therapeutic efficacy resumed.

DIVE DEEPER: Literature Reviews on Clinical Application of Ketogenic Metabolic Therapy from 2021

- Ketogenic diet-induced prurigo pigmentosa: a rising association; Shahrigharakhoshan et al
- Applications of Ketogenic Diets in Patients with Headache: Clinical Recommendations; Di Lorenzo et al
- A Clinical Perspective of Low Carbohydrate Ketogenic Diets: A Narrative Review; Sukkar et al
- Role of ketones, ketogenic diets and intermittent fasting in ICU; Gunst et al
- Adapting Medication for Type 2 Diabetes to a Low Carbohydrate Diet; Cucuzzella et al
- The risk of ketogenic diets while breastfeeding: severe euglycaemic ketoacidosis; Habashy et al





METABOLIC HEALTH SUMMIT

Learn the latest science on
METABOLIC HEALTH & THERAPY



PURCHASE VIRTUAL ACCESS TO MHS 2022 TO WATCH VIDEO LECTURES, IN-DEPTH PANELS, & FORUMS WITH THE WORLD'S TOP THOUGHT LEADERS.



FOLLOW US ON SOCIAL!



WATCH & EARN CME CREDIT AT WWW.METABOLICHEALTHSUMMIT.COM