



By METABOLIC HEALTH INITIATIVE

KETOGENIC METABOLIC THERAPY RESEARCH

YEAR IN REVIEW: 2020

An overview of research & advances in
ketogenic metabolic therapy in 2020.



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» *A Year of Progress Despite Change and Challenge*

2020 was a year for the history books, but not just for the obvious challenges and impacts of a global pandemic. Despite such adversity, scientific knowledge and progress continued to charge forward, and so too did the field of ketogenic metabolic therapy (KMT).

Our goal in preparing this Year in Review eBook is to help guide you towards uncovering some of the newest discoveries in this rapidly evolving field. We hope that you use the links contained within these pages as a jumping off point – a diving board into a sea of new information, research, topics, and ideas. Perhaps you will become acquainted with new aspects and advances in KMT for which you were not yet aware. Perhaps this compendium will serve as a way for you 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 by no means comprehensive in nature. To mention every KMT research study published in 2020 would have been a feat far too great to fit into a work such as this. Rather, this publication is but an overview of some of the exciting and far-reaching work that came out over the past 12 months. 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. Throughout the eBook, you'll also see lists of review articles published in 2020 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 2020 Ketogenic Metabolic Therapy Research Year in Review eBook. We certainly enjoyed taking a close look at the hundreds of new research studies that help expand our understanding and application of these tools. We know that 2021 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!



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NEUROLOGICAL HEALTH

The ketogenic diet was first described a century ago as a proposed method of quelling epileptic seizures. An immediate and resounding success, early researchers discovered its remarkable anti-convulsant properties, and its clinical use for drug-resistant seizures was solidified in the decades that followed. More recently, researchers expanded their work to study the impressive potential of ketogenic metabolic therapies for a wide variety of neurological diseases, and in 2020, progress in this field of research charged forward by leaps and bounds. Advances in our understanding of this tool were made in a remarkable number of seemingly disparate disorders - from seizures to autism, from bipolar disorder to Alzheimer's disease. But one thing is now abundantly clear... these new data highlight the important unifying thread of metabolism being a key feature of neurological health and disease.



A DIETARY KETONE ESTER NORMALIZES ABNORMAL BEHAVIOR IN A MOUSE MODEL OF ALZHEIMER'S DISEASE; PAWLOSKY ET AL.

KETONE PRODUCTION BY KETOGENIC DIET AND BY INTERMITTENT FASTING HAS DIFFERENT EFFECTS ON THE GUT MICROBIOTA AND DISEASE PROGRESSION IN AN ALZHEIMER'S DISEASE RAT MODEL; PARK ET AL.

THE KETOGENIC DIET FOR PAEDIATRIC PATIENTS WITH SUPER-REFRACTORY STATUS EPILEPTICUS IN FEBRILE INFECTION-RELATED EPILEPSY SYNDROME; WANG ET AL.

NEUROPROTECTIVE EFFECTS OF A KETOGENIC DIET IN COMBINATION WITH EXOGENOUS KETONE SALTS FOLLOWING ACUTE SPINAL CORD INJURY; TAN ET AL.

- Ketone ester increased the concentration of multiple important intermediary metabolites in the brains of Alzheimer's mice, including citrate, a-ketoglutarate, glutamate, aspartate, and n-acetyl-aspartate.
- Ketone ester also increased exploratory activity and reduced avoidance behavior in these mice, and these effects were correlated to increased n-acetyl-aspartate in the hippocampus.
- Intermittent fasting, but not a ketogenic diet, improved memory function and lowered deposition of amyloid beta following its infusion in the hippocampus of rats despite producing a similar elevation in ketones.
- Ketogenic diet exacerbated dysbiosis of the gut microbiome in this model.
- The ketogenic diet was successfully initiated in 10 pediatric patients with super-refractory status epilepticus (SRSE) in febrile infection-related epilepsy syndrome (FIRES), with ketosis being achieved within 24-72 hours.
- 2 patients discontinued use of the ketogenic diet, and 8 patients exhibited containment of status epilepticus. 1 patient exhibited a severe adverse event.
- A ketone salt supplemented ketogenic diet (KD+KS) induced a rapid and sustained ketotic state in rats with spinal cord injury.
- KD+KS spared neurons and axons in the dorsal corticospinal tract and also improved motor performance measures for up to 8 weeks post injury.

AMELIORATION OF CLINICAL COURSE AND DEMYELINATION IN THE CUPRIZONE MOUSE MODEL IN RELATION TO KETOGENIC DIET; ZHANG ET AL.

- Ketogenic diet increased distance traveled in the central area of the open field test, suggesting increased exploratory behavior and decreased anxiety, in a mouse model of cuprizone-induced demyelination.
- KD also increased the number of myelinated fibers in the corpus callosum of these mice.
- Protein expression of numerous markers of neuroinflammation, including GFAP Iba-1, CD69, and CD16/32, were down-regulated in KD-treated mice. Similarly, KD inhibited the production of inflammatory cytokines such as IL-1B and TNF-a.

BRAIN MACROAUTOPHAGY ON THE KETOGENIC DIET; LIŚKIEWICZ ET AL.

- Four weeks of ketogenic diet upregulated autophagosome synthesis in the hippocampus and frontal cortex of mice, as visualized by an increase in LC3 II protein.
- The authors suggest that ketogenic diet-induced autophagy in neurons may occur through multiple mechanisms and may be responsible in part for the therapeutic effects of ketosis on neurological conditions.

TO KETO OR NOT TO KETO? A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS ASSESSING THE EFFECTS OF KETOGENIC THERAPY ON ALZHEIMER DISEASE; GRAMMATIKOPOULOU ET AL.

- A systematic review assessing 10 randomized controlled trials examining the effects of ketogenic therapies on mild cognitive impairment or Alzheimer's disease revealed enhanced cerebral ketone uptake and utilization.
- Ketogenic therapies also elicited improvements in general cognition via the Alzheimer's Disease Assessment Scale-Cognitive, and improvements in episodic and secondary memory when administered long-term.
- There were no observed benefits in psychological health, executive ability, or attention.

GESTATIONAL EXPOSURE TO A KETOGENIC DIET INCREASES SOCIABILITY IN CD-1 MICE; ARQOUB ET AL.

- CD-1 mice were exposed to either a standard or ketogenic diet in utero via mother's diet. All pups were fostered by standard diet fed dams after birth, and were only fed standard diet after weaning.
- Gestational ketogenic diet exposure increased sociability and decreased depressive-like symptoms, with no effect on oxytocin expression.

USE OF KETOGENIC DIET THERAPY IN INFANTS WITH EPILEPSY: A SYSTEMATIC REVIEW AND META-ANALYSIS; LYONS ET AL.

- Authors performed a meta-analysis of studies reporting on response of ketogenic diet therapy in infants with epilepsy. 33 studies including a total of 534 infants were included, but authors noted the available studies were low-quality for this vulnerable age group.
- The data indicated approximately 33% of infants achieved seizure freedom and approximately 59% of infants achieved >50% reduction in seizures. The most commonly reported side effects included dyslipidemia (12%) and GI distress, such as vomiting (6%), constipation (4%), reflux (4%) and diarrhea (4%).

ANTI-DEPRESSION EFFECTS OF KETOGENIC DIET ARE MEDIATED VIA THE RESTORATION OF MICROGLIAL ACTIVATION AND NEURONAL EXCITABILITY IN THE LATERAL HABENULA; GUAN ET AL.

- Ketogenic diet reduced depressive-like behaviors in two rodent models of the disorder: the social defeat stress (R-SDS) and lipopolysaccharide (LPS) models.
- The ketogenic diet attenuated abnormal neuronal excitability in the lateral habenula of mice that was present in the models. Similarly, microglial inflammatory activation was also present in the lateral habenula of animals of both model systems, and the ketogenic diet reduced this as well.
- The authors suggest that these pathways may play critical roles in the pathogenesis of depression and may be viable targets for ketogenic therapy.

THE ALTERATIONS OF BLOOD GLUCOSE AND COGNITIVE FUNCTION BY KETONE INJECTION IN MICE; CHA ET AL.

- 28 days of injection of the ketone body beta-hydroxybutyrate increased kidney weight, and decreased lung and spleen weight, of mice. It also increased blood glucose concentration at 2 hours following a glucose challenge compared to controls.
- Chronic ketone injection caused a trend of reduced weight of untorn cotton nesting pads in the nest building test, a marker of general well-being, leading authors to suggest ketosis could be beneficial for maintaining cognitive function.

B-AMYLOID AND TAU DRIVE EARLY ALZHEIMER'S DISEASE DECLINE WHILE GLUCOSE HYPOMETABOLISM DRIVES LATE DECLINE; HAMMOND ET AL.



MEDIUM-CHAIN TRIGLYCERIDES (8:0 AND 10:0) INCREASE MINI-MENTAL STATE EXAMINATION (MMSE) SCORE IN FRAIL ELDERLY ADULTS IN A RANDOMIZED CONTROLLED TRIAL; ABE ET AL.



B-HYDROXYBUTYRATE (BHB) OXIDATION PROMOTES THE ACCUMULATION OF IMMUNOMETABOLITES IN ACTIVATED MICROGLIA CELLS; BENITO ET AL.



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



- Analysis of the Alzheimer's Disease Neuroimaging Initiative dataset shows that elevated amyloid beta and tau protein deposition are better at predicting early dementia status, but glucose hypometabolism and other biomarkers of neurodegeneration are better at predicting later dementia status.
- The authors suggest that treatments for Alzheimer's disease may need to be oriented towards disease stage for efficacy.

- Daily supplementation of 6g of medium chain triglycerides for 3 months improved performance on the Mini-Mental State Examination by an average of 3.5 points in a group of 64 elderly nursing home residents.
- MMSE scores rose over the course of the 3 month study, but had returned to baseline by the 4.5 month post-intervention visit.

- Both human and mouse microglial cells, key cells of the brain's immune system, take in and metabolize BHB.
- When challenged with lipopolysaccharide, BHB exacerbated accumulation of glycolytic intermediates and other key immunometabolites, including alpha-ketoglutarate and fumarate.
- BHB also upregulated the pro-inflammatory state induced by LPS, suggesting that ketones can function as immunomodulators in microglia and work to promote metabolic reprogramming during an inflammatory response.

- The ketogenic diet improved all parameters measured by the Voice Handicap Index (VHI), a clinical and physiological voice assessment test, in a group of seventy-four patients with Parkinson's disease associated voice disorder.

CUPRIZONE-INDUCED DEMYELINATION IN MOUSE HIPPOCAMPUS IS ALLEVIATED BY KETOGENIC DIET; LIU ET AL.

POTASSIUM CITRATE AND METABOLIC ACIDOSIS IN CHILDREN WITH EPILEPSY ON THE KETOGENIC DIET: A PROSPECTIVE CONTROLLED STUDY; BJURULF ET AL.

ANTIEPILEPTIC EFFECTS OF EXOGENOUS B-HYDROXYBUTYRATE ON KAINIC ACID-INDUCED EPILEPSY; SI ET AL.

B-HYDROXYBUTYRATE INHIBITS INFLAMMASOME ACTIVATION TO ATTENUATE ALZHEIMER'S DISEASE PATHOLOGY; SHIPPY ET AL.

- The ketogenic diet improved motor and cognitive performance in mice with cuprizone-induced demyelination, a model of Multiple Sclerosis.
 - Expression of mature oligodendrocytes was increased with KD indicative of reduced demyelination in the hippocampus.
 - Oxidative stress was decreased by KD as marked by reduced malondialdehyde and restoration of glutathione levels in those brain regions.
 - The neuroprotective effects of KD was associated with an upregulation of the SIRT-1/PPAR- γ and SIRT-1/Akt/mTOR pathways.
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- In this study of 51 pediatric epilepsy patients, potassium citrate prevented the development of metabolic acidosis with no effect on anticonvulsant efficacy.
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- Pre-treatment with beta-hydroxybutyrate in the kainic acid-induced rat epilepsy model increased expression of neuronal markers in the hippocampus, suggesting a protection against neuronal damage.
 - Furthermore, GFAP, a marker of inflammation, was inhibited in the BHB-treated rats. Glutathione and GABA were also increased in these animals.
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- Using an autopsy specimen database, BHB was found to be lower in the red blood cells & brain tissue of AD patients compared to non-AD patients post-mortem.
 - Exogenous BHB administration resulted in increased brain ketone levels and reduced plaque formation & microgliosis in the 5XFAD mouse model of Alzheimer's.
 - Furthermore, exogenous BHB reduced Asc speck formation and decreased caspase-1 activation and IL-1B secretion in the cortices of these mice, suggesting an inhibition of NLRP3 inflammasome activation played a role in the observed attenuation of AD pathogenesis.

EFFICACY OF KETOGENIC DIET, MODIFIED ATKINS DIET, AND LOW GLYCEMIC INDEX THERAPY DIET AMONG CHILDREN WITH DRUG-RESISTANT EPILEPSY: A RANDOMIZED CLINICAL TRIAL; SONDHI ET AL.

- In this randomized controlled trial of 158 pediatric refractory epilepsy patients, the ketogenic diet, modified Atkins diet (MAD), and low glycemic index therapy diet (LGIT) induced similar reduction in seizure burden; however, MAD and LGIT groups failed to meet predefined noninferiority criteria (a margin of -15 percentage points).
- Adverse events were lowest in the LGIT group, with data suggesting 1 adverse event can be avoided for every 4.3 children treated with LGIT instead of KD.

KETOGENIC DIET POTENTIATES ELECTRICAL STIMULATION-INDUCED PERIPHERAL NERVE REGENERATION AFTER SCIATIC NERVE CRUSH INJURY IN RATS; LI ET AL.

- In a rat model of sciatic nerve crush injury, the ketogenic diet enhanced peripheral nerve regeneration induced by electrical stimulation.
- The combination treatment increased muscle force generation as measured by EMG, and increased several markers of peripheral nerve regeneration, including axon number, size, and myelination.
- The results were associated with an increase in IGF-1 and IGF-1 receptor expression in the regenerated nerves.

THE KETOGENIC DIET IN THE TREATMENT OF POST-CONCUSSION SYNDROME-A FEASIBILITY STUDY; RIPPEE ET AL.

- An MCT-supplemented ketogenic diet was administered for 2 months in 12 patients with Post Concussion Syndrome.
- KD therapy improved the visual memory domain of the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT). While not statistically significant, the KD also elicited a trend towards increase in scores on the Post-Concussion Symptom Scale (PCSS).
- The KD was deemed to be a feasible potential treatment for PCS, but further research is needed to determine efficacy.

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

- 39 individuals with mild cognitive impairment consumed a ketogenic drink containing medium chain triglycerides twice daily for 6 months.
- Multiple markers of cognition were improved compared to the placebo control group, including aspects of executive function, memory, and language.
- Improvements in four of the cognitive tests correlated with blood ketone levels, suggesting the effect is mediated at least in part by the elevation in ketones.
- The authors suggest that ketogenic drinks may be useful in delaying progression of MCI to Alzheimer's disease.

COGNITIVE EFFECTS OF A KETOGENIC DIET ON NEUROCOGNITIVE IMPAIRMENT IN ADULTS AGING WITH HIV: A PILOT STUDY; MORRISON ET AL

- 12 weeks of ketogenic diet improved executive function and speed of processing in HIV patients with mild-to-moderate neurocognitive impairment compared to a patient-choice diet control group.
- The observed benefits were negated after patients resumed their normal diets.



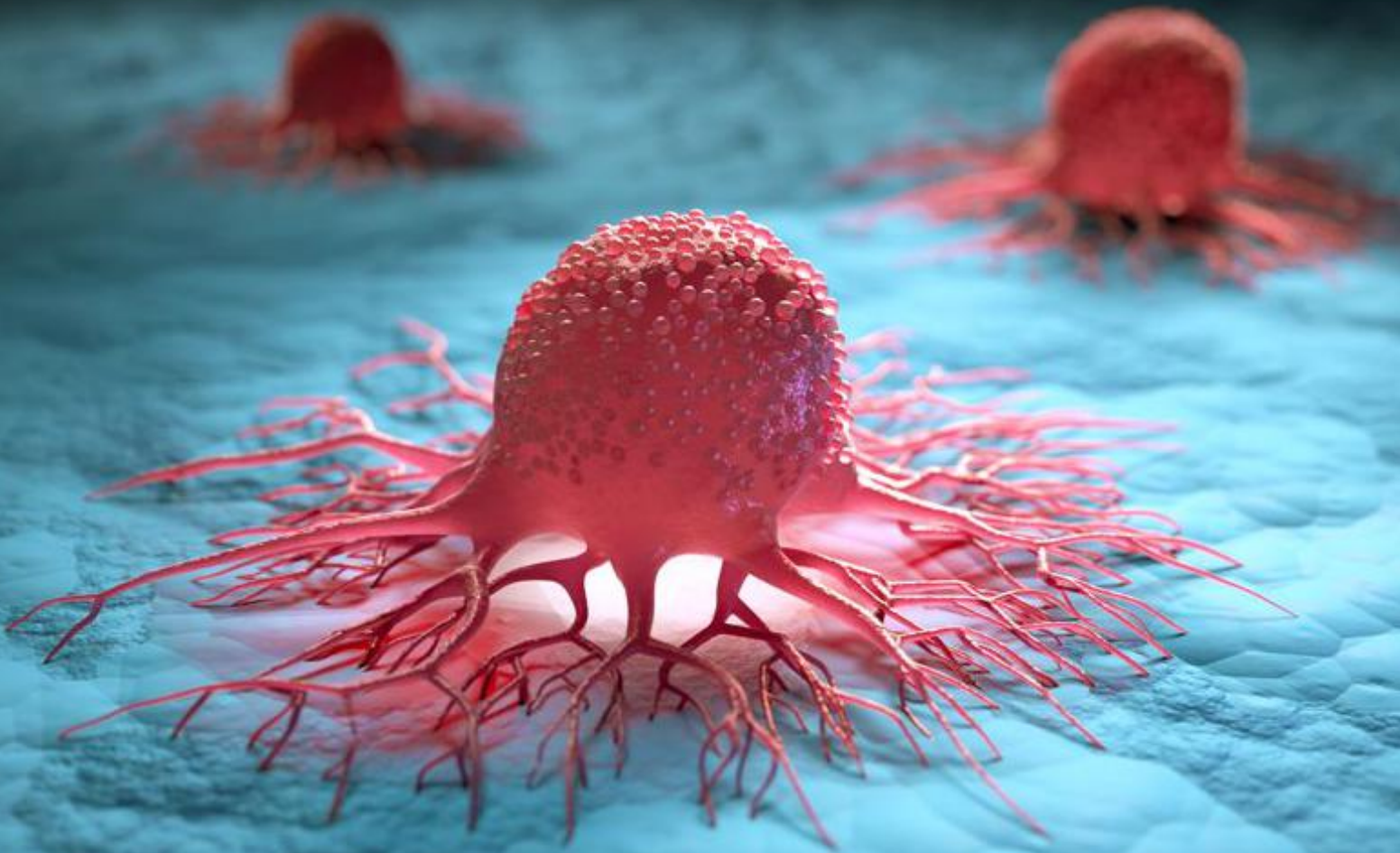
DIVE DEEPER: Literature Reviews on Neurological Health from 2020

- [Not your parents' ketogenic diet - Flexibility in 2020; Blackford R.](#)
- [Mechanisms of Insulin Resistance, Mitochondrial Dysfunction and the Action of the Ketogenic Diet in Bipolar Disorder. Focus on the PI3K/AKT/HIF1 - a pathway; Campbell et al.](#)
- [A gut feeling about the ketogenic diet in epilepsy; Pittman Q.](#)
- [A unifying mechanism of ketogenic diet action: The multiple roles of nicotinamide adenine dinucleotide; Elamin et al.](#)
- [Impact of ketosis on appetite regulation-a review; Deemer et al.](#)
- [Therapeutic strategies for ketosis induction and their potential efficacy for the treatment of acute brain injury and neurodegenerative diseases; Camberos-Luna et al.](#)
- [Nutritional Recommendations to Address Pain: Focus on Ketogenic/Low-Carbohydrate Diet; Masino et al.](#)
- [Ketogenic diet and Neuroinflammation; Koh et al.](#)
- [Ketogenic Therapy in Serious Mental Illness: Emerging Evidence; Sarnyai et al.](#)
- [Exploring the mechanisms of action of the antidepressant effect of the ketogenic diet; Ricci et al.](#)
- [Mental, emotional, and behavioral effects of ketogenic diet for non-epileptic neuropsychiatric conditions; Grigolon et al.](#)
- [Ketogenic Dietary Therapy Controversies for Its Second Century; Kossoff et al.](#)

CANCER

Ketogenic metabolic therapies are an exciting new potential treatment for cancer.

For the past several years, researchers have been peeling away the layers of mechanisms at play between ketosis and cancer. It is now clear this work goes far beyond the “glucose lowering story” as researchers have found that ketosis impacts tumors in numerous ways on a cellular level. But while a significant amount of encouraging pre-clinical data exists, the field is in severe need of high-quality human trials. In 2020, we saw more work being done on these basic mechanisms in cells and animal model systems, and a much-needed continued expansion in the human research needed to truly understand the potential of this novel therapy.



A KETOGENIC DIET COMBINED WITH MELATONIN OVERCOMES CISPLATIN AND VINCRIStINE DRUG RESISTANCE IN BREAST CARCINOMA SYNGRAFT; TALIB ET AL.



THE CONTRIBUTION OF KETONE BODIES TO GLYCOLYTIC INHIBITION FOR THE TREATMENT OF ADULT AND PEDIATRIC GLIOBLASTOMA; VALLEJO ET AL.



SURVIVAL OUTCOMES OF METABOLICALLY SUPPORTED CHEMOTHERAPY COMBINED WITH KETOGENIC DIET, HYPERTHERMIA, AND HYPERBARIC OXYGEN THERAPY IN ADVANCED GASTRIC CANCER; IYIKESICI ET AL.



A KETOGENIC DIET MITIGATES PANCREATIC CANCER-ASSOCIATED CACHEXIA IN MICE; CORTEZ ET AL.



- In breast cancer cells, melatonin altered the expression of several key genes, notably including an inhibition of angiogenesis and chemotherapeutic resistance-related genes, and an activation of apoptosis-related genes.
- In a breast cancer mouse model, combination of melatonin with the ketogenic diet elicited a synergistic therapeutic effect and induced complete remission in 70% of animals tested.

- Analysis of gene expression data from an online patient-histology database revealed that multiple ketolytic enzymes (BDH1, OXCT1, and ACAT1) were significantly downregulated in adult and pediatric glioblastoma multiforme.
- Ultrastructural analysis of GBM mitochondria suggests impaired mitochondrial respiratory capacity.
- In GBM and glioma stem cell culture lines, treatment with a glycolysis inhibitor and the ketone acetoacetate (but not BHB) induced cell death, an effect that was additive when therapies were combined.

- In this retrospective trial, 24 patients with stage III or IV gastric cancer were treated with metabolically-supported chemotherapy, including ketogenic diet, hyperbaric oxygen therapy, and local hyperthermia, over a 2 year period.
- The treatment was well tolerated with no reported significant adverse events, and preliminary analysis of progression free survival and overall survival compared to historical data appears positive. Further research in the form of a randomized trial with a larger sample size is warranted to determine efficacy.

- Ketogenic diet improved grip strength and increased gastrocnemius muscle weight in a mouse model of pancreatic cancer (indicating a reduction in cachexia), but did not affect tumor size or survival time.

KETOGENIC DIET THERAPY FOR AGGRESSIVE PRIMARY BRAIN TUMORS: STRATIFICATION OF SURVIVAL BY PATIENTS' AGE; SCHWARTZ ET AL.

KETOGENIC DIET PROMOTES APOPTOSIS OF TUMOR CELLS AND INHIBITS TUMOR GROWTH THROUGH INHIBITING WNT1/B-CATENIN SIGNALING PATHWAY IN MOUSE XENOGRAFT MODELS OF HUMAN COLON CANCER; WANG ET AL.

LOW CARB (LCD) AND KETOGENIC (KD) DIETS INCREASE QUALITY OF LIFE, PHYSICAL PERFORMANCE, BODY COMPOSITION AND METABOLIC HEALTH OF WOMEN WITH BREAST CANCER BETTER THAN A STANDARD DIET (SD); KÄMMERER ET AL.

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

- 9 patients with glioblastoma multiforme were treated with a ketogenic diet for 6 weeks alongside radiation & temozolomide following initial primary surgery.
- The 3 younger patients (average age 28) were living & working without disease progression at the time of analysis, an average of 46 months post-diagnosis for the group. The 6 older patients (average age 54) all died during the trial, at a 16 months post-diagnosis average.
- The authors conclude that future research on ketogenic diet as an adjuvant therapy for glioblastoma multiforme should focus on younger patients.
- Ketogenic diet reduced tumor size, reduced infiltrating inflammatory cells in tumor, increased apoptosis, and reduced Wnt1/ β -catenin signaling in an immunodeficient mouse model of subcutaneously implanted human colon cancer.
- 152 breast cancer patients self-selected to follow a healthy standard diet (SD), low carb diet (LD), or ketogenic diet (KD) for 20 weeks. All diets were feasible, without adverse effects, & resulted in improved quality of life, body composition, & physical performance.
- KD was superior in improving fatigue, insomnia, physical functioning, and resulted in the best physical performance and highest muscle/fat ratio.
- The KD group increased total cholesterol, but had the best triglyceride/HDL ratio and HOMA-IR scores (marker of insulin resistance) of the three groups. SD lowered total cholesterol dramatically but did not affect triglyceride/HDL ratio or HOMA-IR.
- Ketogenic diet caused an initial significant loss of body weight, fat free mass, & skeletal muscle mass in non-metastasized breast cancer patients undergoing radiotherapy. These effects from diet onset were thought to be related to water loss as no further substantial changes in fat free or skeletal muscle mass was observed.
- The KD also decreased free T3 levels over time and increased global quality of life scores compared to a standard diet group.

LONG-TERM GLUCOSE RESTRICTION WITH OR WITHOUT B-HYDROXYBUTYRATE ENRICHMENT DISTINCTIVELY ALTERS EPITHELIAL-MESENCHYMAL TRANSITION-RELATED SIGNALINGS IN OVARIAN CANCER CELLS; GHAHREMANI ET AL.

- A combination of glucose restriction and beta-hydroxybutyrate (BHB) supplementation reduced cell migration and markers of stemness in chemotherapy-resistant ovarian cancer cells in culture.
- Glucose restriction more significantly impacted different genetic pathways in the two different ovarian cancer lines.
- Glucose restriction reduced ATP in both cell lines tested, and BHB supplementation partially restored ATP levels in one of the lines.
- The authors suggest that understanding a tumor's specific genetic and metabolic phenotype may help predict the potential efficacy of ketogenic diet therapy.

IMPACT OF MODIFIED SHORT-TERM FASTING AND ITS COMBINATION WITH A FASTING SUPPORTIVE DIET DURING CHEMOTHERAPY ON THE INCIDENCE AND SEVERITY OF CHEMOTHERAPY-INDUCED TOXICITIES IN CANCER PATIENTS - A CONTROLLED CROSS-OVER PILOT STUDY; EHRET ET AL.

- A group of patients with gynecological cancers (including breast, endometrial, ovarian, and cervical) performed modified short term fasting (max 25% of individual's daily calorie requirement) for 96 hours during half of their chemotherapy cycles, but a normocaloric diet for the other half.
- Insulin, IGF-1, stomatitis, headache, weakness, and total toxicities' score was reduced, and chemotherapy tolerance was improved, during fasted chemotherapy sessions compared to non-fasted sessions.
- Half of patients consumed a ketogenic diet for 6 days prior to the fasting sessions to test its potential to augment response or improve compliance, but no differences were noted.

FEASIBILITY, SAFETY, AND BENEFICIAL EFFECTS OF MCT-BASED KETOGENIC DIET FOR BREAST CANCER TREATMENT: A RANDOMIZED CONTROLLED TRIAL STUDY; KHODABAKHSHI ET AL.

- In this randomized controlled trial of 60 patients with locally advanced or metastatic breast cancer undergoing chemotherapy, ketogenic diet therapy decreased fasting blood sugar, BMI, body weight, and body fat percentage compared to the control group.
- Overall survival was increased in the KD group in neoadjuvant patients, and no severe adverse side effects were observed.
- The authors conclude that ketogenic diet therapy can potentially improve body composition and certain biochemical markers and prolong survival in some patients with breast cancer.

DOES A KETOGENIC DIET HAVE BENEFICIAL EFFECTS ON QUALITY OF LIFE, PHYSICAL ACTIVITY OR BIOMARKERS IN PATIENTS WITH BREAST CANCER: A RANDOMIZED CONTROLLED CLINICAL TRIAL; KHODABAKHSHI ET AL.

- Quality of life and physical activity scores were improved in patients with locally advanced or metastatic breast cancer after 6 weeks of ketogenic diet therapy undergoing chemotherapy, but this benefit disappeared by 12 weeks of treatment.
- Ketogenic therapy reduced serum lactate and ALP, negative prognostic markers in breast cancer, suggesting a potential benefit.

EXPLORING THE FEASIBILITY AND EFFECTS OF A KETOGENIC DIET IN PATIENTS WITH CNS MALIGNANCIES: A RETROSPECTIVE CASE SERIES; PANHANS ET AL.

- Results from 12 patients with CNS malignancies (GBM or astrocytoma) following a ketogenic diet were analyzed in this descriptive case series.
- Most patients received concurrent standard of care treatment, reported symptom improvements, and were able to achieve nutritional ketosis (<0.5mM BHB) for the duration of the 120 day period observed. An imaging review suggested improvements in disease control and reduction of tumor-associated edema.
- The authors suggest that ketogenic therapy may have a positive impact on this patient population and prospective clinical trials are required to understand efficacy.

A KETOGENIC DIET ATTENUATES PROLIFERATION AND STEMNESS OF GLIOMA STEM-LIKE CELLS BY ALTERING METABOLISM RESULTING IN INCREASED ROS PRODUCTION; JI ET AL.

- Glioma stem-like cells (GSCs) were taken from a patient's tumor and grown in culture with reduced glucose and beta-hydroxybutyrate supplementation.
- A number of effects were observed in the GSCs, including: reduced proliferation, increased apoptosis, decreased expression of stemness markers, reduced self-renewal in culture, and reduced tumorigenic capacity in vivo. Furthermore, the GSCs exhibited reduced glucose uptake and glycolysis as well as morphological and functional mitochondrial abnormalities.
- Scavenging of reactive oxygen species prevented these effects, suggesting that the beneficial effects of this ketosis-based treatment was due at least in part to increased ROS production by the GSCs.

MR-SPECTROSCOPY AND SURVIVAL IN MICE WITH HIGH GRADE GLIOMA UNDERGOING UNRESTRICTED KETOGENIC DIET; CIUSANI ET AL.

- Ketogenic diet prolonged survival in a mouse model of glioblastoma multiforme brain cancer.
- Ketogenic diet decreased GABA, N-acetyl-aspartate, and N-acetylaspartylglutamate, and greatly increased beta-hydroxybutyrate in the tumor tissue.
- The authors suggest that the significant accumulation of BHB in the tumors may indicate that the tumor cells are taking it in or releasing it in large quantities, or are unable to use it for mitochondrial metabolism.

A KETOGENIC DIET IS ACCEPTABLE IN WOMEN WITH OVARIAN AND ENDOMETRIAL CANCER AND HAS NO ADVERSE EFFECTS ON BLOOD LIPIDS: A RANDOMIZED, CONTROLLED TRIAL; COHEN ET AL.



KETOGENIC DIET ELICITS ANTITUMOR PROPERTIES THROUGH INDUCING OXIDATIVE STRESS, INHIBITING MMP-9 EXPRESSION, & REBALANCING M1/M2 TUMOR-ASSOCIATED MACROPHAGE PHENOTYPE IN A MOUSE MODEL OF COLON CANCER; ZHANG ET AL.



- After adjusting for baseline values and weight loss, there were no differences in blood lipids between groups of endometrial and ovarian cancer patients treated with a ketogenic diet or the American Cancer Society diet.
- Dietary adherence ranged between 57% and 80% in the KD group.
- The authors conclude that KD may be a safe and feasible intervention for some cancer patients.

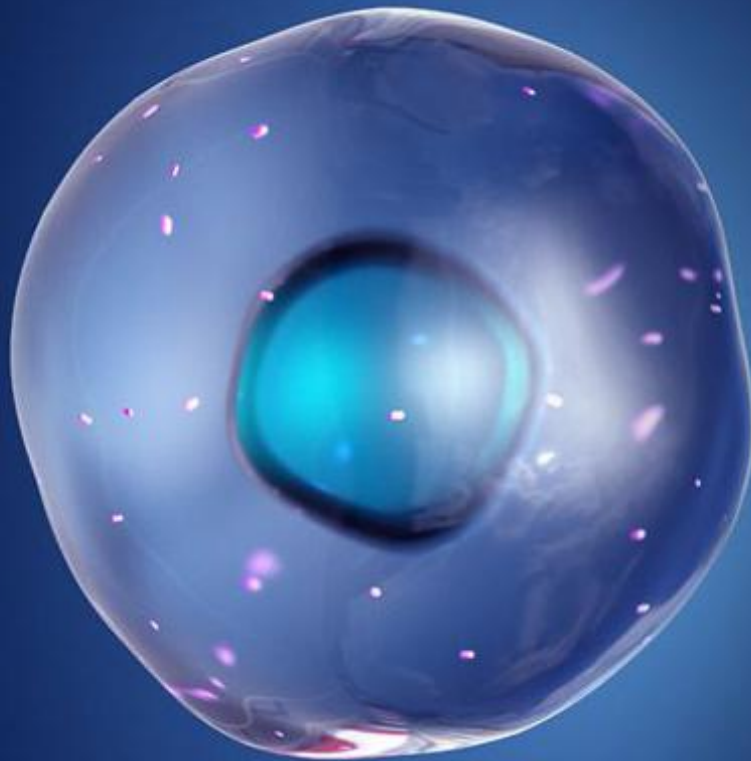
- Ketogenic diet increased tumor oxidative stress and increased apoptosis in a mouse model of colon cancer.
- MMP-9 expression and HDAC3/PKM2/NF-kB65/p-STAT3 signaling was decreased by ketogenic therapy, and the researchers also observed a switch from M2 to M1 tumor associated macrophages.
- The authors conclude that ketogenic therapy may prevent colon cancer progression via these mechanisms.

DIVE DEEPER: Literature Reviews on Metabolic Therapy for Cancer from 2020

- [Ketogenic diet in the treatment of cancer - Where do we stand? Weber et al.](#)
- [Ketogenic diets in medical oncology: a systematic review with focus on clinical outcomes; Klement et al.](#)
- [Ketotherapy as an epigenetic modifier in cancer; Bandera-Merchen et al.](#)
- [Consideration of Ketogenic Metabolic Therapy as a Complementary or Alternative Approach for Managing Breast Cancer; Seyfried et al.](#)
- [The Role of Diet in Cancer Prevention and Chemotherapy Efficacy; Mittelman S.](#)
- [Ketogenic Diet for Malignant Gliomas: a Review; Thomas et al.](#)
- [Does nutrition for cancer patients feed the tumour? A clinical perspective; Bozzetti et al.](#)
- [Nutritional traditional and complementary medicine strategies in pediatric cancer: A narrative review; Diorio et al.](#)



METABOLIC DYSFUNCTION



Perhaps the field of medicine most promising of benefit from metabolic therapies is that of its namesake. By nature, metabolic dysfunction appears most susceptible to manipulation by ketogenic therapies, as a shift to nutritional ketosis impacts a vast number of cellular and physiological metabolic features simultaneously. In recent years, interest in the use of low carbohydrate or ketogenic diets to combat the obesity epidemic has grown exponentially, both in the public and clinical realm. Quickly following were numerous reports revealing similar beneficial impacts on common comorbidities of obesity, such as other core components of metabolic syndrome: hyperglycemia, hypertension, and hypertriglyceridemia to name a few. In 2020, this line of work continued with much needed additional insight into the longer-term multifaceted effects of such diets in humans, along with growing insight into other important related conditions, such as hormonal imbalances and reproductive health.

THE EFFECTS OF DIFFERENT DEGREES OF CARBOHYDRATE RESTRICTION AND CARBOHYDRATE REPLACEMENT ON CARDIOMETABOLIC RISK MARKERS IN HUMANS—A SYSTEMATIC REVIEW AND META-ANALYSIS; FECHNER ET AL.

MRI ESTIMATED CHANGES IN VISCERAL ADIPOSE TISSUE AND LIVER FAT FRACTION IN PATIENTS WITH OBESITY DURING A VERY LOW-CALORIE-KETOGENIC DIET COMPARED TO A STANDARD LOW-CALORIE DIET; CUNHA ET AL.

COMPARISON OF LOW CARBOHYDRATE DIETS ON RENAL AND GLUCOSE FUNCTION IN SUBJECTS WITH TYPE 2 DIABETES: A SYSTEMATIC REVIEW AND META-ANALYSIS; COUCH G.

IN VITRO HUMAN COLONIC MICROBIOTA UTILISES D-B-HYDROXYBUTYRATE TO INCREASE BUTYROGENESIS; SASAKI ET AL

- In this systematic review and meta-analysis, researchers investigated the effect of degree of carbohydrate restriction - very low (<30% kcal), low (<30-40%) or moderate-low (>45-40 E%) - on metabolic health biomarkers.
- Overall, low carbohydrate diets resulted in weight loss, improved blood pressure, & increased total cholesterol and HDL cholesterol, with no significant differences on these measures between groups based on the degree of carbohydrate restriction.
- Triacylglycerol (TAG) decreases were more robust in low and very-low carb groups, and higher HDL was observed.

- Two months of a very low carbohydrate ketogenic diet caused greater weight loss (- 9.7kg vs -1.7 kg) and reduction in liver fat content (-4.8% vs. -0.8%) compared to a standard low-calorie diet in 39 obese patients.

- In this systematic review and meta-analysis of 10 articles with a total of 921 subjects, there was no difference in estimated glomerular filtration rate or serum creatinine between type 2 diabetic patients on low carbohydrate diets compared to control diets, but HbA1c was lower in the LCD group.
- This data suggests low carbohydrate diets may improve blood sugar control without adversely affecting the kidneys in this patient population.

- In this cell culture setting, bacteria from more than half of the human gut microbiome models tested were shown to consume significant amounts of beta-hydroxybutyrate in order to increase butyrate production.
- The authors suggest that these BHB utilizers may be generating butyrate in part for its beneficial effects on human health such as reported anti-cancer effects in the colon, or its glucose/insulin lowering potential.

VERY-LOW-CALORIE KETOGENIC DIETS WITH WHEY, VEGETABLE, OR ANIMAL PROTEIN IN PATIENTS WITH OBESITY: A RANDOMIZED PILOT STUDY; BASCIANI ET AL.

- The effects of a 45-day isocaloric very low calorie ketogenic diet (VLCKD) with various protein sources (whey, vegetable, or animal) on metabolic health and gut microbiome was tested in 48 obese patients.
- All VLCKDs reduced body weight, BMI, blood pressure, waist circumference, insulin, HOMA index (a marker of insulin resistance), total and LDL cholesterol.
- Subjects in the whey protein group showed greater improvement in muscle strength, and those in the animal protein group showed a slight worsening of markers of renal function.

INTERMITTENT KETOGENIC DIET AMELIORATES DIET-INDUCED OBESITY AND FATTY LIVER WITH IMPROVED FGF21 SIGNALING; GUO ET AL.

- Despite increased energy intake, mice consuming an intermittent ketogenic diet exhibited improvements in body weight, fasting blood glucose, insulin sensitivity, body fat mass, liver weight, hepatic steatosis, and epididymal, subcutaneous, and brown adipose tissue compared to mice fed a high fat (moderate carbohydrate) diet.
- The beneficial effects were associated with a robust upregulation of liver FGF-21 and reduction in liver inflammation, as well as upregulation of uncoupling proteins and PGC1a in the three adipose types tested.

THE EFFECT OF PERIODIC KETOGENIC DIET ON NEWLY DIAGNOSED OVERWEIGHT OR OBESE PATIENTS WITH TYPE 2 DIABETES; LI ET AL.

- 12 weeks of periodic ketogenic diet improved weight, BMI, waist circumference, triglycerides, total cholesterol, LDL, HDL, fasting blood glucose, fasting insulin, and HbA1c in newly diagnosed overweight or obese type 2 diabetic patients, but participants expressed more reluctance towards long-term adherence than those in the diabetic diet control group.

A KETOGENIC DIET IS PROTECTIVE AGAINST ATHEROSCLEROSIS IN APOLIPOPROTEIN E KNOCKOUT MICE; WHALEN ET AL.

- Ketogenic diet (81% fat, 1% carbohydrate, 18% protein) reduced inflammatory cytokines, altered the serum metabolome, and reduced aortic plaque burden in a mouse model of human atherosclerosis compared to a “high fat diet” (40% fat, 42% carbohydrate, 18% protein).

VERY LOW-CALORIE KETOGENIC DIET: A SAFE AND EFFECTIVE TOOL FOR WEIGHT LOSS IN PATIENTS WITH OBESITY AND MILD KIDNEY FAILURE; BRUCI ET AL.

- In a group of obese patients with mild kidney failure, a very low calorie ketogenic diet resulted in 20% weight loss, reduction in fat mass, lean body mass, blood pressure, HbA1c, total cholesterol, and triglycerides, with no effect on biochemical markers of liver and kidney function.
- Importantly, 27.7% of patients experienced a normalization of glomerular filtration rate during the diet study, leading the authors to suggest that despite common theoretical concern, a VLCKD may be a safe and effective treatment for obese patients with mild kidney failure.

THE EFFECTS OF A LOW CALORIE KETOGENIC DIET ON GLYCAEMIC CONTROL VARIABLES IN HYPERINSULINEMIC OVERWEIGHT/OBESE FEMALES; MICHALCZYK ET AL.

- In a group of hyperinsulinemic overweight or obese females, 12 weeks of hypocaloric (20% reduction) whole-foods focused low carbohydrate ketogenic diet improved all biochemical and body composition variables tested, compared to a group who maintained their previous western style “conventional” diet.
- Specifically, the following factors improved from baseline in the LCKD-treated women: glucose, insulin, HbA1c, HOMA-IR, triglycerides, HDL cholesterol, body mass, BMI, waist circumference, hip circumference, and thigh circumference.

THE KETOGENIC DIET CORRECTS METABOLIC HYPOGONADISM AND PRESERVES PANCREATIC B-CELL FUNCTION IN OVERWEIGHT/OBESE MEN: A SINGLE-ARM UNCONTROLLED STUDY; LA VIGNERA ET AL.

- Twelve weeks of very low calorie ketogenic diet treatment decreased body weight, BMI, blood glucose, insulin, HOMA index (marker of insulin resistance), C-peptide, and proinsulin in a group of 20 overweight or obese patients with metabolic hypogonadism.
- At the end of the treatment, serum total testosterone (TT) had increased by 218% on average for the group, and none of the patients' TT values fell within the hypogonadal range.

LONGITUDINAL CHANGES IN INSULIN RESISTANCE IN CHILDREN WITH EPILEPSY ON KETOGENIC DIET: PREVALENCE AND RISK FACTORS; KONG ET AL.



- Insulin resistance as measured by HOMA-IR increased in children with epilepsy on a ketogenic diet for an average of 2.1 years.
- Younger age of seizure onset, younger age at initiation of anti-epileptic drugs, younger age of KD initiation, and higher serum LDL and triglycerides were associated with higher HOMA-IR levels.

VERY LOW CALORIE KETOGENIC DIETS IN OVERWEIGHT AND OBESITY TREATMENT: EFFECTS ON ANTHROPOMETRIC PARAMETERS, BODY COMPOSITION, SATIETY, LIPID PROFILE AND MICROBIOTA; DI ROSA ET AL.



- A literature review revealed that very low calorie ketogenic diets elicit improvements in weight loss, body mass index, waist circumference, fat mass reduction and satiety, while preserving lean body mass and resting metabolic rate.

INGESTION OF AN EXOGENOUS KETONE MONOESTER IMPROVES THE GLYCEMIC RESPONSE DURING ORAL GLUCOSE TOLERANCE TEST IN INDIVIDUALS WITH IMPAIRED GLUCOSE TOLERANCE: A CROSSOVER RANDOMIZED TRIAL; NAKAGATA ET AL.



- A single ingestion of ketone monoester (KME) elevated AUC of beta-hydroxybutyrate and decreased AUC of glucose in 9 adults with impaired glucose tolerance undergoing an oral glucose tolerance test.
- AUC of insulin was enhanced by KME in the early, but not late, phase of the OGTT.

EFFECT OF A 90 G/DAY LOW-CARBOHYDRATE DIET ON GLYCAEMIC CONTROL, SMALL, DENSE LOW-DENSITY LIPOPROTEIN AND CAROTID INTIMA-MEDIA THICKNESS IN TYPE 2 DIABETIC PATIENTS: AN 18-MONTH RANDOMISED CONTROLLED TRIAL; CHEN ET AL.



- Compared to the traditional diabetic diet (TDD), a low carb diet (LCD) induced greater benefits in glycemic control, blood pressure, weight, body composition, and medication effect score in a group of poorly controlled type 2 diabetic patients.
- There were no significant differences in blood lipid profiles, markers of liver function, and carotid intima-media thickness (IMT) between the two groups.

EFFECT OF THE KETOGENIC DIET ON GLYCEMIC CONTROL, INSULIN RESISTANCE, AND LIPID METABOLISM IN PATIENTS WITH T2DM: A SYSTEMATIC REVIEW AND META-ANALYSIS; YUAN ET AL.

EFFECTS OF A KETOGENIC DIET IN OVERWEIGHT WOMEN WITH POLYCYSTIC OVARY SYNDROME; PAOLI ET AL.

SEMEN QUALITY IMPROVEMENT AFTER WEIGHT LOSS BY VERY LOW-CALORIE KETOGENIC DIETARY: A REPORT OF TWO CASES; RENCK ET AL.

IN VIVO FAT QUANTIFICATION: MONITORING EFFECTS OF A 6-WEEK NON-ENERGY-RESTRICTED KETOGENIC DIET IN HEALTHY ADULTS USING MRI, ADP AND BIA; BUECHERT ET AL.

- In this systematic review and meta-analysis of 13 studies, the effects of a ketogenic diet on glycemic & lipid metabolism in diabetic patients included (on average): a reduction of fasting blood glucose by 1.29 mM, of HbA1c by 1.07, of triglycerides by 0.72 mM, of total cholesterol by 0.33 mM, of LDL by 0.05 mM, of weight by 8.66 kg, of waist circumference by 9.17 cm, of BMI by 3.13 kg/m², & an increase in HDL by 0.14 mM.
- 12 weeks of a mediterranean style ketogenic diet with phytoextracts elicited the following changes in 14 overweight women with polycystic ovary syndrome: reduction in body weight, BMI, fat body mass, visceral adipose, lean body mass, blood glucose, blood insulin, triglycerides, total cholesterol, LDL cholesterol, LH/FSH ratio, LH total & free testosterone, DHEAS blood levels, elevation of HDL cholesterol, & an improvement in HOMA-IR.
- The Ferriman Gallwey Score - a method of evaluating and quantifying hirsutism (excessive body hair) in women - trended towards reduction, but the difference was not statistically significant.
- In two obese men with metabolic syndrome, a very low calorie ketogenic diet resulted in significant weight loss and improvements in metabolic and hormonal profile.
- Semen characteristics also improved markedly, including an increase in sperm total, progressive motility, normal sperm morphology, and total motile sperm count.
- Six weeks of non-energy-restricted ketogenic diet decreased body mass index, total mass, total fat mass, total subcutaneous mass, and subcutaneous fat mass in a cohort of 12 healthy adults.
- Despite the reduction of subcutaneous fat, there were no observed changes in internal fat distribution including liver fat content over the trial period.

KETOGENIC, HYPOCALORIC DIET IMPROVES NONALCOHOLIC STEATOHEPATITIS; BELOPOLSKY ET AL.

- 38 patients with nonalcoholic steatohepatitis who were placed on a hypocaloric, ketogenic, “ideal protein” diet reduced body weight, blood pressure, triglycerides, HbA1c, and markers of liver function abnormalities (AST and ALT).

EFFICACY OF A 2-MONTH VERY LOW-CALORIE KETOGENIC DIET (VLCKD) COMPARED TO A STANDARD LOW-CALORIE DIET IN REDUCING VISCERAL AND LIVER FAT ACCUMULATION IN PATIENTS WITH OBESITY; CUNHA ET AL.

- In this randomized controlled, prospective trial, patients with nonalcoholic fatty liver disease (NAFLD) consuming a very low calorie ketogenic diet (VLCKD) demonstrated superior weight loss, reduction in visceral adipose tissue, and reduction in liver fat fraction compared to those on a standard low calorie diet.
- The authors suggest that VLCKD may be an effective treatment for NAFLD.

A RANDOMIZED, CONTROLLED TRIAL COMPARING THE IMPACT OF A LOW-CALORIE KETOGENIC VS A STANDARD LOW-CALORIE DIET ON FAT-FREE MASS IN PATIENTS RECEIVING AN ELIPSE™ INTRAGASTRIC BALLOON TREATMENT; SCHIAVO ET AL.

- Compared to a standard low-calorie diet, patients prescribed a low-calorie ketogenic diet following Elipse™ intragastric balloon placement exhibited a greater decrease in fat mass, and a lower decrease in free fat mass and resting metabolic rate, with no impact on renal function..

EFFECTIVENESS OF A VERY LOW CALORIE KETOGENIC DIET ON TESTICULAR FUNCTION IN OVERWEIGHT/OBESE MEN; MONGIOÍ ET AL.

- 8 weeks of very low calorie ketogenic diet elicited body weight loss, improvements in glucose homeostasis and blood lipids, an increase in serum vitamin D, LH, and TT levels, and a decrease in PSA, in a group of 40 overweight or obese men.

DIVE DEEPER: Literature Reviews on Metabolic Dysfunction from 2020

- [Very low-calorie ketogenic diet \(VLCKD\) in patients with psoriasis and obesity: an update for dermatologists and nutritionists; Barrea et al.](#)
- [Low carbohydrate ketogenic therapy as a metabolic treatment for binge eating and ultraprocessed food addiction; Dalai et al.](#)
- [The biochemistry of low-carbohydrate and ketogenic diets; Fienman R.](#)
- [Beneficial effects of the ketogenic diet on nonalcoholic fatty liver disease: A comprehensive review of the literature; Watanabe et al.](#)
- [Dietary Recommendations for Familial Hypercholesterolaemia: an Evidence-Free Zone; Diamond et al.](#)

HUMAN OPTIMIZATION AND AGING

The pursuit of optimizing human health as we age is central to the human condition. Early studies revealed the potential of calorie restriction to increase both healthspan and lifespan in animals from worms to monkeys, and more recent research suggests that nutritional ketosis may replicate – or be responsible for – some of these properties. This, and similar work, has inspired researchers to investigate the numerous ways that health is impacted over time when influenced by a state of ketosis. Although not always designed to directly test effects on longevity or aging, a variety of research published in 2020 provides novel insight into this fascinating question.



PRIOR INGESTION OF A KETONE MONOESTER SUPPLEMENT REDUCES POSTPRANDIAL GLYCEMIC RESPONSES IN YOUNG HEALTHY WEIGHT INDIVIDUALS; GREAVES ET AL.



KETOGENIC DIET ACTIVATES PROTECTIVE $\gamma\delta$ T CELL RESPONSES AGAINST INFLUENZA VIRUS INFECTION; GOLDBERG ET AL.



KETOGENIC DIETS ALTER THE GUT MICROBIOME RESULTING IN DECREASED INTESTINAL TH17 CELLS; ANG ET AL.



SHORT-TERM PHYSIOLOGICAL EFFECTS OF A VERY LOW-CALORIE KETOGENIC DIET: EFFECTS ON ADIPONECTIN LEVELS AND INFLAMMATORY STATES; MONDA ET AL.



- A single ingestion of ketone monoester elevated blood BHB and decreased blood glucose and non-esterified fatty acid area under the curve (AUC) compared to placebo in 19 healthy young volunteers.
- Plasma insulin AUC and gastric emptying were unaffected.

- Ketogenic diet, but not a non-ketogenic high-fat diet nor exogenous ketone supplementation with beta-hydroxybutyrate, protected mice from death by influenza A infection.
- Accompanying the protection was an expansion of $\gamma\delta$ T cells in the lung which enhanced antiviral resistance by improving airway epithelial barrier function, a potential explanatory mechanism of action.

- In both mice and humans, ketogenic diet induced marked changes in the gut microbiome, and notably a reduction of bifidobacteria which was shown to be due to an inhibition in growth by ketone bodies.
- KD also reduced the amount of proinflammatory Th17 immune cells in the intestine of mice following human microbiome transplantation.

- 8 weeks of very low calorie ketogenic diet therapy in obese patients reduced weight, BMI, visceral adipose tissue, fat mass, triglycerides, total cholesterol, LDL cholesterol, blood glucose, insulin, CRP, and multiple markers of liver damage.
- Many of these beneficial effects were correlated with an observed increase in adiponectin, a hormone and adipokine involved in metabolic homeostasis that also elicits an anti-inflammatory effect.

INTERMITTENT FASTING ENHANCED THE COGNITIVE FUNCTION IN OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT BY INDUCING BIOCHEMICAL AND METABOLIC CHANGES: A 3-YEAR PROGRESSIVE STUDY; OOI ET AL.

SAFETY AND EFFECTIVENESS OF THE PROLONGED TREATMENT OF CHILDREN WITH A KETOGENIC DIET; HERRERO ET AL.

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

KETONE BODIES ATTENUATE WASTING IN MODELS OF ATROPHY; KOUTNIK ET AL.

- Regular intermittent fasting (rIF) over a 36 month period increased the likelihood of reverting to successful aging with no cognitive impairment and disease in elderly subjects with mild cognitive impairment, compared to those who irregularly practiced intermittent fasting and non-fasters.
- rIF subjects also showed improvements in body weight, insulin, fasting blood glucose, and markers of oxidative stress and inflammation.
- In this observational study of 26 pediatric epilepsy patients on ketogenic diet therapy, approximately 60-75% of patients experienced a >90% reduction in seizure frequency.
- 50% of patients experienced some type of side effect, which were typically mild and most commonly digestive issues, changes in lipid metabolism, and hypercalciuria. Height was slightly reduced in children who began KD prior to the age of 2.
- High-fat and high-protein low carbohydrate diets were compared to control high carbohydrate, low fat diet in a mouse model using transverse aortic constriction to induce pressure overload as a mimic of hypertension.
- Both low carbohydrate diets attenuated development and progression of cardiac hypertrophy and heart failure in the model system.
- The authors present evidence for a novel model system to study Cancer Anorexia Cachexia Syndrome in mice with VM-M3 metastatic cancer.
- In both this novel cachexia model, as well as a model of lipopolysaccharide-induced atrophy, ketone ester treatment reduced multiple markers of atrophy and catabolism and comorbid symptoms of inflammation, including attenuation of body weight, adipose, and skeletal muscle loss and relative reductions in multiple pro-inflammatory biomarkers.

A KETOGENIC DIET COMBINED WITH EXERCISE ALTERS MITOCHONDRIAL FUNCTION IN HUMAN SKELETAL MUSCLE WHILE IMPROVING METABOLIC HEALTH; MILLER ET AL.

- Muscle biopsies were taken before and after a group of physically active adults completed a 12 week ketogenic diet and exercise program.
- Compared to a habitual mixed diet group in the same program, the KD group had increased whole body resting fat oxidation, reduced fasting insulin, reduced insulin resistance by HOMA-IR, reduced visceral fat, a small reduction in muscle glycogen, an increase in muscle triglyceride.
- Mitochondria isolated from the KD group participants displayed altered functionality compared to controls, showing increased respiratory control ratio and ATP production with fat-based substrate, and reduced ATP production with ketone-based substrate, highlighting changes in skeletal muscle mitochondrial efficiency with ketosis.

MODIFIED KETOGENIC DIET IS ASSOCIATED WITH IMPROVED CEREBROSPINAL FLUID BIOMARKER PROFILE, CEREBRAL PERFUSION, AND CEREBRAL KETONE BODY UPTAKE IN OLDER ADULTS AT RISK FOR ALZHEIMER'S DISEASE: A PILOT STUDY; NETH ET AL.

- A Modified Mediterianian Ketogenic Diet (MMKD) improved multiple metabolic biomarkers in older adults at risk for Alzheimer's disease (positive for subjective memory complaints or mild cognitive impairment), including a reduction of fasted glucose, HbA1c, and insulin, a reduction of VLDL cholesterol and triglycerides, and a trend towards increased HDL cholesterol. In contrast, the American Heart Association Diet (AHAD) did not affect any of these markers, except that it lowered HDL cholesterol.
- MMKD, but not AHAD, increased cerebral blood perfusion, increased cerebral ketone uptake, and improved CSF AD biomarker profiles including increased in CSF A β 42, decreased CSF tau (only in subjects with mild cognitive impairment), and increased CSF A β 42/tau ratio.
- Memory performance was improved by both diets, but authors suggested that practice effects may have played a role in these results.

METABOLOMICS - HIGH RESOLUTION CHARACTERIZATION OF HUMAN METABOLISM AND BIOCHEMICAL STATUS ON HABITUAL DIET AND KETOGENIC DIET; PETTERSEN, ET AL.

- Global metabolomics analysis of plasma from healthy normal weight subjects following a ketogenic diet for 3 weeks revealed significant changes in a diverse set of compounds of the metabolome, including an increase in ketone bodies, lipids, GABA, Kreb's cycle intermediates such as citric acid, malic acid, and alpha-ketoglutarate.
- Several amino acids, including threonine, asparagine, tryptophan, proline, b-alanine, leucine, arginine, methionine, glutamine, and alanine were reduced by KD, but valine was elevated.
- There was a positive correlation between histidine amino acid and change in LDL-C.

KETONES CAN BECOME THE MAJOR FUEL SOURCE FOR THE HEART BUT DO NOT INCREASE CARDIAC EFFICIENCY; HO ET AL.

- In isolated mouse hearts, perfusion of β -hydroxybutyrate alongside glucose and palmitate increased cardiac oxidation of ketones but did not increase cardiac work, suggesting that the supplemental ketones decreased cardiac efficiency in this model system.

KETONE DIETS CAN REVERSE SOME BRAIN ACTIVITIES THAT ARE LOST IN AGING; WEISTUCH ET AL.

- The functional signature of age-related cognitive decline was partially reversed by a ketogenic diet as visualized by ultra-high field (7T) fMRI in conjunction with network activity modeling.

A 3-WEEK, LOW-CARBOHYDRATE, HIGH-FAT DIET IMPROVES MULTIPLE SERUM INFLAMMATORY MARKERS IN ENDURANCE-TRAINED MALES; WALDMAN ET AL.

- In a cohort of middle-aged endurance-trained athletes, 3 weeks of ketogenic diet reduced multiple serum markers of inflammation both immediately following, and 24 hours after, exercise.

EXOGENOUS KETONE SUPPLEMENTS IMPROVED MOTOR PERFORMANCE IN PRECLINICAL RODENT MODELS; ARI ET AL.

- A variety of exogenous ketone supplement formulations (1,3-butanediol, ketone ester, ketone salts, and combinations of individual components) were administered to both healthy rodents, and animals with neurological deficits (a model of absence epilepsy and a model of Glucose Transporter Deficiency Syndrome Type 1).
- Some benefits in motor performance were observed, but were highly dependent on rodent strain, age, and species, ketone formulation used, and exposure frequency and duration. Similarly, in some but not all conditions, a rise in postexercise glycemia was attenuated with ketone supplementation.

KETOGENIC DIET ATTENUATES AGING-ASSOCIATED MYOCARDIAL REMODELING AND DYSFUNCTION IN MICE; YU ET AL.

- Four months of ketogenic diet delayed cardiac aging in aged male mice. Some of the specific changes observed in the myocardium included:
 - Reduced cardiomyocyte cross-sectional area, fibrosis, and expression of ANP and alpha smooth muscle actin.
 - Enhanced antioxidant activity and a reduction of markers of oxidative stress.
 - Improvements in markers of mitochondrial function, including reduced mitochondrial ROS, enhanced mitochondrial ATP production, and preservation of electron transport chain function.
 - Enhanced autophagic flux.

EFFECTS OF KETOGENIC DIETING ON BODY COMPOSITION, STRENGTH, POWER, AND HORMONAL PROFILES IN RESISTANCE TRAINING MEN; WILSON ET AL.



EFFECTS OF A KETOGENIC DIET ON BODY COMPOSITION AND STRENGTH IN TRAINED WOMEN; VARGAS-MOLINA, ET AL.

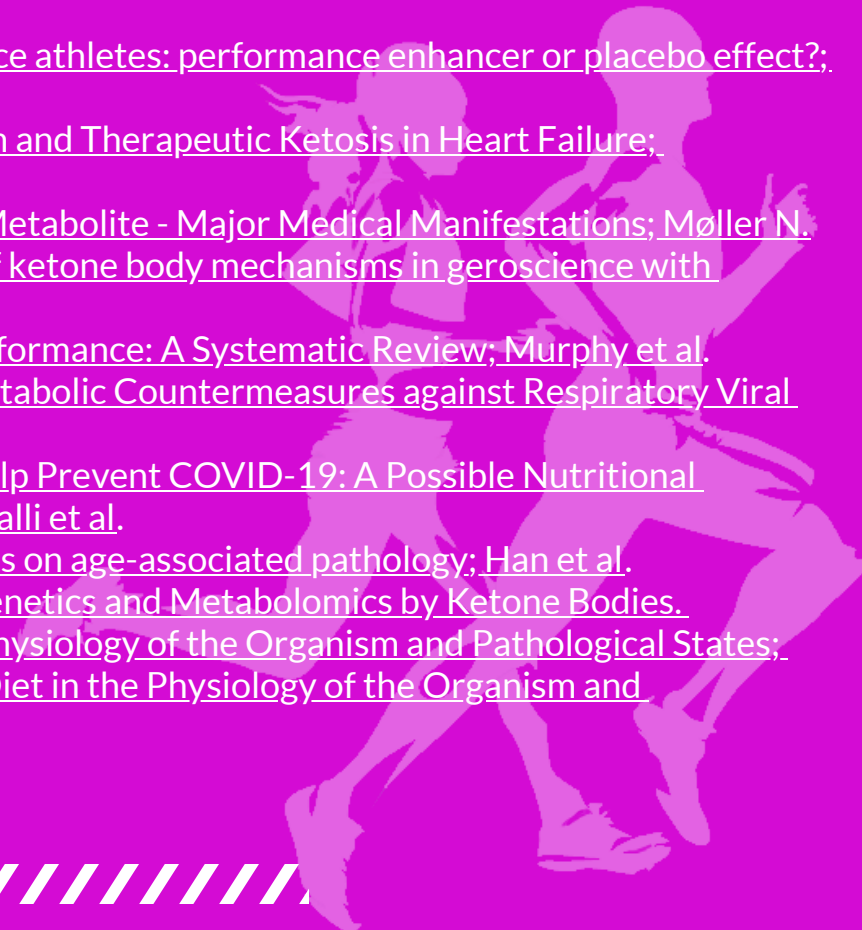


- 10 weeks of KD increased total testosterone in a group of college-aged men participating in a resistance training program compared to a group consuming an isocaloric and isonitrogenous traditional western diet.
- In both groups, lean body mass increased, fat mass decreased, and strength and power increased similarly over the trial period. Insulin was unaffected. Blood lipids were not changed during the study, but the KD group experienced an increase in triglycerides after reintroduction of carbohydrates.

- In a cohort of 21 strength-trained women (average age 27.6 years), 8 weeks of ketogenic diet was superior to non-KD in reducing fat mass, but non-KD subjects showed increases in bench press, squat, and countermovement jump strength levels that was not observed in the KD group.

DIVE DEEPER: Literature Reviews on Human Optimization & Aging from 2020

- [A review of the ketogenic diet for endurance athletes: performance enhancer or placebo effect?; Bailey et al.](#)
- [Implications of Altered Ketone Metabolism and Therapeutic Ketosis in Heart Failure; Selvaraj et al.](#)
- [Ketone Body, 3-Hydroxybutyrate: Minor Metabolite - Major Medical Manifestations; Møller N.](#)
- [From bedside to battlefield: intersection of ketone body mechanisms in geroscience with military resilience; Stubbs et al.](#)
- [High-Fat Ketogenic Diets and Physical Performance: A Systematic Review; Murphy et al.](#)
- [Investigating Ketone Bodies as Immunometabolic Countermeasures against Respiratory Viral Infections; Stubbs et al.](#)
- [How Immune T-Cell Augmentation Can Help Prevent COVID-19: A Possible Nutritional Solution Using Ketogenic Lifestyle; Kamepalli et al.](#)
- [\$\beta\$ -hydroxybutyrate and its metabolic effects on age-associated pathology; Han et al.](#)
- [Modulation of Cellular Biochemistry, Epigenetics and Metabolomics by Ketone Bodies. Implications of the Ketogenic Diet in the Physiology of the Organism and Pathological States; Dąbek et al.](#)
- [Implications of the Ketogenic Diet in the Physiology of the Organism and Pathological States; Dąbek et al.](#)



CLINICAL APPLICATION

As the research on ketogenic metabolic therapy expands rapidly, so too must our understanding of the nuances required for their successful implementation in the clinic. Every year, scores of new physicians embrace the utility of ketogenic diets and related metabolic therapies for their patients with one condition or another. In 2020, several new reports were published highlighting important details, methods, considerations, indications, and contraindications alike. These clinical pearls of wisdom must be shared widely amongst providers in a collective effort to optimize the safe and effective application of these exciting new treatments.



CONSUMER REPORTS OF "KETO FLU" ASSOCIATED WITH THE KETOGENIC DIET; BOSTOCK ET AL.



- The authors performed a search of online forums to characterize the symptoms, severity, and time course of "keto flu" as reported by forum users.
- The search criteria returned 448 posts from 300 unique users with 54 discrete symptoms described. The most common symptoms included: "flu", headache, fatigue, nausea, dizziness, "brain fog", gastrointestinal discomfort, decreased energy, feeling faint, and heartbeat alterations.
- Symptoms were largely reported to peak in the first week and resolve after 4 weeks.

A CASE OF HYPOGLYCEMIA ASSOCIATED WITH THE KETOGENIC DIET AND ALCOHOL USE; SPOKE ET AL.



- In this case report, a 69 year old woman who had followed a strict ketogenic diet for one year experienced symptomatic hypoglycemia (39 mg/dL) after consuming alcohol.

INCIDENCE OF LEUKOPENIA IN KETOGENIC DIET: A SINGLE-CENTER EXPERIENCE; SEGAL ET AL.



- In a retrospective review of 79 medical charts from pediatric epilepsy patients on ketogenic diet therapy, approximately 15% of patients developed leukopenia after diet initiation.
- For patients that were weaned off the diet, they experienced an improvement or normalization of labs.
- The authors note that the observed leukopenia may not necessarily warrant medical intervention, and a review of the current practice guidelines is needed.

PRURIGO PIGMENTOSA: AN ACUTE COMPLICATION OF KETOGENIC DIET; LEVRAN ET AL.



- A 22 year old Type 1 Diabetic patient developed pruritic erythematous papules, papulovesicular rash, & vesicles on her axillary region, upper back, & groin four weeks after initiating a low carbohydrate diet.
- Increasing carbohydrate intake to 75 grams/day resolved her condition, but lesions returned when she subsequently entered ketosis again. All lesions resolved with a sustained increase in carbohydrate intake.

KETOGENIC DIET AS A NORMAL WAY OF EATING IN ADULTS WITH TYPE 1 AND TYPE 2 DIABETES: A QUALITATIVE STUDY; WONG ET AL.

- Adults with type 1 or 2 diabetes who had followed a ketogenic diet for ≥ 3 months reported that their main motivations for doing so included: improved blood glucose control, reduction or cessation of diabetes medications, weight loss, and diabetes reversal.
- Reported benefits included improved glycemic control, weight loss, and satiety. Primary reported challenges included lack of support from healthcare professionals and lack of information; however, the patients largely viewed the KD as a lifelong normalized way of eating.

LACTATION KETOACIDOSIS: A SYSTEMATIC REVIEW OF CASE REPORTS; ALAWI ET AL.

- In this systematic review, 18 patients from 16 case reports and 1 case series were found reporting instances of lactation ketoacidosis caused by high anion gap metabolic acidosis in breastfeeding mothers.
- 14/18 patients reported dieting and exercising to lose weight at the time of presentation.
- Treatments included IV dextrose, sodium bicarbonate, insulin, rehydration, monitoring and replacement of electrolytes, and resumption of a balanced diet. Prognosis was good in all cases.

SEVERE METABOLIC ACIDOSIS: A CASE OF TRIPLE HIT WITH KETOGENIC DIET, VINEGAR, AND METFORMIN IN AN OBESE PATIENT; RANA ET AL.

- In this case report, a 43 year old female with Type 2 Diabetes Mellitus and several other comorbidities experienced severe metabolic acidosis after eating a ketogenic diet while consuming apple cider vinegar and taking metformin.
- The authors suggest that physicians should be aware of complications that can be caused by novel weight loss supplements and dietary trends, and should engage in such discussions with patients seeking to lose weight.

CAPILLARY BLOOD TESTS MAY OVERESTIMATE KETOSIS: TRIANGULATION BETWEEN THREE DIFFERENT MEASURES OF B-HYDROXYBUTYRATE; NORGREN ET AL.

- In this study, venous whole blood, plasma, and capillary beta-hydroxybutyrate, along with total ketones (BHB + acetoacetate) were measured simultaneously in 15 healthy volunteers at 12 time points in order to determine correlation and agreement between methods.
- Absolute values of venous whole blood & plasma BHB correlated highly, but regression modeling indicated that capillary BHB read substantially higher.
- The authors conclude that all methods were valid to detect relative changes in ketosis, but that capillary BHB measured unexpectedly higher than venous whole blood measured at the same time point with the same point of care device.

CONFUSION IN THE NOMENCLATURE OF KETOGENIC DIETS BLURS EVIDENCE; TRIMBOLI ET AL.

- The authors argue that the field of ketogenic diet therapy is plagued by inconsistency in terminology, abbreviations, and protocols used, resulting in confusion and inappropriate interpretation of the available evidence.
- The authors suggest adopting the following descriptions and abbreviations for ketogenic diets:
 - Very low calorie ketogenic diet (VLCKD) - Carb: <30-50g/d, Calories: <700-800 kcal/d; Lipids: <30-40g/d
 - Low calorie ketogenic diet (LCKD) - Carb: <30-50g/d, Calories >700-800 kcal/d and <Total Energy Expenditure (TEE); Lipids: >30-40g/d
 - Isocaloric ketogenic diet (ICKD): Carb: <30-50g/d, In line with TEE; Lipids: 70-80% of daily calorie intake.

HYPERCALCEMIA IN CHILDREN USING THE KETOGENIC DIET: A MULTICENTER STUDY; HAWKES ET AL.

- In this multicenter case series, 14 patients (median age 6.3) were found to develop hypercalcemia an average of 2.1 years after beginning a ketogenic diet.
- Parathyroid hormone and 1,25-dihydroxyvitamin D were low in the group, and 50% had impaired renal function at presentation.
- This study suggests that ketotic hypercalcemia can occur years following initiation of the ketogenic diet, and most often occurs in the context of renal impairment. As the disorder is thought to be related to impaired bone formation, the authors recommend paying close attention to bone health in children on ketogenic diet treatment and screening for the development of hypercalcemia.

PRURIGO PIGMENTOSA INDUCED BY KETOSIS ("KETO RASH"): A DEMONSTRATIVE CASE AND INTERNET SEARCH RESULTS; DELALEU ET AL.

- Authors report on a young woman who presented in their dermatology clinic for a pruritic skin rash which the patient herself suggested may be "keto rash." Reintroduction of carbohydrates and doxycycline treatment resolved the issue within 2 weeks.
- The authors then performed a Google search on "keto rash" to see what information is available to patients online. Their findings indicate that most of the results readily available on a basic internet search do not contain evidence-based information and recommendations. The authors suggest that physicians should be aware of the latest information available on the internet so that they can appropriately counsel patients on any potential misinformation they have consumed.

REMISSION FROM CHRONIC ANOREXIA NERVOSA WITH KETOGENIC DIET AND KETAMINE: CASE REPORT; SCOLNICK ET AL.

- A patient with a 15 year history of severe and enduring anorexia nervosa exhibited complete remission with ketogenic diet followed by IV ketamine infusions.
- This is the first report of ketogenic diet used for this life threatening condition.

DIVE DEEPER: Literature Reviews on Clinical Application of Ketogenic Metabolic Therapy from 2020

- Protocol for the Use of the Ketogenic Diet in Preclinical and Clinical Practice; Kraeuter et al
- Medication Adjustments for Ketogenic Meal Plans; Isaacs et al.
- Scientific evidence underlying contraindications to the ketogenic diet: An update; Watanabe et al.
- Ketogenic diet treatment of children in the intensive care unit: Safety, tolerability, and effectiveness; Worden et al.
- The Ketogenic Diet: Evidence for Optimism but High-Quality Research Needed; Ludwig D.
- A Standard Lipid Panel Is Insufficient for the Care of a Patient on a High-Fat, Low-Carbohydrate Ketogenic Diet; Norwitz et al.
- Ketogenic diet therapy provision in the COVID-19 pandemic: Dual-center experience and recommendations; Kossoff et al.



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