PERSPECTIVES

Advanced nutritional research from a physiological standpoint

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ABSTRACT

Research areas in nutrition science is in infancy. As an interdisciplinary science it can be intertwined with all the different subjects from economics, social science, psychology to high level molecular genomics engineering science and artificial intelligence. The present article deals with research areas of nutrition which are relevant to physiology. Present-day microbiome research depicts the commensals and pathogens be it in gut or other mucosal barriers which include conjunctiva, skin, vagina, urethra, placenta, bladder, uterus, placenta, biliary tract, oral cavity, nasal cavity, lung or breast milk. The translation of the knowledge in basic nutritional science into clinical dietary advices is the basic challenge that gave rise to a new area of research the precision or personalised nutrition which considers genetic factors, microbiome, metabolome, dietary habits, food behaviour, physical activity. Human genome project has given us the tools needed for the development of a new area of knowledge, foodomics that includes nutrigenetics and nutrigenomics epigenetics. The cause of autoimmune diseases may be traced back to the dietary component of the mothers. Fasting, a lifestyle regime, that is related to different religious rituals may be studied from physiological scientific view point. The health promoting effects of intermittent fasting may be proved using different strategies. Nutrient timing and nutrient after exercise are important issues of molecular research that can strengthen dieticians' approach towards combatting lifestyle diseases. Wellbeing gives importance equally to physical, mental, and social health. Dietary practices leading to mental health wellbeing is a new advanced area of research in nutrition. Even a terminally ill patient may be treated with personal dietary approaches that can help in combatting the diseases with proper nutrition. Exploring the relationship between dietary practices and mental health, including potential dietary interventions for mental well-being. Nutri-informatics helps us to deal with huge data sets related to nutrition. Using imaging techniques to study nutrient absorption, distribution, and metabolism in the body, contributing to a deeper understanding of nutritional processes may serve as a pivotal point that can significantly change the nutritional research scenario.

Keywords: Probiotics, prebiotics, microbiome, Nutr-informatics, Nutrigenomics, nutrigenetics, nutraceuticals.

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Introduction

The evolution of nutritional research has markedly enhanced our comprehension of prevailing nutritional disorders, offering invaluable insights into their prevention and management. Gastrointestinal physiology, an amalgamation of endocrinology, neural physiology, microbiology, and immunology, constitutes the pivotal nexus through which nutritional understanding unfolds.

Recent years have witnessed profound advancements in nutritional research, particularly when viewed through the lens of physiology. Scientists and researchers persistently delve into the intricate interplay between nutrients and the human body. This ongoing exploration has yielded a nuanced understanding of how dietary components intricately influence human health. Some key advances include:

Microbiome Research

The gut microbiome, consisting of trillions of microorganisms in the digestive tract, has been a focal point of research. Scientists have discovered its role in nutrient absorption, metabolism, and even its influence on mental health. Understanding how specific diets impact the microbiome can have profound implications for overall health. Human microbiome research is an amalgamation of biomedicine, bioinformatics, statistics, microbiology, genomics, epidemiology, and other fields.

The gut microbiome, as well as microbes from fermented food, are capable of synthesizing vitamins. Species of *Bifidobacterium* can produce vitamin K and various types of vitamin B like thiamine (B1), riboflavin (B2), nicotinic acid (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folates (B9), and cobalamin (B12) etc.[1]

CVD, a worldwide problem, is associated with gut microbiome. Cholesterol may be regulated by short-chain fatty acids (SCFs) and secondary bile acids. Microbial bile hydrolases increase secondary bile secretion, which ultimately reduces cholesterol. Some beneficial commensals may serve as next-generation probiotics, such as *Akkermansia muciniphila, Bacteroides spp.*[2]

The tool that has been constructed to report microbial epidemiological data is called STORM or 'Strengthening The Organization and Reporting of Microbiome Studies.' In other words, it is a checklist of 17 items organized into six sections.[3,4] Dysbiosis, an abnormal microbiome, is reported to be associated with obesity, inflammatory bowel syndrome, malnutrition, neurological dysfunctions, and cancer.[5] The

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vulnerability to autoimmune disorders like type 1 diabetes, arthritis, multiple sclerosis, and allergies may be regulated by gut microbiome.[6] The gut microbiome develops the gut immunity linked with gut-associated lymphoid tissue, inducible regulatory T (Treg) cells, T-helper 17 cells (Th-17), innate lymphoid cells, and IgA-producing B cells. The gut microbiome fights the pathogens by competing for the same food and by increasing the capability of host defense mechanisms, but still, the pathogens develop different mechanisms to solve the direct competition and irradiate the commensals leading to diseases. The pathobionts hoard the gut and lead to irritable bowel syndrome. Manipulation of gut microbiota may be effective in decreasing BMI and child obesity.[7] Probiotic supplementation and antibiotics may not be effective in maintaining the gut microbiota, as shown in a meta-analysis study.[8] *M*icrobial ecology studies, *in-vitro* host–microbe co-culture methods, and gnotobiotic mice models are limited in their capacity to understand the bidirectional functions of host-microbe interaction. At present, physiological and ecological advantages can be studied in Gut-microbiome-on-chips. It can be connected to gut–liver, gut–lung, or gut–brain axes. Thus, future studies on gut microbiome with gut-microbiome on chips can give an idea of the diet-microbiome interaction, drug-microbiome interaction, and mechanistic studies on gut pharmaceutics interaction. Thus, ample room is available for research in this field.

Precision or personalized Nutrition

Advances in genetic research have led to the development of precision nutrition, which tailors dietary recommendations based on an individual's genetic makeup.[9,10] Personalized nutrition considers factors such as genetic variations, metabolism, and nutrition absorption to provide targeted dietary advice. Precision Nutrition research intends to exploit personal data or data from groups of people to provide dietary recommendations that seem to be more useful than generic guidelines. Predictive models on Precision Nutrition were developed using Machine learning, a sub-category of Artificial Intelligence.[11] Consensus regarding overlapping the phrases Precision nutrition and personalized nutrition has still not been achieved.[12]

Since 1975, the data from WHO expressed concern over the rise of obese persons, which doubled in numbers, and the occurrence of diabetes increased four times since 1980. The cases of high blood pressure have risen twice since 1975. These conditions are multifactorial, making it difficult to indicate the precise cause. Thus, the present-day approach is to manage the condition, taking into account individual variability. The recommendations are based on large clinical and epidemiological trials, where generic cut-off points or levels are framed to provide nutrients to the population at large. However, the physiological outcome of nutrition is not considered at a personal level. Variability exists in weight gain to similar dietary interventions, postprandial glycemia, the body's response to salt, caffeine metabolism, vitamin metabolism, and many others. Sex, ethnicity, genetic and metabolic traits, gut microbiota composition, and environment are the major factors responsible for these variabilities. Thus, personalized nutrition is one of the most important solutions to address the problem of variability.

Epigenetic and Nutrigenomics

With the completion of the human genome project, single nucleotide polymorphisms (SNPs), copy number variations (CNVs), and other structural variants were discovered that lead to a vivid impression about the cause of illness or the prediction of vulnerability to disease. Common chronic diseases were associated with SNPs through interactions with the consumption of macro- and micronutrients or with the food pattern and dietary intake. For example, dyslipidemia in Mexican people with a large portion of carbohydrates and fats in their diet is associated with genes for sweet taste receptor (TAS1R2)[13] and cluster of differentiation 36 (*CD36*),[14] respectively.

Epigenetic memory has a prolonged effect that determines the fate of the cell. Numerous dietary molecules and intermediate metabolites can act as signals for epigenetic programming. Specific nutrient molecules, intermediate energy molecules, and vitamins act as signals for transcription factors and chromatin modifiers. Epigenetic memory develops both in the pre and postnatal phases of life. Vitamin D-triggered epigenetic programming of immune cells is an example of how nutrients control metabolic and immune disorders and cancer.[15] Child Obesity is an important problem in the developed world and is an outcome of the developmental programming influenced by the nutritional environment. The high-calorie maternal diet causes modification in fetal chromatin by histone modification. Using the ovine model, it has been shown that in maternal obesity, the expression of fetal muscle miRNA was modified, which led to adipogenesis in intramuscular fetal muscle development.[16] The insulin-like growth factor-2 (IGF2) gene is a site for methylation, and a post-weaning synthetic diet can hypermethylate this gene and modify gene expression. Thus, childhood diet is important and can cause changes in gene methylation, changing the expression of IGF2 in later stages of life.[17] At the fetal stage of development, maternal deficiencies of micronutrients can prime metabolic disorders in offspring, causing intrauterine growth restriction. Epigenetics explores how environmental factors, including diet, can modulate gene expression without modifying the underlying DNA sequence. Nutrigenomics focuses on understanding how specific nutrients interact with genes, influencing health outcomes. This field has implications for preventing and managing diseases through dietary interventions.[18]

Metabolic Flexibility

Research has delved into the concept of metabolic flexibility, which addresses the body's capacity to acclimatize with its fuel source based on dietary and environmental changes. Understanding how different diets affect metabolic flexibility can affect weight management, type 2 diabetes, and metabolic health. The change of fuel selection in the shifting from fasting to fed states and stimulation of insulin secretion in the fasting state may be described as metabolic flexibility. In insulin resistance, diabetes, and obesity, there is elevated muscle glucose oxidation and diminished fatty acid oxidation due to metabolic inflexibility.[19]

In exercise, high energy requirements entail metabolic flexibility and muscle plasticity is involved in changing the metabolic pathways and the metabolic machinery. Alteration in skeletal muscle epigenome,[20] training responsive transcriptome[21] and proteome,[22] were shaped by exercise that creates anabolic flexibility to encounter changes in energy requirements during exercise. More research is required to establish the molecular interactions leading to metabolic flexibility.

Intermittent Fasting and time-restricted eating

Reports on intermittent fasting and time-restricted eating have gained attention for their potential health benefits.[23] Research suggests that these dietary approaches may influence metabolic health, improve sensitivity, and contribute to weight management. Dietary protocols consider time and calorie restrictions, *i.e.*, time-restricted and calorie-restricted eating. A low-calorie diet includes a low carbohydrate diet, a low-fat diet, a low protein diet, and a very low-calorie diet allows 800 kcal/day, whereas a time-restricted diet includes time-restricted eating, intermittent fasting and fasting-mimicking diets. The continuance of weight loss and the difference in metabolic changes in intermittent fasting and time-restricted fasting require more exploration. Fasting-mimicking diets are protocols that provide low calorie replacing fasting. In animal studies, diet is given *ad libitum,* whereas humans feed thrice daily. Thus, intermittent fasting with 60% energy every alternate day or 2 days a week, periodic fasting consuming 700 to 1100 cal five days a week, and time-restricted feeding are some of the ways of weight loss that also alleviate mitochondria damage, autophagy and DNA repair.[24] Intermittent fasting has been shown to improve aging-related diseases. It is mainly a plant-based diet low in sugar and protein.

Nutrient timing

The timing of nutrient intake concerning exercise has been a subject of interest. Optimal nutrient timing, such as consuming specific nutrients before, during, and after exercise, can impact performance, recovery, and adaptation to training. The total calorie intake is important in training but timing of intake of nutrient is also very important. Nutrient periodization and carbohydrate restricted training are advanced concepts in research.[25] Throughout exercise the physiological and metabolic responses are prevalent. The heart rate and blood flow are increased along with glycolysis and lipolysis. During exercise, there are changes in insulin and hormones such as glucagon, epinephrine, norepinephrine, cortisol, growth hormone, etc. The increase of insulin counter-regulatory hormones causes oxidation of fatty acids and glycogen in muscles. The metabolic byproducts signal the translocation of GLUT4 to the muscle cells, increasing glucose uptake by the muscle cells. Diet after exercise causes a shift from a catabolic to an anabolic state. During the post-anabolic state, there is an increase of GLUT4 in muscles and uptake of glucose to replenish glycogen. Pre-exercise, intra-exercise, and post-exercise nutrition are important nutrient timings that have been studied for the training of athletes.[26] Nutrient periodization and carbohydrate-restricted diets for athletes are some of the areas for future research. The timing of nutrients is contradictory and needs more research.

Dietary influences on mental health

Presently, about 30 crore individuals are suffering from depression, and 26 crore are suffering from anxiety disorder. There is a change in diet composition, and traditional dietary patterns are being replaced with Western diets with high energy content. This dietary shift leads to CVD, insulin resistance, and metabolic disorders and also affects mental health. Sleep deprivation may be due to inflammation, reduced synaptic plasticity, hippocampal neurogenesis, and changing neurotransmitters. Mental disorders like anxiety and depression are linked to sleep disorders, and inflammation is prevalent in such cases.[27] The connection between dietary patterns and mental well-being is an evolving area of study. Research has explored how several nutrients and dietary intake may influence mood, cognition, and the risk of mental health disorders.[28] About 30% of the world's population is obese and suffering from obesity-related diseases. Brain-derived neurotrophic factor (BDNF) is responsible for plasticity and neurodegenerative diseases, and is derived from food. Dietary changes reduce anxiety, depression, and suicidal tendencies. S-adenosylmethionine, *N*-acetylcysteine, zinc, omega-3 fatty acids, and B vitamins like folic acid and vitamin D are associated with mental health. *N*-acetylcysteine intervention in the therapy of schizophrenia, bipolar affective disorder, or trichotillomania was observed.[29]

Functional Foods and Nutraceuticals

Advances in identifying bioactive compounds in foods have led to the emergence of functional foods and nutraceuticals. These products aim to impart therapeutic value beyond their inherent nutritional attributes, such as promoting heart health, reducing inflammation, or supporting immune function. Research globally is searching for new nutraceuticals and mechanisms of action of these nutraceuticals, which also comprises viable interfaces with physiological system, drugs or therapeutics, or foodstuffs themselves.[30] Bioactive compounds have antioxidant, anti-inflammatory, or other health-promoting properties. For example, some may target heart health by promoting cardiovascular function and reducing the risk of heart disease. Others may focus on reducing inflammation, supporting immune function, or even improving cognitive health. Understanding the mechanisms of action of nutraceuticals is crucial for validating their efficacy and ensuring their safety. Researchers investigate how these compounds interact with cellular pathways, enzymes, receptors, and other biological processes to exert their beneficial effects. Researchers are exploring potential synergies or interactions between nutraceuticals and other bioactive compounds, pharmaceuticals, or even whole foods. This interdisciplinary approach aims to optimize health outcomes and minimize any adverse effects.

Role of inflammation

Excess intake of macronutrients in the diet is responsible for generating oxidative stress and inflammation in the physiological system. Metabolic changes lead to insulin resistance, increased circulating FFA, triacylglycerol and pro-inflammatory cytokines, TNF-α and IL-6. Activation of inhibitor K kinase β in adipocytes and hepatocytes by FFAs and TNF-α leads to phosphorylation of insulin receptor substrate 1 (IRS 1). An ultimate drop in insulin-dependent tyrosine phosphorylation of IRS-1 and glucose transport leads to diabetes. Oxidative processes seem to be crucial in developing atherosclerosis. Clinical trials on Vit E supplementation have depicted that Vit E supplementation reduced deaths, as observed in a meta-analysis. Slow food intake is associated with decreased pro-inflammatory cytokines, and fast-food intake may be associated with increased pro-inflammatory cytokines.[31]

Chronic inflammation is implicated in various diseases. Obesity is associated with chronic low-grade inflammation. With high energy intake, there will be increased fat deposition and adipose tissue that cause penetration of pro-inflammatory immune cells. Adipose tissue macrophages are an important group of cells that are responsible for pathogenesis due to obesity. The pro-inflammatory immune system leads to the development of co-morbidities related to obesity, such as insulin resistance, type-2 diabetes, cardiovascular diseases (CVD), and non-alcoholic fatty liver diseases. Obesity-induced inflammation is also observed in the peripheral and CNS. Adipose tissue macrophages are responsible for obesity-induced inflammation.[32] C-reactive protein (CRP) and tumor necrosis factor-α (TNF-α) are the biomarkers of age-related inflammation, also termed inflammation. Calorie-restricted diet, gut microbiome, and Mediterranean diet are crucial for reducing inflammation. Age-associated dysbiosis leads to improper brain function, metabolic and immune impairment, and poor health. Several pathways of inflammation have been characterized that can be modulated with a calorie-restricted diet and the modified gut microbiome. Future research may develop specific molecules from postbiotic microbes to modulate the immune system that can reduce age-related metabolic disorders.[33] Nutritional research explores the impact of diet on inflammatory markers and how anti-inflammatory diets may contribute to overall health.

Advanced Imaging Techniques

Advanced imaging techniques, including magnetic resonance imaging (MRI) and positron emission tomography (PET), enable researchers to visualize and study the metabolic processes in the body, providing valuable insights into how different diets affect organ function and overall physiology. Dual x-ray absorptiometry (DXA), computed tomography (CT), magnetic resonance imaging (MRI), and three-dimensional (3D) (photonic) imaging techniques are used for the assessment of undernutrition.[34]

Nutri-informatics

Another area of nutrition research where computational science[35] or bioinformatics has been applied to understand the nutrition of some specific nutraceutical molecule at the biological interface. It also includes the application of computational science for analyzing data from food and nutrients, government regulations, community nutrition, epidemiological studies, and clinical and individual nutrition to generate information for a healthier life.[36]

In the realm of biological research, the field of nutrition research is relatively nascent and remains in its early stages of development. The genesis of modern nutrition research can be traced back to the seminal discovery of vitamins. Clinical trials involving various nutrient molecules, such as vitamins and minerals, demand comprehensive examination on a larger scale, encompassing considerations of genetics, diverse ethnicities, dietary habits, food sources, and the technologies employed in food processing.

Food habits are intricately influenced by many factors, including social, economic, cultural, and religious attributes, as well as agricultural practices and geo-environmental conditions. The emergence of innovative areas such as 3D food printing, gastro-tourism, gastro-physics, space nutrition, and sports nutrition presents exciting avenues for exploration within the realm of food and nutrition. These domains warrant thorough investigation, considering their potential implications on human health and dietary practices.

Moreover, a multitude of other advanced areas in nutritional research hold promise for advancing our understanding of physiology and pharmacology. The collective progress in these domains contributes significantly to unraveling the intricate relationship between nutrition and physiology. This, in turn, lays the foundation for more precise dietary recommendations and the development of personalized approaches to promote health and wellness.

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