Medical nutrition in mental health and disorders

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Dr. Prasad Rao Garu, distinguished guests and friends, I have been looking forward to this moment with much trepidation for almost a year, because the unwritten law of the society lays down the rule that its presidents must speak on any topic of their liking, or disliking as the case may be, on a day like this. I have been a sort of an up-and-down all-rounder in psychiatry all my life in the armed forces and the “civilized” existence after bidding adieu to uniform. Over the years, I have had the privilege, as a teacher, of putting some brilliant minds through their paces in psychiatry, dabbled in surface-skimming research on a variety of topics ranging from schizophrenia, substance use, imaging, phospholipids, genetics, neuroendocrinology, sleep, and dreams; I have an abiding interest in military psychiatry and I am a clinician with some interest in the currently unglamorous unconscious processes. As I mulled over the looming specter of the speech, several topics clamored for attention. To my utter unease, I was not finding any one of the topics interesting enough to excite my little grey cells. Fortunately, a couple of weeks ago, I traveled to my native village in Odisha to pay obeisance to our family deity. It so happened that I was required to attend to a lady there who was in some distress. Besides some words of comfort, I was obliged to procure and provide the medicines as well to her. She took the proffered pills as if they were an offering of the Gods and then asked me what she should eat. Unwittingly the tribal lady made the unease in my mind cease at that very moment. I decided to speak on food and all the good, and in certain cases bad, it does to a person in sickness and health. It is very common for the patients in India to ask what food substances they should and should not have while undergoing treatment.

It is a way of life in traditional homes in India to consider food as the manifestation of the immanent and transcendent unity called Brahma or Atman: “Annam Parabrahma Swaroopam” are the oft-quoted words of the elders to the young. The Taittiriya Upanishad, a treatise of philosophy of more than 3000 years antiquity, states “Annam Bhootanam Jyeshtam tasmat annam sarvaushadam ucyate” which when translated means “Food verily is the eldest born of beings and therefore it is the healing herb for all.”[1] I still remember vividly the surges of energy and sense of luminescent wellness that coursed through my person on eating small cups of cooked rice with warm lentil soup after getting thoroughly shaken and stirred by bouts of malaria in childhood. Intuitively, we all recognize the healing qualities of food but somehow we seem to have lost the way as we started focusing exclusively on molecules. Fortunately, there is a resurgence of interest in nutrition in mainstream psychiatry of late.[2,4,6]

THE WORLD OF NUTRITION

The world is facing a nutritional crisis. Approximately 3 billion people of the world have low-quality diets. Despite the gains of reducing hunger over the past 25 years, malnutrition prevails in all forms affecting one in three people worldwide. Poor diet is responsible for the largest burden of global ill health: six of the top 11 risk factors are diet related. The “double burden” of undernutrition on one side and obesity on the other is a phenomenon of this century.[7] Nutrition continues to be a central health, economic, and sustainable development challenge for every region on the planet.[8] Globally, while 794 million are calorie deficient and 2 billion suffering from micronutrient malnutrition, 1.9 billion are overweight/obese, 161 million children under 5 years of age have stunted growth indicating chronic malnutrition, and 57 million of children <5 years of age show wasting indicating acute malnutrition while 42 million are overweight.[9] In April 2016, the UN General Assembly declared the period 2016–2025 as the International Decade of Nutrition to step up both national and international efforts to meet the nutritional-related targets of the new sustainable development agenda. At a high-level symposium on nutrition on April 02, 2016 at Rome, member countries were reminded of the importance of promoting healthy diets for everyone and eradicate hunger and malnutrition by the year 2030.[8] Fast-changing India also mirrors the global trend of double burden. Forty-eight million (39%) and 19 million (15%) children under 5 years of age in India show stunted growth and wasting indicating chronic and acute malnutrition, respectively, while 13% of adolescents are overweight and obese. Forty percent of women are thin while 7% are obese. About 48% of women of reproductive age have anemia.[10] In a recent systematic review by Steel et al., the 12-month and lifetime prevalence of common mental disorders were found to be 17.6% and

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29.2%, respectively.\textsuperscript{[11]} Although the determinants of mental health and mental disorders are complex, the emerging and compelling evidence for nutrition as a crucial factor in the high prevalence of mental disorders suggests that diet is as important to psychiatry as it is to cardiology, endocrinology, and gastroenterology.\textsuperscript{[2,5]} The recent progress in the science of nutrition has brought in much terminology that we need to be conversant with to keep ourselves abreast of the developments on the nutrition front.

**NUTRITION TERMINOLOGY**

Nutrition is the intake of food considered in relation to the body's dietary needs.\textsuperscript{[12]} The field of science which is concerned with the study of nutrition is also called nutrition. It can be defined as the science that interprets the interaction of nutrients and other substances in food in relation to maintenance, growth, reproduction, health, and disease of an organism.\textsuperscript{[13]}

Nutrient is a component in foods that an organism uses to survive and grow. Macronutrients (proteins, carbohydrates, and fats) are nutrients which are required in large quantities to provide building blocks and bulk energy that an organism's metabolic system needs to function. Micronutrients (vitamins, minerals) provide the necessary cofactors for metabolism to be carried out. They are required in very small amounts. Essential nutrients cannot be synthesized internally and therefore must be consumed by an organism from its environment. Essential fatty acids, essential amino acids, and vitamins can be considered as essential nutrients.\textsuperscript{[14]} Nutritional status is the condition of the body in those respects influenced by the diet, levels of nutrients in the body, and the ability of those nutrients to maintain normal metabolic integrity.\textsuperscript{[15]} Neutraceutical is a product isolated or purified from food that is generally sold in medicinal forms. Dietary supplements containing nutrients are provided as pills, capsules, or liquids while “functional foods” are foods enriched with nutrients.\textsuperscript{[16]}

Medical nutrition is the clinical application of the current substantial knowledge about the roles played by nutrients in health and disease. A specialist in medical nutrition can investigate a person's nutritional status and suggest nutrient therapies which could assist in achieving optimal health, preventing disease, or fighting disease.\textsuperscript{[17]}

**ROLE OF MACRONUTRIENTS**

We acquainted ourselves with the high-energy requirements of the brain and the fact that it extracts 20% of arterial glucose.\textsuperscript{[20]} Carbohydrates are required to be burnt in the furnaces of the cells to supply the high-energy requirement of the brain. Some of the glucose is stored as glycogen in astrocytes and release energy on demand, but the brain largely is at the mercy of extra brain sources for its energy requirements. Rapidly absorbed glucose contributes to greater release of cortisol which affects memory adversely. Therefore, carbohydrates with low glycemic index are more beneficial for mental functioning. It is seen that carbohydrate mouth washes release dopamine in the reward systems of striatum! Obviously, it is not related to glucose level in the blood.\textsuperscript{[22]} Carbohydrates also elevate mood through the release of tryptophan which is a precursor of serotonin.\textsuperscript{[23]}

Phospholipids are the major constituents of the neuronal and glial membranes and form 60% of the nonaqueous weight of the brain (there is no shame if somebody calls you a fat head! In fact my wife calls me so whenever she thinks I did something good!) Phospholipids have a three carbon backbone with the first two attached to fatty acids and the last one attached to a phosphorous molecule which in turn attached to any one of the four head group molecules – choline, serine, ethanolamine, and inositol. Phospholipids are rich in highly unsaturated fatty acid (HUFA), n-6 (linoleic acid [LA]), and n-3 (alpha linolenic acid [ALA]). They are also called essential fatty acids because the body cannot synthesize them and therefore had to be obtained from diet. Arachidonic acid is a metabolite of LA while eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are metabolites of ALA. EPA and DHA form the bulk of HUFA.\textsuperscript{[21]}

**BRAIN AND NUTRIENTS**

Kandel and Hudspeth famously stated that what we commonly call the mind is a set of operations carried out by the brain and as a corollary all the behavioral disorders result from disturbances of brain function.\textsuperscript{[18]} To understand the influence of nutrition on mental health and disorder, it is important to know two things: first, nutrients are not just packets of energy and building blocks of the body; second, nutrients dynamically interact with the systems of the body to develop and maintain structural and functional integrity of the body and brain. Brain though one-fiftieth of the body weight by weight uses up to a quarter of the energy requirement of a person at a constant rate. Eighty percent of this energy is used up in active signaling process correlated with glutamate cycling.\textsuperscript{[19]} Brain extracts 50% of oxygen and 20% of glucose from the arterial blood.\textsuperscript{[20]} Its hundred billion neurons and much larger number of neuroglia have cell membranes that are dynamic structures composed of lipids and proteins.\textsuperscript{[21]} Brain has not much energy stores and dependent entirely on aerobic metabolism. Nutrients are needed for regular supply of energy and the building blocks that erect and maintain integrity of neural structure. Nutrients also influence neurotransmission, mitochondrial integrity, and genetic expression.\textsuperscript{[14]} The contribution of widely prevalent malnutrition to impaired structure and functioning of brain and the resulting neuropsychiatric disorders is not difficult to appreciate if we look at the roles played by carbohydrates, fats, amino acids, vitamins, and minerals in the brain's structure and function.

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Phospholipids rich in HUFA because of their flexibility allow rapid change in membrane shape which occurs in the synthesis of dendritic spines and fusion of membranes during neurotransmitter release from synaptic vesicles. EPA and DHA are of high functional importance because of their involvement in signal transduction, eicosanoid metabolism, regulation of genetic expression, and regulation of glutamine, dopamine, and serotonin transmission as well as interaction with neurotrophic factors. Decreased B12 levels cause loss of HUFA from phospholipids. Free HUFAs are easily oxidized, creating an increased amount of free radicals which can attack neural membrane. In view of the complex nature of functions of omega fatty acids, diet should contain n-6 and n-3 HUFA in adequate quantity and proportion. N-6 fatty acids are pro-inflammatory. Hence, the proportion of n-6 to n-3 should ideally be 1:1–5:1. According to Simopoulos in modern Western diets, the proportion is as much as 20:1.

Physiological concentrations of amino acids and their metabolites (nitric oxide, taurine, glutathione, etc.) are required, while elevated levels (phenylalanine) and their products (ammonia, homocysteine, etc.) are neurotoxic. Optimal balance of amino acids in diet and circulation is crucial. Increased immune sensitivity to wheat protein gluten has been reported in some cases of schizophrenia.

**ROLE OF MICRONUTRIENTS**

B Vitamins are a group of eight water-soluble vitamins that perform essential role in cellular functioning. Thiamine, riboflavin, niacin, and pantothenic acid, as coenzymes, play direct role in Krebs cycle, and the electron transport chain plays a crucial role in generating adenosine triphosphate (ATP) which is the currency of cellular energy. Folic acid and B12 are involved in folate and methionine cycles. Dietary folate enters the folate cycle to generate carbon atoms required for synthesis of DNA and RNA. The methionine cycle catalyzed by B12 generates methionine from homocysteine. Methionine through S-adenosyl methionine is responsible for genomic and nongenomic methylation reactions. The two cycles are interlinked with the process of resalvaging tetrahydrobiopterin which is a cofactor in catecholamine synthesis. Vitamin B6 is a cofactor for 140 enzymes while pantothenic acid is a cofactor for 4% of all enzymes. Ascorbic acid is a reducing agent. It is a cofactor to many enzymes involved in collagen synthesis, tyrosine metabolism, and dopamine beta-hydroxylase synthesis. It is also involved in carnitine synthesis. Carnitine is necessary for transport of fatty acids into mitochondria and ATP generation.

Vitamin D is a fat-soluble secosteroid. By itself, it is inactive and gets converted into its active form calcitriol by double hydroxylation in kidney and liver. Besides its role in mineral homeostasis, it is considered as a neurosteroid and implicated in apoptosis and regulation of genetic expression of many genes. A recent meta-analysis by Anglin et al. in 2013 showed that low levels are significantly associated with depression. Both low and high levels in neonates are associated with increased risk for schizophrenia. For the sake of brevity I am not touching upon the role of other micronutrients.

**EARLY HISTORY OF MEDICAL NUTRITION**

Beriberi, pellagra, scurvy, and phenylketonuria (PKU) are some of the earliest descriptions of human diseases that were linked to nutrition and sought to be treated by nutritional factors establishing a definite proof of the concept that mental problems can be caused by nutritional factors. After preliminary attribution to diet, causative substances were identified, isolated, and used to effectively treat these conditions. Kancheiro Takaki, a Japanese naval physician, established diet as the cause of Beriberi in 1883 by feeding nutrient-rich diet to sailors of one ship and nutrient-poor diet to sailors of another ship. Around this time, Karl Wernicke and Sergei Korsakoff independently identified the syndrome consisting of amnesia and neurological signs. Christian Eijkman and Sir Fredrick Hopkins got the Nobel Prize in 1929 for tracing the “accessory factor,” the deficiency of which caused beriberi, to rice bran. It was left to Jansen and Donath to isolate the active substance from rice bran.

The cognitive and emotional symptoms of pellagra were well known. Lorenz cited a study where 52 out of 130 pellagra patients (40%) had mental symptoms. Joseph Goldberger from the USA identified nutritional deficiency as the cause of pellagra in 1926 by actually producing features of pellagra by feeding 11 prisoners with poor diet. Conrad Elvehjem isolated nicotinic acid from liver and showed that it could cure pellagra. Scurvy was known to seafarers for long. The Scottish surgeon James Lind proved that scurvy can be treated with citrus fruit juice in 1753. It was known to be associated with mental illness and alcoholism. Apart from bleeding gums, corkscrew hair, delayed wound healing, depression, and anxiety were common. Albert Szent-Gyorgyi isolated a substance which he called hexuronic acid in 1928. It was later named as ascorbic acid after its antiscorbutic action came to be known. Asbjorn Folling discovered PKU in 1934, an autosomal recessive condition manifesting with pale skin, blue eyes, and feeble mindedness. In the 1950s, hepatic phenyl alanine hydroxylase was shown to be deficient in PKU and that it can be treated by restricting phenylalanine in diet. It was a paradigm shift in medicine that a genetic condition manifesting with mental symptoms could be rationally treated with appropriate diet.

Nutrients do not lend themselves to be investigated by randomized controlled trials. Ancel Keys et al. (1950) conducted one of the earliest experiments to study the physiological and psychological effects of starvation. During 1944, when the war raging in Europe, 36 “conscientious
objectors” voluntarily subjected themselves to be starved and be investigated. They were given a starvation diet of 1800 calories diet for 6 months in the so-called “Minnesota experiment.” All the volunteers lost a quarter of their body weight, became apathetic, and suffered from anemia, extreme weakness, fatigue, and nerve degeneration. Normal diet restored the personality changes to normal within 1 year.

It is not possible to conduct experiments of the nature conducted by Goldberger, Kanehiro Takaki, or by Ancel Keys now because of ethical considerations. Two rather unfortunate episodes of history presented painful but useful “natural experiments” on the effects of nutrition on mental health. After the Allied landing in Normandy, the German occupation forces placed an embargo on food supplies to Holland during winter of 1944–45 (Dutch Winter Hunger). During the blockade, 20,000 people perished due to famine. The people who suffered and survived the starvation became a cohort for study. It was found that the children born to women who suffered starvation during pregnancy were at higher risk for low birth weight, diabetes, obesity, and schizophrenia. What is curious is that the second generation offspring of low birth weight cohort also had higher incidence of low birth weight, indicating possible epigenetic influence of starvation. The offsprings of Dutch Winter Hunger mothers were also found to be at an increased risk for depression. During the marked socioeconomic upheaval of the Great Leap Forward in the late fifties, severe famine occurred in the Anhui province of China. An estimated 30–40 million people perished as a result of starvation. It was found that the increased risk for schizophrenia in the birth cohorts of this famine was same as that of Dutch cohorts.

Meanwhile Pauling, the only person who won two Nobel Prizes singly, had proposed his concept of orthomolecular psychiatry. He cited a study of Edwin et al. (1965) who found low cyanocobalamin levels in 15.4% of psychiatric patients (n = 396) whereas the prevalence of that in the general population was 0.5% and a study of Cleckley et al. (1939) who reported improvement of symptoms of schizophrenia in all 19 patients who were treated with nicotinic acid. He also cited a study of Akerfeldt et al. (1957) who reported that serum of schizophrenic persons had greater power of oxidizing dimethyl-p-phenylenediamine than that of other persons which was shown to increase the rate of metabolism of ascorbic acid. Further, he reported in 1973 that 82% of schizophrenic patients retained a loading dose of ascorbic acid whereas only 39% of normal people retained the loading dose which he inferred was due to low reserves of ascorbic acid in schizophrenia. He contended that the brain was more sensitive than other organs to the rate of chemical reactions and that “mental diseases” (he called them diseases!) are for the most part caused by abnormal reaction rates determined by genetic constitution and diet and that significant improvement in mental health might be achieved by the provision of optimum molecular concentrations of substances that are normally present in the human body. He noted that psychosis associated with pernicious anemia may manifest several years before other manifestations become noticeable, so he speculated that there could be localized cerebral deficiencies of vitamins or other substances due to decreased rate of transfer across blood–brain barrier or increased rate of destruction of vital nutrients.

Puri and Richardson administered 2 g of EPA to a single case of schizophrenia and followed the patient over a 3-year period and found ventricular dilation reverted to normal. Significantly, Valdiya et al. found no difference in ventricular volumes of fifty male adult soldiers suffering from schizophrenia and twenty normal controls. It is significant to note that soldiers consume high calorie-balanced diet. Objective assessment of their nutritional status could have provided the clue whether nutritional deficiency had something to do with ventriculomegaly in schizophrenia and other psychiatric disorders.

**RECENT ADVANCES**

Ames et al., found that reduced coenzyme binding, and the resulting reduction in enzyme activity, brought about by genetic polymorphisms can be remedied by raising cellular concentrations of cofactors through high dose vitamin therapy. It is now known that mental disorders are caused by several genes of small effect. Given that vitamins are co-factors for many enzyme reactions, perhaps this study gives a rationale for vitamin therapy in mental disorders.

Rao et al. in an elegant review highlighted the role of various macro- and micro-nutrients in the onset, severity, and duration of depression. Amminger et al., 2010, conducted a randomized controlled trial of administering omega 3 fatty acid to 41 persons considered as at ultra-high risk for schizophrenia and compared with forty controls on placebo. At 1 year, only two persons developed schizophrenia while 11 persons in the control group developed schizophrenia. There was a highly significant difference in symptoms as well as in function.

In a recent randomized controlled study, Ross et al. administered phosphotidylycholine at twice the dietary levels during pregnancy to mothers and 16-week postpregnancy. Child Behavior Checklist was administered to children at 40 months. The children had lesser social and attentional problems in comparison to controls. Jacka et al. followed up 1046 women over a 10-year period. Information about diet was obtained by a standardized food frequency questionnaire. A traditional dietary pattern consisting of vegetables, fruits, meat, fish, and whole grains was associated with lower odds for major depression, dysthymia, and anxiety disorders.
Akbaraly et al. followed up a cohort of 3486 participants over a period of 5 years, assessed their diet, and measured depression by the Center for Epidemiologic Studies Depression Scale (CES-D). Persons in the highest tertile for whole food pattern had lower odds of CES-D depression (odds ratio: 0.74, confidence interval: 0.56–0.59) than those in the lowest tertile.[49]

Sánchez-Villegas et al. followed up 10,094 participants over a 10-year period and assessed their dietary pattern by a 136-item food frequency questionnaire. Highest adherents to Mediterranean diet consisting of vegetables, fruits, nuts, cereals, legumes, fish, and monounsaturated fatty acids had lower risk of depression.[50] We studied 38 first-episode drug-naive schizophrenic patients and found decreased membrane DHA levels, decreased plasma B12, and increased homocysteine levels.[51] We also found that reduced hippocampal volumes were correlated with membrane DHA levels.[52]

Nanri et al. followed up 40,752 male and 48,285 female participants for 10 years by administering 134-item food frequency questionnaire. They found that a high intake of vegetables, fruits, soya products, mushrooms, seaweed, and fish decreased the risk for suicide.[53] Sarris et al. conducted a randomized controlled study involving S-adenosyl methionine (SAMe), escitalopram, and placebo on 144 major depressive disorder patients from 2005 to 2009. The effect size for SAMe versus placebo was 0.74. SAMe was also found to be superior to escitalopram.[54] Dean et al. administered 2400 mg/day N-acetyl cysteine to 75 bipolar disorder patients and noted significant improvement. They also administered 1000 mg along with antipsychotic drugs and found significant improvement.[55]

In a recent meta-analysis, Sarris et al. analyzed forty studies involving 1829 patients and found that adjunctive use of SAMe, methylfolate, omega 3 fatty acids, and Vitamin D with antidepressants reduced depressive symptoms.[56] Besides the obvious functional value of various nutrients, the emotional value of food and its role in erecting a sound personality structure cannot be underestimated. Experience of food insecurity itself influences mental health adversely leading to anxiety and depression.[57]

CONCLUSION

Over the past several years, evidence has been steadily growing in favor of a relationship between quality of diet and mental health. Besides the early observations, the recent prospective studies with large sample sizes, systematic reviews, and randomized controlled trials have established the importance of nutrients as agents for prevention, treatment, or augmentation of treatment for mental disorders. Perhaps, it is necessary now to remind ourselves of the Hippocratic dictum that it is necessary to understand the “whole things” when confronted with disease. Nutritional psychiatry is an emerging and genuine area of study and practice not only because of the dynamic role that the nutrients play in the integrity and functioning of brain, but also because of the emotional value and significance that humans had imparted to food over the eons. Empathic interactions and rational nutrition along with specific pharmacological and physical interventions could form an ideal and humane patient-friendly package in psychiatric practice. The economic and general health spinoffs of taking nutrition into consideration while formulating and implementing health policies could also, for obvious reasons, be quite salutary from the mental health point of view. Nutritional psychiatry should form an essential subject to be taught in psychiatric training as it has the potential to reestablish the missing human connection between the professionals and people in distress in a pervading atmosphere of near-absolute medicalization that prevails in psychiatry today.

Ladies and gentlemen, I consider it a great honor for me to speak to such an enlightened audience here today. I owe you all my deep sense of gratitude for giving me a patient hearing. Jai Hind!

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