Diet Restrictions, Epigenetics and Depression

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Major depressive disorder (MDD), a looming cause of disability worldwide, is a multifactorial and a complex disorder. Its rising prevalence is being linked with the deficiency of essential nutrients. Diet and the vital environmental factor, is influenced by eating disorders and unbalanced or low micronutrients intake which can leave epigenetic marks on the DNA consequently compromising the signalling and expression mechanisms. MDD has been ranked globally as the third cause of the burden of diseases by the World Health Organization (WHO), in their 2008 report, predicting it to be number one by 2030.[1]

Seven eating disorders have been described in DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) by the American Psychiatric Association. But besides these 7 eating disorders, Pakistan's population especially women, is hit by unplanned dieting, impromptu starvation and intermittent 14 hours of fasting and depriving themselves of essential nutrients. On the other hand, the younger generation is on constant hang on to environmental stressors which include ultra-processed fast foods and improper western diets type, causing macronutrient imbalance by eliminating essential nutrients in their diet and deficiencies at micronutrient levels. These diet insults impair certain cellular processes which leads to metabolic changes such as immunomodulation which in our body is shaped by our nutritional players such as vitamins, minerals, or omega 3 polyunsaturated fatty acids (ω-3 PUFA).

The MDD globally accelerated during the last two years, overburdened by COVID-19 pandemic.[2] The consequences of MDD include absenteeism, decreased workplace productivity, and functional impairment and disability. Furthermore, in young men not only the risk of suicide increases but also the risk of cardiovascular deaths. These events, on the whole, are a cause of huge economic losses, attributed mainly to treatment and management which neither help in treating depression nor its complications.[3]

Psychiatric disorders result from an interaction of environmental factors and genetics termed as Epigenetics. These key factors drive a set of multifactorial conditions that lead functional changes in the entire body and also in the brain due to molecular, cellular, circuitry, and structural alterations.

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Epigenetic marks were found in patients with MDD.

Epigenetics, without altering the DNA sequence, brings modification in the expression of genes and the function of their products by activating them or shutting them down [National Human Genome Research Institute]. Studies on identical twins have shown discordance among them due to exposure to environmental stressors that prompted epigenetic marks in the genetic expression compromising neuronal function and behaviour.[4] The key mediators that drive aberrant epigenetic mechanisms are DNA methylation, histone modification, microRNAs (miRNAs), and long-noncoding RNAs (lncRNAs) targeting pathways that have been implicated in major depression.[5]

Histones are the foundation pillars where the organisation of the human genome stands. For the formation of nucleosomes, histones group into five dual sets for DNA packaging, in which H2A, H2B, H3, H4, are used for wrapping DNA strands around them, whereas, H1/H5 is involved in the linking of multiple nucleosomes. Since histones basically are proteins rich in lysine, arginine, serine and threonine, they undergo posttranslational modifications including methylation, acetylation and ubiquitylations. Researchers have found many prodepressive epigenetic alterations in the DNA. Such as in Hippocampus, a decrease has been found in acetylation of H3/H4 and H3K9me3 and increase in the activity of HDAC and expression of HDAC5 that is the action of enzymes responsible for acetylation or deacetylation of histones.

Methionine and **folate** are the epigenome-diet hallmarks, providing S-Adenosyl methionine (SAMe), the universal methyl donor for the methylation reactions of DNA and histones. Besides, SAMe, the absence of other cofactors and methyl donors in the diet such as B6, B9, B12, and zinc lead to metabolic deficiencies. These nutritional deficiencies are correlated to high levels of homocysteine and methylmalonic acid, which are also associated with MDD as well as psychosis, suicide ideation, or alexithymia, mania, psychotic symptoms and obsessive compulsive disorder.[6] B12 levels are now proposed to be part of the assessment of neurodegenerative diseases and neuro-psychiatric disorders.

Imbalance or absence of nutrients also causes dysbiosis due to the destabilization of microbial community. This leads to vitamin B12 deficiency because of the inability to produce microbial B12 and deficiency of other metabolic vitamin levels like B6, B9, and B12 due to the restriction of diet. Low levels of these vitamins affect methylation levels of redox-related

genes, causing oxidative stress. This stress in adding up with deficiencies of -3 PUFA, especially DHA, is critical for brain function and protection, neuronal membrane fluidity and neurotransmitter release, as well as functions of neurons affecting monoamine oxidase production, repair of phospholipids leading to imbalanced neurotransmission synthesis.[7] Diet restrictions can hamper protein intake imposing limitations on essential amino acids which are precursors for neuro-transmitter and neuro-modulator synthesis, such as phenylalanine and tyrosine are the precursors for epinephrine, norepinephrine and dopamine.

Vitamin D deficiency, another most common manifestation in MDD, originates from deficient dietary intake as well as insufficient exposure to the sun. Role of vitamin D in the development of dopaminergic neurons and the expression of GDNF is well known. Besides this protection against protein oxidation from oxidative stress-related proteins, defense against infections as well as a significant role during DNA repair are some of the many functions of vitamin D.[8]

Thus, many nutrient-related studies have shown overlapping aetiology with aspects altering the pathophysiology of neurodegenerative diseases like MDD or Parkinson's and Alzheimer's. To improve prognosis of MDD or prevent its onset and the related neurological impairments or diet-related epigenetic alteration require a thorough understanding of nutritional neuroscience and nutritional psychology for an integrative study of MDD.

Ortega *et al*. in their recent article[9] regarding the epigenetic consequences of malnutrition, proposed diet as the potential aid in the clinical management of MDD, recommending two very simple ways of nutritional intervention:

(1) Limiting the consumption of unhealthy products and nutrients.

(2) Addressing nutritional deficiencies.

Our epigenome is shaped by nutritional states and dietary components have the power to influence pathways that change DNA methylation patterns. Thus, we can conclude that there are biochemical routes between diet quality and mental health. It is hence, advisable for people who restrict their diet to ensure nutrient-rich bioactive foods as part of their diet plan rich in vitamins, minerals, polyphenols, ω-3 Poly Unsaturated Fatty Acids and a long list of herbal compounds with unprecedented health benefits, to prevent non-communicable multifactorial diseases and mental disorders.

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