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Review

Nutrition in autism spectrum disorders: A review of evidences for an emerging central role in aetiology, expression, and management

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Abstract: Autism spectrum disorders (ASDs) are a group of neurodevelopmental disorders whose aetiology remains largely unknown, but for which environmental factors appear to be important. Emerging evidences suggest that nutrition may play a major role in the aetiology of ASD; also, specific maternal nutritional-deficiencies appear to be associated with an increased risk in offsprings. In addition, studies are beginning to reveal the beneficial effects of dietary supplementation or restriction in the management of ASD; while at the same time debunking the myths that surround certain purportedly-therapeutic dietary manipulations. In this narrative review (using information from internet databases such as Google scholar, PubMed, Scopus and authoritative texts), we examine the emerging central role of nutrition in relation to aetiology, symptomatology, management, and indices of outcome in ASD; by highlighting available scientific evidences pertaining to the impacts of different dietary manipulations and nutritional supplementation. We also consider the likely future roles of nutrition in ASD, as science continues to grapple with the understanding of a group of neurodevelopmental disorders that are emerging to be largely "nutritional illnesses".

Keywords: autism; nutrition; neurodevelopmental; cognition; nutritional supplements

1. Introduction

The term, autism spectrum disorders (ASD) refers to a group of neurodevelopmental disorders [1] with an apparently puzzling aetiology; whose features generally become obvious within the first three years of life [2] and tend to persist through the lifetime. Clinically, ASD is defined by the presence of core symptoms which include deficits in social interaction/communication and restricted/repetitive patterns of behaviour [3]. Behavioural disturbances and co-morbidities like aggression, anxiety, impulsivity, hyperactivity, tantrums and self-injuries are also frequently observed. Data from the last few decades point to an exponential rise in ASD prevalence worldwide [4–7]; and recent figures (based on a parent survey that was designed to track the prevalence of developmental disorders in children aged 3 to 17 years) say 1 in 45 children in the USA have ASD [8]). Weintraub [6] suggested that broader diagnostic criteria, lower thresholds for clinical diagnosis, or higher parental age could only account for 50% of the observed increase in ASD prevalence, leaving a substantial number of cases unaccounted for. Similarly, using data from Danish children, Hansen and colleagues [9] were of the opinion that although up to 60% of the observed rise in ASD prevalence could be accounted for by factors such as improved and broader diagnostic criteria, a certain degree of real increase in prevalence also exists [9]. The rising prevalence figures has increased interests in examining not only the relationship between genetic and environmental factors [10,11], but also the possible increasing roles of environmental factors in the occurrence of ASD.

At different times, environmental factors like mercury toxicity (Palmer et al., 2006), vaccines [12], certain foods [13], prenatal infections such as viral infection [14], other heavy metals, pesticides, and illicit drugs have been evaluated as possible aetiological factors, or predisposing factors to the development of ASD. However, reports from studies that have implicated factors like vitamin D [10,11,15,16], Zinc [17], maternal nutritional deficiencies, diet-induced nutritional deficiencies [18] and gastrointestinal co-morbidities with the development of nutritional deficiencies in autistic children, point to the possible importance of nutrition in the development of ASD. A number of studies have also associated low concentrations of dietary polyunsaturated fatty acids (PUFA) with the development or severity of ASD [19–24]. Reports (from parents with autistic children) on the benefits of early introduction or continuous use of nutritional supplementation on: quality of life, behavioural outcomes and general wellbeing; and the results of a few studies that have evaluated the beneficial effects of nutritional modification/dietary supplementation [21] as viable therapeutic options in the management of ASD also suggest that nutrition may be key to the unravelling of ASD aetiopathogenesis and management. However, scientific evidence in support of the efficacy of aspects of diet or nutrition-based therapy is still weak, leaving their application in the realm of trial and error.

In recent times, a consensus has been reached regarding the importance of nutrition in brain development; with a large number of studies demonstrating that dietary factors are crucial to the sustenance and maintenance of brain health [25–29]. Studies have also demonstrated the value of essential nutrients (amino acids, fatty acids, vitamins, trace elements and minerals) in proper neural development and functioning of the central nervous system [28–30]. The developing brain, due to the rapid progression of a large number of neurobiological processes such as synapse formation and myelination [17,31] occurring between the 24^{th} and 42^{nd} week of gestation, is particularly vulnerable

to nutritional deficiencies and/or toxicities. Along this line, there have been suggestions that the pathogenesis of ASD begins prenatally [32–34], with scientific evidence implicating maternal nutritional deficiencies occurring before and during pregnancy [35]. Therefore, attention to adequate nutrition during periods that are crucial for normal brain development (pregnancy, infancy and adolescence) may be important aspects to consider in relation to ASD; although, how these factors influence brain development in the long term may also be secondary to epigenetic [36] and/or genetic regulation. In this review, we discuss the roles of nutrition in influencing the aetiology, disease expression and management of ASD; with emphasis on diet and/or nutrition-based therapeutic regimens, mineral/vitamin supplements, and current evidences relating to their efficacy and safety.

1.1. Nutrition, nutritional deficiencies and brain development

From time immemorial, food has been considered to only serve the needs for rejuvenation and meeting the body's energy demands. However, in the last few decades, the importance of food and adequate nutrition in ensuring normal central nervous system development [17,28–30,37–39]; and the influence of diets that are rich in specific nutrients (like the omega-3 fatty acids) on the maintenance of mental function [24,40,41], is changing our perception regarding the relationships that exist between nutrition and the brain. Adequate nutrition and nutrients have been shown to be essential in the upregulation of molecular mechanisms that maintain synaptic function and plasticity in rodents [42]. Nutrients also serve as building blocks that aid cell proliferation, deoxyribonucleic acid (DNA) synthesis and metabolism of hormones/neurotransmitters in the brain [43–45]. On the other hand, diets may also have deleterious effects on brain development and cognitive processing. For example, diets that are high in saturated fat have been associated with impairment of cognitive processing and an increased risk of neurological deficits in humans [46] and animals [47].

Brain development is complex and usually begins in utero during the early prenatal phase, with proliferation of neurons and the different types of neuroglia (e.g radial glia) which continues postnatally until almost 3 years of age [48]. The neural plate begins to fold inward to form the neural tube (from about the 22nd day after conception) and this tube eventually develops into the brain and spinal cord [49]. Compared to the rest of the body, brain development is rapid in the early years of life [50], making it more vulnerable to dietary deficiencies.

Studies have shown that nutritional deficiencies of folic acid, copper and vitamin A, occurring during this early period of brain and spinal cord development can lead to neural plate or tube defects. The process of central nervous system development involves cell division within the neural tube, which results in the formation of neurons and glial cells, followed by extensive neuronal migration, synapse formation (which is critical to normal functioning and development) and myelination. As groups of neurons form pathways linking one to another, the process of programmed cell death refine these connections by eliminating of nerve cells, synapses and connections that are not activated; while strengthening those that are, and this continues throughout childhood and adolescence [29]. This process which is known as neural plasticity is considered a primary mechanism that allows the brain to organise and adapt, either in health or disease.

Generally, all nutrients are important for normal neuronal growth and development, although during the late foetal and neonatal time periods, nutrients like zinc, iron, folate, selenium, iodine, choline, vitamin A and long-chain polyunsaturated fatty acids are essential to ensure normal brain

development and functioning. Studies involving animals have demonstrated that poor nutrition during critical periods of brain development is associated with alterations in neurotransmitter systems, and reduction in: myelin production, number of brain cells and synapses [30]. The hippocampus and cerebellum are particularly vulnerable to the effects of early postnatal under-nutrition [51]. Foetal under-nutrition has also been associated with deficits in behaviours and cognition functioning which may persist even after nutritional rehabilitation [51,52]. In humans, research has also demonstrated that foetal under-nutrition and/or malnutrition have long-lasting implication for brain development and normal brain functioning [53,54]; with prenatal under-nutrition/malnutrition being linked to cognitive impairments and learning disabilities. Also, evidence from population studies has associated healthy dietary patterns with improved brain function [55–57] and reduced risk of cognitive impairment [27,58–60]. The effects of nutritional deficiencies on the brain have also been shown to be time and duration of exposure dependent [53]. Equally important is the appropriate timing of nutrient availability and concentration, because a nutrient that promotes normal brain development at a time may be toxic at another point in development. Also, minute alterations in nutrient concentration may be toxic to the brain because several nutrients are regulated within a relatively-narrow range. The effects and extent of nutrient deficiencies on the brain also vary from one region to the other, largely depending on which area of the brain is developing rapidly, or requires specific nutrients for essential metabolic pathways. Generally, the use of nutritional supplementations has been shown to have beneficial effects in brain development and cognitive functioning; and there have been reports of improved cognition in students following micronutrient supplementation [61], especially in educationally-underperforming children, or those living in low socio-economic areas [62]. A reduction in violent behaviours was also reported in juveniles with impaired mental health following micro-nutrient supplementation [63] and omega-3 polyunsaturated fatty acid (n-3 PUFA) supplementation [64].

While the impact of adequate nutrition or nutritional deficiencies on brain development in ASD continues to be studied; rodent studies have demonstrated causal links between maternal dietary deficiencies and neurodevelopmental disorders, including ASD [65]. Polyunsaturated fatty acids (PUFAs) are essential fatty acids which are required for brain development and maturation [66]. In rodents, developmental n-3 PUFA depletion has been associated with behavioural and neurochemical changes similar to those observed in autistic children; such a decreased levels of serotonin in the prefrontal cortex [67,68] and profound alterations in GABAergic, dopaminergic and cholinergic neurotransmission [69–72]. Again, long-term dietary deficiency of n-3 PUFA triggers the development of behavioral impairments such as reduced pre-pulse inhibition [73], social interactions [74–76] and increased anxiety [75] in rodents. N-3 PUFA-enriched diet has also been demonstrated to alleviate ASD-like symptoms in a rodent maternal immune activation model, probably via n-3 PUFA's ability to regulate neuroinflammation, microglia activity and synaptic plasticity in the developing brain [77,78].

1.2. Nutritional excesses, nutritional deficiencies and neurodevelopmental disorders

Nutritional excesses and deficiencies may cause neurodevelopmental disorders such as neural tube defects (spina bifida and anencephaly), schizophrenia, mental retardation and cretinism that result in physical disability and emotional sequelae. Maternal folate deficiency has been linked with neural tube defects, while iodine deficiency has been associated with a spectrum of

neurodevelopmental disorders that include severe mental retardation and cretinism. Excessive or inappropriate use of nutrients has also been associated with neurodevelopmental delays or disorders, for instance, iron supplementation in baby milk formula has been linked to lowered intelligence quotient and neurodevelopmental delays [79]. Effects of nutrition on the pathogenesis of neurodevelopmental disorders were demonstrated by data generated from the Dutch famine study. This originated from a "natural experiment" based on an extraordinary historical event known as the Dutch Hunger Winter (1944–1945), which involved six of Netherlands' largest cities (Amsterdam, Rotterdam, Hague, Utrecht, Leiden and Haarlem). Data assessing the effects of prenatal famine on neurodevelopment revealed an increase in congenital birth defects like neural tube defects, hydrocephalus and cerebral palsy [80], initially. A later re-evaluation revealed an increased incidence of schizophrenia and schizoid personality; thus, affirming the importance of prenatal nutrition in the development of schizophrenia in birth cohorts exposed to famine [81–83]. Studies involving children from poor socioeconomic backgrounds or from low income economies have also strengthened the association between nutrition and neurodevelopmental and neurocognitive disorders [54]. For decades, orthodox or conventional medical practice had mostly dismissed any relationship between nutritional factors such as vitamins, minerals and plant-derived nutrients and the symptoms of some neurodevelopmental disorders like attention deficit hyperactivity disorder (ADHD); with parents being discouraged from administering nutritional supplements to their children. However, recent studies have been able to demonstrate beneficial effects of the use of nutritional supplements in these children [84]. Also maternal nutritional deficiency of folic acid [85] and vitamin D [86] among others has been linked to the development of ASD.

2. Nutrition and the development of ASD

A number of parents or professionals working with children having one of the autism spectrum disorders have noted an association between the child's diet and severity or frequency of symptomatology; with different mechanism proffered in the explanation of this association [87]. There have also been suggestions that food additives or food substances may play important roles in the aetiology of ASDs; and recently, animal studies have demonstrated that propionic acid (PA), a dietary short chain fatty acid and common food additive induces neuroinflammatory responses and a number of behavioural changes in rats that are similar to that observed in ASD [88–90]. The alteration in behaviour, as well as neuropathological and biochemical effects of intraventircular administration of PA [88,89] also increased support for the hypothesis that autism may be a systemic metabolic encephalopathy [90].

2.1. Nutrition, neural plasticity and neurotransmitters in ASD

Earlier studies had demonstrated that impairments in synapse formation/synaptic plasticity, culminating in functional and cognitive impairments are core causative factors that underlie ASD pathology [90,91]. Genetic studies have also proven that several identified risk genes for ASD are involved in the regulation of synaptic plasticity; and changes in the protein products of these genes can alter brain neuronal connectivity by affecting the strength or number of synapses in the brain [93]. Brain alterations such as aberrant cortical plasticity and metaplasticity had been

implicated in the pathophysiology of ASD, and are also demonstrable in both animal models of ASD and in humans with ASD [94].

The role of nutrition in modulating neural plasticity has been reported; and two nutrient (iron and choline) deficiencies and their effects on brain synaptic plasticity have been studied extensively. Hypotheses suggesting that foetal/neonatal nutritional deficiencies could compromise the integrity of the dendritic arbors or result in epigenetic chromatin modifications that may decrease the expression of (or permanently cause a dysregulation of synaptic plasticity) genes that regulate protein polymerisation have been suggested as possible mechanisms [95]. Studies have shown that nutritional components such as N-3 polyunsaturated fatty acids play important roles in the pathogenesis of ASD through their ability to regulate synaptic plasticity; hence, its deficiency during critical periods of brain development is strongly linked to the development of ASD [96–98].

Abnormalities in the functioning of several neurotransmitters [γ-aminobutyric acid (GABA), glutamate (Glu), serotonin (5-HT) and dopamine (DA)], their receptors, and transporters had been implicated in ASD [99]. Harada et al. [100] demonstrated low levels of GABA in the left frontal lobe of autistic subjects, when compared with controls; while evidence from post-mortem examination of the cerebellum had demonstrated decreased $GABA_A$ and $GABA_B$ receptor expression in autism [101]. There have been reports associating anomalies on chromosome 15 (15q11–15q13) with a dysregulation of $GABA_A$ receptor subunit genes (GABRB3, GABRA5, and GABRG3) and the development of ASD [102]. Other genes such as GABRB1 and GABRA4 which encode $GABA_A$ receptors have been associated with the development of ASD [103]. Alterations in glutamate levels have also been reported in ASD; also, chromosomal anomalies involving chromosomes 6 and 7 [104,105] and GRIK2, GRIN3B and GRIA3 which encode glutamate (Glu) receptors have been implicated in ASD [103]. Again, decreased levels of glutamic acid decarboxylase in cerebellar Purkinje cells [106], but increased plasma or serum Glu levels have been reported in subjects with ASD [107,108].

Studies have related multiple alleles at the serotonin (5-HT) transporter locus and genes (encoding 5-HT transporter and the enzyme acetylserotonin O-methyltransferase) to an increased risk of developing ASD [109]. Hyperserotonaemia is also common among subjects with ASD, occurring in about 25% of the subjects [110]. In some ASD family studies, multiple rare serotonin transporter (SERT) amino acid variants have been associated with an increase in serotonin uptake in cell models; and a knock-in mouse model of a variant of serotonin transporter (SERT Gly56Ala) exhibits hyperserotonaemia, increased brain serotonin clearance, increased serotonin receptor sensitivity, and altered social communication with repetitive behaviours [111].

There is ample evidence that dopaminergic system abnormalities are related to deficits observed in subjects with ASD [112]; and more recently, there have been suggestions of a possible dopamine hypothesis linking alterations in the midbrain dopamine system with behavioural symptomatology in ASD [113]. Positron emission tomography (PET) studies have shown increased dopamine transporter (DAT) levels in the orbitofrontal cortex in subjects with high functioning autism [114]. Subjects with ASD also have high levels of homovanillic acid (a dopamine metabolite) in their urine, which might be related to an increased DA turnover; also, genes encoding DA receptors and the enzyme dopamine beta-hydroxylase have been implicated in ASD [115].

Nutrition has been considered an important factor in the maintenance of not only brain function but also brain biochemistry. Studies have demonstrated that alterations in vitamin and mineral nutrient intakes may impact brain biochemistry, through their roles as coenzymes. Also, the synthesis of a number of these neurotransmitters (including serotonin and dopamine) are regulated by dietary

fluctuations in the availability of their nutrient precursors [116,117]. In ASD, there have been reports linking alterations in brain levels of dopamine, serotonin, acetylcholine and γ-aminobutyric acid with derangement in vitamins, minerals and trace elements; although, the exact relationship among these factors and their interaction with genes and proteins that are important in brain development and growth are still been studied. Increasingly there are suggestions that daily nutrient supplements including essential vitamins, minerals, specific amino acids and omega-3 fatty acids may be effective in ASD management, due to their ability to modulate neurotransmitter levels.

2.2. Maternal nutrition and the development of ASD

Maternal nutritional deficiency is believed to play a role in the development of ASD in offsprings. Nutrients, whose deficiencies have been linked to increased risk of ASD include folic acid [85] and vitamin D [86]. More recently, low iron intake in pregnancy was associated with a 5-fold greater risk of autism in the offspring of mothers aged 35 or more, or those with conditions such as obesity, hypertension or diabetes [118]. Effect of maternal vitamin D deficiency on the occurrence of ASD has gained considerable attention. Experimental induction of vitamin D deficiency in pregnant rat dams has been reported to affect foetal neurodevelopment, and behaviour in adult offsprings [119]. Also, in humans, prenatal vitamin D deficiency is known to be associated with a range of brain-related outcomes in offsprings, including impairment of language development [120,121] and cognitive functioning [122,123]. Children born to dark-complexioned women who reside in high-latitude countries (such as Sweden) are at a particularly high risk of ASD with intellectual disability [124], and this has been linked to very low maternal vitamin D levels due to melanin absorption of ultraviolet B radiation [125].

In a large Dutch birth cohort where mid-gestation (maternal sera) and neonatal (sera from cord blood) samples were examined for vitamin D levels, its deficiency was associated with a significantly higher (more impaired) Social Responsiveness Scale (SRS) scores [126]. While evidences continue to emerge that early-life vitamin D deficiency is a possible risk factor for ASD; the exact mechanisms that may underlie this are not known, leaving the relationship open to continuous investigation.

2.3. Nutritional status of children with ASD

Intake of macro and micronutrients in children with ASD has been a matter of scientific investigations; with authors reporting lower, higher, or normal levels of intake (compared to the recommended amounts) which may be a reflection of the highly- heterogeneous nature of the disorders [127]. However, evidences still weigh in favour of deficiencies of several micronutrients, and macronutrient imbalance may contribute to the higher rates of obesity in these children [128]. Over the years, it had been shown that children with ASD tend to harbour nutritional deficiencies that may be less seen in the normal population. Studies conducted in children with ASD (examining different body tissues such as blood and hair) had reported lower levels of selenium, zinc [129], magnesium [130], vitamins A and E [129], vitamin B complex [129,131], vitamin D [132,133] and carnitine [134]. Other deficiencies that had been reported include those of potassium and choline. More studies are showing that children with ASD tend to consume significantly fewer macronutrients compared with children without ASD; a reflection of a general challenge regarding

their nutrition [127]. In a study that was conducted comparing 22 children with ASD with age-matched normally-developing control group, selective-eating and nutritional deficiencies were found to be more common in the autistic children; and the children with ASD were found to consume significantly fewer foods on the average, compared to normally-developing children. They were also found to have taken lower amounts of protein, calcium, vitamin B_{12} and vitamin D [135]. Hence, in children with ASD, selective-eating and a significantly-higher risk for the development of nutrient deficiencies tend to go hand-in-hand. Food-selectivity in children with ASD has been found to typically involve strong preferences for starchy, processed and snack foods, along with a bias against fruits and vegetables; also, this food-selectivity is usually a chronic condition that persists into adolescence and adulthood [136]. Food-selectivity is a behaviour that is likely to worsen micronutrient deficiencies and increase the risk of associated metabolic disorders, over time. Tackling micronutrient deficiency in ASD is a difficult task, and as shown by a cross-sectional study; deficits in vitamin D, calcium, potassium, pantothenic and choline may persist in a significant percentage of patients, despite intake of nutritional supplements [137]. Micronutrient deficiency may also correlate with the severity of behavioural symptoms in children with ASD. In a study conducted in Chongqing, China, in which serum ferritin, folate, vitamin B_{12}, 25(OH) vitamin D, and vitamin A concentrations in children with ASD were determined and correlated with behavioural assessment of severity of ASD using the Childhood Autism Rating Scale (CARS); after adjusting for sex, vitamin A concentration (in particular) was found to be negatively correlated with the CARS score [127]. Therefore, the finding supports the notion that a low serum vitamin A level may be a risk factor for exhibiting the symptoms of ASD; however, a direct explanation of the underlying mechanism is not yet available.

Presently, with regards to nutritional deficiencies and ASD, the following are obvious: a) maternal malnutrition (in relation to certain nutrients) is a risk factor for development of ASD in the offsprings; b) deficiencies of certain nutrients are associated with expression or increasing severity of ASD symptoms; c) some eating habits that are found in ASD patients may likely lead to or worsen bodily deficiency of certain nutrients. Therefore, while it is still difficult to establish that certain early-life nutritional deficiencies will definitely cause ASD; available evidences are in favour of strong associations between nutritional deficiencies and ASD, and these associations are in the area of causation, severity of symptoms, and as co-morbidity.

3. Therapy of ASD

ASDs are a heterogeneous group of disorders; therefore, individualised management that addresses the peculiar needs of each patient is generally encouraged. Behavioural, educational and psychological therapies; combined with pharmacological, and recently nutritional therapies are all very important in the management of ASD. However, management of ASD suffers the constraint of a limited understanding of its aetiology; therefore, interventions generally focus on the symptoms and co-morbid conditions. Pharmacological interventions are usually targeted against behaviours such as hyperactivity, irritability, psychosis, depression, aggression and repetitive behaviour [138]. It involves the application of drugs such as fluoxetine for anxiety or depression, typical and atypical antipsychotics (risperidone and aripiprazole) for aggression and irritability, methylphenidate for inattention and hyperactivity, and selective serotonin reuptake inhibitors (sertraline, fluoxetine, fluvoxamine and citalopram) for anxiety [138]. Application of drugs for the management of ASD also benefits from the knowledge of neurotransmitter abnormalities that are seen in ASD. While

studies are still being conducted to determine the efficacy of GABAergic agents (such as valproate, acamprosate and arbaclofen) in the clinical management of ASD, and while some drugs may have shown promise in studies, the quantity of available evidence is still insufficient to suggest their use clinically [139]. Also, depending on the age of the patient, selective serotonin reuptake inhibitors (SSRIs) may be efficacious in reducing some of the core symptoms of ASD [140,141]. However, while some studies have associated the use of SSRIs in pregnant women with an increased risk of ASD in their offspring [142], the serotonergic system still appears to be a candidate for the development of drug treatment for at least a sub-set of ASD patients [111]. DA antagonists that are prescribed to subjects with ASD include drugs such as haloperidol and risperidone. Treatment with the atypical antipsychotic risperidone has been associated with improvements in stereotypic behaviour, irritability, aggression, self-injury and hyperactivity [112,143,144]. Other drugs include SSRIs which target both 5-HT and DA receptors leading to some clinical benefits [145]. Also, oxytocin treatment has shown promising results (regarding the social domain) in a number of autism clinical trials [146,147]. Generally, limitations such as risk of side-effects and an inability to arrest progression of the disorders are the shortcomings of drug therapy. These limitations are pointers to a pressing need to find other viable approaches to ASD management. Along this line, recent research is beginning to support the crucial roles of nutrition, nutritional supplements and bodily disposition of nutrients in the expression of symptoms and management of ASD.

3.1. Role of nutrition in the management of ASD

The human gastrointestinal tract is tasked with the digestion of food and absorption of nutrients; therefore, an impairment of its function might cause nutritional deficiencies. Gastrointestinal dysfunctions (causing diarrhoea, constipation, abdominal pain and abdominal distension) and immunological dysfunctions (presenting as food allergies and metabolic abnormalities) are common in children with ASD; with studies reporting that 30–80% of children with ASD have gastrointestinal dysfunction [148,149]. This suggests that to further our understanding of ASD, the roles of the gastrointestinal system, and the impacts of its abnormal functioning on nutritional status and symptomatology in ASD can no longer be ignored. Therefore, in recent times, a lot of attention is being focused on nutrition, and the roles that nutrition may play in the expression and management of the symptoms of ASD [150]. However, despite this attention, there is still a lot to learn regarding the details of the nutritional requirements of the autistic child. What is obvious for now is that management of symptoms of ASD through nutritional adjustments is already gaining ground, with studies as far back as 2006 reporting that a large number of families with autistic children were using nutrition as a form of complementary and alternative medicine [150].

Nutritional management of ASD symptoms is based on two approaches: a) an additive approach that attempts to supplement macro or micronutrients that are generally known to be insufficient in children with ASD. Supplements in use include vitamin B_6, vitamin C, vitamin D, vitamin B_{12}, dietary fatty acids (omega-3 fatty acid and cod liver oil), melatonin, folic acid, probiotics, L-carnitine, iron, magnesium, zinc and copper [150,151]; b) a subtraction approach that focuses on subtracting or eliminating certain foods or food items from the diet. These are the foods that are believed to trigger allergies and food intolerance (for example, casein and glutein); and contribute to the symptoms of ASD [152]. Dietary approach to the management of ASD is becoming increasingly-popular; however, scientific evidence of its effectiveness is only partially-available, with studies still ongoing.

Presently, most studies that had supported the notion of significant benefits from nutritional interventions lack the statistical power for evidence-based treatment recommendations for managing symptoms of ASD. Also, differences in study designs add up as confounders.

3.1.1. Nutritional therapy: Additive approach

a) Vitamin A

Cod liver oil supplementation had been suggested by some to improve symptoms of ASD, through its rich content of vitamin A which is beneficial for cell growth and maintenance of epithelial integrity; as improved gut epithelial integrity leads to better digestion and assimilation of nutrients [153,154]. Despite claims of benefit emanating from a number of sources, there appears to be a scarcity of published scientific studies examining the use of vitamin A; also, the use of cod liver oil could be potentially dangerous due to a risk of heavy metal poisoning, and potential vitamin A overdose if given with other multivitamins. Therefore, it had been suggested that liquid fish oil may be safer in children with ASD [148,149].

b) Vitamin B and magnesium

In its active form of pyridoxal-5-phosphate (P5P), vitamin B6 is an important co-factor for metabolic processes that involve several important neurotransmitters, such as dopamine, gamma amino-butyric acid (GABA), serotonin, epinephrine and norepinephrine [155]. Magnesium, a mineral that is necessary for several enzyme-catalysed metabolic pathways may have an additive effect on vitamin B_6. Low levels of the B-complex vitamins are seen in many ASD sufferers [131]; and magnesium deficiency is also observed. Earlier reviews of some ASD studies conducted using vitamin B_6 supplement (in combination with magnesium), concluded that the combination yielded positive results, with no significant adverse effects [153,154]. In a study involving 30 children with ASD, supplementation of vitamin B_2, vitamin B_6 and magnesium for 3 months, decreased the level of dicarboxylic acid (a marker of energy metabolism) in the urine [156]. Other studies have also suggested that pyridoxine/magnesium combination is associated with improvements in behavioural parameters in ASD [157]. However, the present weight of evidence does not confirm efficacy and side-effects may develop at high doses, and with prolonged administration [148–150]. Therefore, optimism regarding such a combination needs to be managed, as studies continue.

c) Vitamin C

Vitamin C has antioxidant and anti-inflammatory effects; and it is a cofactor for a number of enzymes that are important in neurotransmitter synthesis. It is also involved in the regulation of brain excitatory signalling. While oxidative stress is common in ASD, the benefits of vitamin C supplement are still not well-defined; however, at least one small study involving 18 children claimed a reduction in severity of behavioural symptoms [151,158]. In another study, vitamin C also appears beneficial in decreasing the level of oxidative stress in children with ASD [159]. However, since variable tolerance of vitamin C is seen in ASD; caution is advised regarding its use [151].

d) Vitamin D

The association between ASD and vitamin D deficits is strengthened by the observation that ASD occurs with more frequency in areas of impaired ultraviolet B penetration (such as pole-ward latitudes, urban areas, areas with high air pollution, and areas of high precipitation). In these areas, ASD is also more common in offsprings of dark-skinned persons; and severe maternal vitamin D deficiency is commoner in the dark-skinned [116]. A growing body of literature had linked vitamin

D deficiency to various immune-related conditions such as allergy and autoimmunity; and in a subgroup of patients, autoimmunity might have a role in the pathogenesis of ASD. In some autistic children, there is presence of brain-specific auto-antibodies; and there is also an increase in the frequency of autoimmune disorders among autistic families [155]. Vitamin D deficiency had been demonstrated in some autistic children and this deficiency may contribute to the induction of the production of serum anti-myelin associated glycoprotein (MAG) auto-antibodies in these children [10]; also, vitamin D supplementation may be beneficial in ASD. In a case report involving a 32-month-old boy with ASD and vitamin D_3 deficiency; a significant improvement in the core symptoms were observed after vitamin D_3 supplementation [161]. Also, in a randomised placebo-controlled study involving 109 children with ASD; four months of vitamin D_3 supplementation was associated with a significant improvement in symptoms such as hyperactivity and social withdrawal [162]. The advocacy for the inclusion of vitamin D supplementation in the management of ASD has also been strengthened by recent demonstrations that genotype AA/A-allele of GC rs4588 (which encodes the vitamin D binding protein) is associated with ASD [163].

e) Fatty acids

Omega-3 fatty acids are known to be important for normal brain development. As a supplement, it is also commonly used in ASD, with small studies supporting its benefits. In a randomised, double blind study (which was completed in 27 children) using omega-3 supplementation and placebo; small, but non-significant improvement in symptoms such as irritability, stereotypy and lethargy were seen in the omega-3 treated group [153,154]. However, a summary of reports on the effects of omega-3 fatty acids had shown conflicting results. A placebo-controlled trial in 13 autistic children who were treated with 1.5 g of omega-3 fatty acids or placebo for 6 weeks did not demonstrate significant improvement in hyperactivity and stereotypy scores; while three uncontrolled studies, and a case report suggested some improvements in the core features of ASD, but another uncontrolled study could not confirm their findings [164]. No large studies had supported the efficacy of omega-3 supplementation, and there are safety concerns, especially when used in large doses [148,149].

f) Melatonin

Sleep disorders are commonly associated with ASD, with many children having difficulties in falling asleep or maintaining sleep; and studies have shown that sleep disorders occur in an estimated 50% to 80% of children with ASD [165]. According to several studies, melatonin levels have been found to be low in individuals with autism; and an analysis of 18 studies of people with autism found that melatonin supplementation (in doses ranging from 0.75 mg to 25 mg daily) significantly shortened latency to fall asleep and increased sleep duration, also, there was improvement in daytime behaviour in some of the patients [166]. In another study, a daily dose of 1 mg or 3 mg of melatonin improved sleep latency in children with ASD [165]. Further studies are likely to reveal if melatonin supplements will be beneficial in other aspects of ASD management.

g) Probiotics

Gastrointestinal symptoms like diarrhoea and constipation are common in children with ASD, and probiotics may be helpful in alleviating some of these symptoms. Probiotics are also believed to improve intestinal permeability, enhance the attainment of a balanced intestinal microflora, and alter mucosal immune response [148,149,167]. Behavioural symptoms such as increased irritability, tantrums, aggressive behaviour and sleep disturbances have been associated with abnormal gut microbiota and gastrointestinal dysfunctions in children with ASD. Abnormal activation of the mucosal immune response and the presence of abnormal gut microbiota are also

commonly observed [167]. Therefore, studies examining the use of probiotics have been proposed. A preliminary animal study discovered that a specific bacterial strain, *Bacteroides fragilis*, improved gut permeability and autism-like behaviours in mice [168]. In humans, a recent prospective open label study that assessed the efficacy of probiotics in children with ASD {by examining the gastrointestinal flora of 30 autistic children (aged 5 to 9 years old) following a 3 months period of probiotics nutritional supplementation} reported that, compared to the baseline, colony counts of Bifidobacteria and Lactobacilli increased significantly; this was also associated with a decrease in body weight and an improvement in autistic behaviours [169].

h) Others

Twice daily administration of ubiquinol (the active form of CoQ10) for three months was found to improve communication, sleep, and decrease food rejection in a small study of children with autism; via a mechanism that probably involves reduced oxidative stress [170]. However, it may not be well-tolerated by some children, especially at the beginning of therapy, and a transient worsening of some behavioural parameters like aggression was seen in some children [170]. Also, it must be noted that the results were based on parental reports; therefore, further studies will be of benefit.

According to the results of a randomised controlled trial, L-carnitine liquid supplement (administered at 50 mg/kilogram-bodyweight/day, for 3-months) was found to significantly improve clinical measures of ASD in children, probably through a reduction of mitochondrial dysfunction [170]; while in another trial, oral N-acetylcysteine (NAC) has been found to reduce irritability in children with ASD [172]. Administration of L-carnosine for 8 weeks in children with autism has also been found to significantly-improve scores on the Gilliam Autism Rating Scale in a small clinical study [173]. Iron and folic acid supplements have also been considered in ASD management.

3.1.2. Nutritional therapy: Subtractive approach

a) The Glutein Free Casein Free diet (GFCF diet)

GFCF diet is perhaps the most tried and tested diet for children with ASD. This diet aims to eliminate the usage of casein (dairy products) and glutein (wheat) in the diet. GFCF diet is believed to lead to clinical improvement by ameliorating both core and associated behavioural symptoms, and improving developmental outcome in at least some cases of ASD. A number of children with ASD are believed to suffer from “leaky gut”, abnormalities in intestinal permeability that allows large peptides to be absorbed directly into the bloodstream and reach the brain, leading to behavioural symptoms [174]. The application of GFCF diet is based on the “opioid-excess theory” which assumes that some ASD sufferers have insufficient production of enzymes required for the digestion of glutein and casein-related foods, and increased gut-permeability. A large proportion of peptides derived from the glutein and casein are incompletely converted to amino acids. With increased gut permeability, the peptides to enter into the blood stream, and reach the brain by crossing the blood-brain barrier. Their binding to opioid receptors produces symptoms of ASD [175].

The effectiveness of GFCF diet has been supported by the results of a number of small studies. In a study involving 50 children with ASD (28 males, 22 females), Cade et al. [176] found that 87% had immunoglobulin (Ig)-G antibodies to glutein, compared to 1% in age and gender-matched controls; and 90% had Ig-G antibodies to casein compared to 7% in the controls. In a follow-up involving 70 autistic children who were maintained on a GFCF diet for 1–8 years; it was found that 81% showed significant improvement in symptoms such as social isolation, eye contact, mutism,

learning skills, hyperactivity, stereotypic activity and panic attacks by the third month, with improvements continuing over the next 12 months [176]. In a two-stage, 24-month, randomised, controlled trial involving 72 Danish children (aged 4 years to 10 years 11 months) who were randomised into GFCF diet or non- GFCF diet groups at beginning of study; it was deduced that GFCF diet leads to general improvements in core ASD behaviours in at least a subset of the subjects, and may positively affect developmental outcome for some children diagnosed with ASD [177]. While the efficacy of GFCF diet appears supported by results of small studies, a number of small clinical trials had yielded conflicting results [147,148]; and for now, studies are still ongoing. However, it should not be surprising that the GFCF diet may not be a magic bullet after-all as even small studies had shown that a number of children do not show significant improvements while on the diet; and when we consider the heterogeneity of ASD, it is obvious that it may take a little while before we can conclude with certainty what the GFCF diet can or cannot do.

b) Ketogenic diet

This diet regimen that was developed about eight decades ago for patients with seizures, is based on the notion that autistic behaviours result from abnormalities in cellular carbohydrate metabolism, and that ketogenic diet may offset this mitochondrial dysfunction [150,178]. The ketogenic diet is high in fat, low in carbohydrate and contains carefully-regulated protein levels. An open label study conducted using 30 autistic children, over a 6 month period reported that 60% had various improvements in measures such as social interaction, stereotypy, hyperactivity, cooperation, and learning [179]. A few studies have also compared the effectiveness of ketogenic diet (as modified Atkins diet) in autism with the effects observed with gluten free casein free diets, and concluded that while both diet groups showed improvement in the Childhood Autism Rating Scale (CARS) and Autism Treatment Evaluation Test (ATEC) scores, compared to children fed normal diet; the children in the ketogenic diet group had better cognition and sociability scores compared to those in the gluten free casein free diet group [180].

c) Monosaccharides as dietary carbohydrates

A diet based on monosaccharides, which is easier to digest and bye-passes some of the problems arising from deficiencies in enzymes needed for carbohydrate metabolism had been proposed; however, there is limited data on safety and efficacy [148,149]. Some have also proposed a general reduction in carbohydrates as an alternative to this approach [181].

4. Conclusion

Our knowledge of the roles of nutrition in ASD pathogenesis and management has increased over the past few years; and presently, the possibility of a formal adoption of nutritional manipulation/regimens, and its incorporation into orthodox medical practice as a core management option for ASD may be worth some consideration. A nutrition-based therapy will allow a greater participation of patients and their families in the care of ASD; and it might also significantly reduce the cost of care. However, the heterogeneity of disease aetiology and symptoms presents a unique challenge to nutrition-based therapy and packages must be adapted to suit individual needs of patients; also, the wide variety of potential nutritional intervention makes the idea of the development of a “standardised package” a challenging prospect. For researchers in this field, it is imperative to continue to strive to acquire definitive scientific evidences regarding the exact roles of

different nutrients in the prevention, pathogenesis and expression of ASD; and in support of the benefits (if any) of their supplementation in management.

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Conflict of interest

Both authors of this paper declare that there is no conflict of interest related to the content of this manuscript.

Ethical statement

This article does not contain any studies with human participants or animals performed by either of the authors.

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