Fasting Physiology and Therapeutic Diets: A Look Back to the Future

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Abstract

The evidence presented at this event demonstrated the multiple clinical benefits of fasting physiology and points toward a future in which the clinical applications of dietary approaches will be well understood and successfully utilized. The conference reflected the scope and breadth of current research efforts in this important clinical area. Clearly, the application of the important new concepts related to fasting physiology that are emerging will require the advocacy and participation of professionals who are well trained in the fields of clinical nutrition and personalized lifestyle medicine.

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If you look far enough back in history and your search includes works of philosophy, religion, and art, you will find many interesting examples of fasting being used as a therapeutic treatment for epilepsy. It is described in the writings of Hippocrates. In the *King James Bible*, a story of Jesus curing a boy with epilepsy is told—one that some believe is depicted in Raphael's classic painting *The Transfiguration of Christ*. One of the first medical reports on the use of fasting for the treatment of epilepsy was recorded by French physicians Guelpa and Marie in 1911.[1] A decade later—in 1921—the prominent New York endocrinologist and diabetes expert Henry Rawle Geyelin published a report about the successful use of a 20-day fasting regime to treat 21 children with epilepsy.[2]

That year—1921—proved to be significant for a number of reasons. Roland T. Woodyatt, from Rush Medical Center in Chicago, Illinois, made the important observation that acetone and beta-hydroxybutyrate (BHB) increase in the blood by fasting or by consuming a diet containing a high proportion of fat.[3] Russell M. Wilder, at the Mayo Clinic in Rochester, Minnesota, applied this concept to the development of a diet low in carbohydrate and high in fat that included 1 gram of protein per kilogram of body weight. This diet produced ketonemia without fasting, which allowed the program to be applied for a longer term.[4] In 1930, H. M. Keith and H. F. Helmholtz, also from the Mayo Clinic, published an article in the *Journal of the American Medical Association* that described their experience with using this ketogenic diet in the treatment of epilepsy during an 8-year period.[5] Several decades later, in 1971, Huttenlocher and colleagues introduced a new fat source into the diet—medium chain triglycerides (MCTs) from palm oil—which was more ketogenic per calorie, allowing for less restriction of foods.[6]

During the early application of using dietary intervention to treat epilepsy, it was speculated that ketogenesis may be effective due to the potential "sedative" properties of ketones in the blood. Eventually, further study revealed that even low levels of BHB and other ketone bodies, such as acetone and acetoacetate produced during states of fasting physiology, influence the tricarboxylic acid cycle (also known as the Krebs cycle) in very specific ways that alter brain energetics in a favorable manner. This was work done by Dr Douglas R. Nordli, Jr, and Dr Darryl C. De Vivo, from the Division of Pediatric Neurology and the Comprehensive Epilepsy Center at Columbia Presbyterian Medical Center in New York City.[7] In subsequent publications from other researchers, the effects of BHB on brain chemistry were found to be very different than the mechanism of action of anesthetic drugs. In 2001, Dr Kristopher J. Bough and Dr Douglas A. Eagles of Georgetown University reported that the ketogenic diet was as successful in treating most forms of epilepsy as were the common antiepileptic drugs valproic acid and phenytoin, but without the neurotoxic side effects of the drugs.[8] According to the earlier work of Nordli and De Vivo, blood levels of BHB and acetoacetate (ie, total ketones) in the range of 2 to 4 mM were documented in epileptic children on the ketogenic diet. These amounts are lower than the levels of ketones found in the dangerous medical condition ketoacidosis, but may be a metabolic issue for some people depending on their tolerance to the acidifying properties of the ketones.

Given this history of successful use of the ketogenic diet for the treatment of epilepsy, it is somewhat surprising that this nutritional therapy never gained greater medical acceptance. The development of antiepileptic drugs made the treatment of epilepsy easier for clinicians, although there can be significant adverse events associated with these drugs. As time passed, fewer dietitians and clinical nutritionists were taught about the administration of the ketogenic diet. Then came October 1994. *Dateline*, a popular news show on NBC, aired a segment about an epileptic toddler named Charlie, who was the son of Jim Abrahams, a successful Hollywood film director, and his wife, Nancy. Charlie was placed on a ketogenic diet under the supervision of researchers at Johns Hopkins University, and the improvement in his condition as a result of this therapy was dramatic. A resurgence of interest in the ketogenic diet was seen following the broadcast. That same year, Jim and Nancy Abrahams established The Charlie Foundation for Ketogenic Therapies.[9]

An Assembly of Experts in 2018

During the last 2 decades, our understanding of the metabolic and neurobiological effects of the ketogenic diet has increased and this has led to greater and more widespread interest in fasting physiology and the successful application of this state of metabolism. In November 2018, a very important conference took place at the Keck School of Medicine at the University of Southern California (USC): the First International Conference on Fasting, Dietary Restriction, Longevity and Disease. I attended this event and had an extraordinary experience, highlights of which I will share in the paragraphs that follow.

The meeting opened with introductory remarks by the conveners of the conference: Michael Quick, PhD, USC provost; Pinchas Cohen, MD, dean of the USC School of Gerontology; and Valter Longo, PhD, the Edna M. Jones professor of gerontology at the USC Leonard David School of Gerontology. The first speaker was David Sabatini, MD, PhD, a professor at the Whitehead Institute for Biomedical Research, who discussed his work related to the role that diet has on tissue regeneration and how low calorie states (such as those achieved through intermittent fasting) can improve adult stem cell function and reduce age-associated loss of tissue function.[10] Dr Sabatini described elegant mechanistic work that demonstrates how fasting-induced ketogenesis favorably influences cellular signal transduction networks related to the mammalian target for rapamycin (mTOR) system.[11,12] He shared data indicating that fasting activates lysosomal activity, which acts as a sensor of nutrients and regulates autophagy. The amino acid leucine and the tripeptide leucine-arginine-lysine have very important influences on lysosome activity and represent sensors for controlling autophagy. Dr Sabatini indicated that methionine restriction also plays a role in controlling lysosomal activity through influences on *S*-adenosylmethionine-mediated methylation activity.

Mark Mattson, PhD, chief of neurosciences at the National Institutes on Aging, described his expansive research on the neurobiology of aging and the role that fasting physiology has on the protection of brain function.[13] He summarized his work indicating how 3-hydroxybutyrate, which is increased in fasting states, regulates energy metabolism and brain-derived neurotrophic factor (BDNF) in cerebral cortical neurons.[14] Dr Mattson discussed how intermittent fasting physiology influences metabolic switching, neuroplasticity, and brain health.[15,16] He described interesting work that demonstrated that oral supplementation with ketone esters in the absence of a ketogenic diet was found to enhance neuronal function. In addition, he provided data showing how the ketogenic diet mimics the neuroprotective properties of a calorie restricted diet through the regulation of mitochondrial bioenergetic function and the reduction in oxidative stress.[17]

Raphael de Cabo, PhD, senior research investigator for the Translational Gerontology Branch of the National Institutes of Health, presented new insights into the influence of calorie restriction on health and longevity. He pointed out that during the next 30 years, Canada and China will have the largest numbers of people older than 65 years; historically this translates to a reduction in function and increases in disability. According to Dr de Cabo, the only proven way (to date) to curtail reduced function associated with aging is calorie restriction and regular exercise, but new discoveries are being made that mimic these effects with specific cell signaling substances such as rapamycin, metformin, and resveratrol. He highlighted new data showing that periodic fasting improves health and survival in animals independent of diet composition and calories.[18,19] He summarized much of the research on gerontology by saying that dietary interventions that induce fasting physiology and ketogenesis along with a reduction in the insulin-like growth factor pathway and inhibition of the mTOR-S6 kinase network, as well as activation of adenosine monophosphate kinase (AMPK) and specific sirutins, represent the emergent approaches to reducing biological aging. In a 2014 article in *Cell*, Dr de Cabo and his coauthors stated: "The phenomenon of aging is an intrinsic feature of life. Accordingly, the possibility to manipulate it has fascinated humans likely since time immemorial. Recent evidence is shaping a picture where low calorie regimes and exercise may improve healthy senescence . . ."[20] After listening to Dr de Cabo's presentation, my takeaway is that the door is now open to several strategic approaches to counteract aging.

Satchidananda Panda, PhD, professor, Regulatory Biology Laboratory at the Salk Institute, described his groundbreaking research on time-restricted feeding for the prevention and treatment of metabolic disease.[21] Dr Panda's work has dealt with understanding the role of the biological clock in circadian rhythms and how this is related to metabolism and the diet.[22] At the conference, he

shared results from studies demonstrating that time-restricted feeding has positive effects on body weight and metabolic disease risk.[23,24] He indicated that understanding the mechanistic link between nutrients, circadian rhythms related to eating, and the benefits of fasting physiology has led to the development of fasting-mimicking diet programs that achieve the benefits caused by fasting.[25] He stated that a majority of mammalian genes exhibit daily fluctuations in expression levels, making circadian expression rhythms the largest known regulatory network in normal physiology. Circadian expression of secreted molecules and signaling components allows for intercellular communication and regulates metabolism and bioenergetics. The concept of a 12-hour window (at least) between meals is a practical way to harness the benefits of fasting physiology. According to Dr Panda, time-restricted feeding that imposes daily cycles of fasting and eating without calorie restriction represents a new way of approaching the prevention and treatment of metabolic diseases.[26]

James Mitchell, PhD, associate professor of genetics and complex diseases at the Harvard TH Chan School of Public Health, discussed his very interesting work on the role of dietary restriction as an approach to improving resilience and resistance to stress, including postsurgical recovery.[27,28] Dr Mitchell discussed discoveries his group has made on the effect of endogenously produced hydrogen sulfide activated by calorie restriction as a signaling agent that has a positive influence on lifespan.[29,30] The administration of sodium hydrogen sulfide has been shown to mimic the effects of calorie restriction. Based on animal studies Dr Mitchell has participated in, it appears that a protein restricted diet (approximately 7-9 calorie %) can result in improved metabolic function in calorie restricted feeding, whereas carbohydrate and fat were found to have limited effects on gene expression compared to protein intake. Dietary protein intake had a powerful impact on hepatic gene expression in older animals, with some overlap with genes previously reported to be involved with calorie restriction and longevity.[31] Earlier work done by Dr Mitchell demonstrated that calorie restriction has a positive effect on regulating the expression and activity of the xenobiotic phase II detoxifying enzyme nuclear regulatory factor-2 (NRF2) and antioxidant/redox recycling in the mitochondria.[32]

Valter Longo, PhD, cochair of the conference, was, of course, a keynote speaker. He shared his work on the role of fasting-mimicking diets (FMD) on longevity and disease.[33] Dr Longo described how the FMD concept can influence a wide variety of chronic diseases, including cardiovascular disease, autoimmune diseases such as multiple sclerosis, diabetes, and cancer.[34,35,36,37,38] At the meeting, it was reported that the application of the FMD twice per month decreased tumors in animal models by 40% and activated multistress protection genes. In animal models, FMD was found to regenerate white blood cells by activating autophagy and hematopoietic stem cell activity. The FMD formulation for humans was described as a daily intake of 770 to 1100 calories with the following composition: 10% plant-based protein, 44% fat, 47% complex carbohydrate, low in simple sugars. The therapeutic dietary program is administered in 5-day cycles. It is suggested that a person employ 3 cycles of the FMD in a 3-month period of time to produce the desired physiological effects on the immune system. The work that Longo's group has done indicates that this dietary composition and calorie level shifts the body into fasting physiology without fasting and results in the desirable level of BHB for promoting hematopoietic stem cell renewal and metabolic conditioning. In 2017, the results of a collaborative intervention trial of the fasting-mimicking diet on markers/risk factors for aging, diabetes, cancer, and cardiovascular disease were published. Researchers from the University of Southern California, the Charité University Medical Center in Berlin, Germany, and the FIRC Institute of Molecular Oncology in Milan, Italy, were involved in this effort. The study randomized 100 generally healthy participants from the United States into 2 study arms and tested the effect of the FMD on markers/risk factors to age-related diseases. The investigators compared participants who followed 3 months of an unrestricted diet to participants that followed the FMD program for 5 consecutive days per month for 5 months. It was found that 3 FMD cycles reduced body weight, trunk, and total body fat; lowered blood pressure; and decreased insulin-like growth factor 1 (IGF-1). No serious adverse effects were reported. After 3 months the control diet participants were crossed over to the FMD program, resulting in 71 of the 100 participants completing the 3 FMD cycles. A post hoc analysis of the data from both FMD arms demonstrated consistent reductions in body mass index, blood pressure, fasting glucose, IGF-1, triglycerides, total and low-density lipoprotein cholesterol, and C-reactive protein. Those participants who had the most disturbed metabolic markers going into the study had the greatest reduction in risk.[39] This study indicated that the FMD program was safe, led to high compliance, and was effective in improving markers of metabolic functional status.

Krista Varady, PhD, associate professor of nutrition at the University of Illinois, was a valuable member of the conference faculty. She discussed various dietary approaches and the clinical benefits of fasting physiology, including alternate-day fasting and time-restricted feeding of differing durations.[40] She described the results of clinical studies done by her group that demonstrated improved body weight, body composition, and metabolic biomarkers related to insulin signaling and lipid metabolism achieved with alternate-day fasting.[41,42]

Dr Varady's observations concerning the positive metabolic effects of various hypocaloric dieting procedures were reinforced by a follow-up presentation by Michelle Harvie, PhD, a research dietitian with the Prevent Breast Cancer Research Unit, Manchester University NHS Trust.[43,44]

Dr Harvie was one of the first investigators to demonstrate in a controlled clinical study that weight loss can reduce the risk to breast cancer.[45] At the conference, she reviewed the extensive work that has been done by her group and others demonstrating that intermittent energy restriction and intermittent fasting can reduce cancer risk in obese women due to a reduction in tumor stimulating hormonal and metabolic factors.[46,47] In terms of the clinical application of these concepts, a 5:2 program—5 days of prudent eating and 2 days of a modified fast—is described as one of the methods that people have used with success.[48]

Effects of Fasting Physiology on Cancer

This focus on cancer and the effects of fasting physiology at the USC conference was tremendously interesting. Two researchers from Italy—Alessio Nencioni, MD, of the University of Genoa, and Claudio Vernieri, MD, PhD, of the Instituto Nazionale dei Tumori in Milan—shared the results of their work on intermittent fasting and the fasting-mimicking diet in animal models and in human patients undergoing chemotherapy. They reported that in tumor-bearing mice, a 48-hour fast prior to chemotherapy reduced adverse effects and greatly potentiated the effectiveness of the chemotherapy.[49] This team indicated that cancer cells are vulnerable to nutrient deprivation, and fasting or fasting-mimicking diets can result in a reduction in growth factors and specific metabolite levels that are necessary for cancer cells to adapt, survive, and proliferate. In addition, they have discovered that fasting or fasting-mimicking diets can increase resistance to chemotherapy in normal cells but not cancer cells, and can also promote regeneration in normal tissues. They have reported that fasting and fasting-mimicking diets potentiate the anticancer activity of tyrosine kinase inhibiting chemotherapeutics as a result of enhancing MAP kinase signaling inhibition.[50,51]

Three quarters of women with breast cancer are estrogen receptor positive and receive antiestrogen therapy. In the xenograph animal model of breast cancer, it has been found that FMD can improve the success of antiestrogen therapy, as well as lower tumor growth factors IGF-1 and leptin. Conference attendees were told about a clinical trial that is now underway involving 10 women with breast cancer who are undergoing endocrine chemotherapy. To date, the women in the study have done very well with improved grip strength, body composition, and fat-free mass after FMD cycles. Dr Longo reported that in animal tumor models the exogenous administration of ketones did not improve tumor response, suggesting that the effects of FMD are likely to be due to the reduction of serum glucose, insulin and IGF-1, and other stimulators of cellular division.

Hanno Pijl, MD, professor of diabetology at Leiden University, described the results of a randomized pilot study that examined the feasibility of short-term fasting influencing the tolerance to chemotherapy in HER2-negative breast cancer patients. Dr Pijl and his fellow investigators found that short-term fasting during chemotherapy was well tolerated and reduced the hematological toxicity of chemotherapy. Moreover, they reported that short-term fasting suggested a transient decrease in DNA injury and faster DNA repair in peripheral blood mononuclear cells after chemotherapy.[52] He suggested that dietary sugars and excess protein represent the dietary agents most responsible for increasing growth factors and reducing autophagy.

Andreas Michalsen, MD, PhD, is head physician in the Department of Naturopathy at Immanuel Hospital of Berlin. Dr Michalsen has been studying the effects of fasting on inflammatory conditions for more than 20 years. He shared his insights as well as results from various studies he has participated in on the effects of fasting on chronic pain, rheumatoid arthritis, metabolic syndrome, hypertension, and cancer.[53,54,55]

Summary and Takeaway

My attendance at the First International Conference on Fasting, Dietary Restriction, Longevity and Disease was transformational. The evidence presented at this event demonstrated the multiple clinical benefits of fasting physiology and points toward a future in which the clinical applications of dietary approaches will be well understood and successfully utilized.[56,57] The conference reflected the scope and breadth of current research efforts in this important clinical area. Clearly, the application of the important new concepts related to fasting physiology that are emerging will require the advocacy and participation of professionals who are well trained in the fields of clinical nutrition and personalized lifestyle medicine.

The clinical themes I want to highlight are the following:

1. A state of fasting physiology can be achieved without prolonged total fasting.
2. Fasting physiology is a state of metabolism associated with altered gene expression and lowered growth stimulating signals, as well as reduced inflammatory activity and increased immune system renewal.
3. Fasting physiology is associated with increased levels of ketones, including the important signaling molecule beta-hydroxybutyrate, which regulates metabolism and epigenetics.[58,59]
4. The effects of fasting physiology are due to more than just the impact of ketones on metabolism.
5. Approaches to achieving states reflecting that of fasting physiology can include: significant calorie restriction, total fasting, intermittent fasting, time-restricted feeding, and fasting-mimicking diets.
6. Fasting physiology resulting in sustained mild-to-moderate ketonemia (1-3 mM) is dependent upon lower calorie consumption (<1000 cal/day), lower

total carbohydrate intake, elimination of simple sugars, increased fat as monounsaturated MCTs and omega-3 oils, and lower protein intake (<1g/kg) that mostly consists of vegetable protein (40:50:10 calorie percent carbohydrate to fat to protein, respectively).

In *Science* in 2018, 4 authors from the Translational Gerontology Branch of the National Institute on Aging made the following comment in a review article that appeared in a special section on diet and health: "Adjustment of Meal Size and Frequency Have Emerged as Powerful Tools to Ameliorate and Postpone the Onset of Disease and Aging."[60] Evidence is accumulating from multiple fields of study—evolutionary biology, genomics, systems medicine, and nutritional biochemistry—that transient states of fasting physiology are desirable for maintaining resilience and metabolic fitness.[61,62] Justifiably, we have witnessed a surge in interest in longevity science and the concept of biological aging in recent years. There is no reason to doubt that future research may focus on personalized lifestyle medicine therapies that result in periodic states of fasting physiology that may slow aging and reduce the prevalence of age-related diseases.[63]

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