Specialty and Importance of Micronutrients in Lifespan development

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Elements are present in different forms in the nature, and these elements are very essential for the body to perform different functions. Trace elements are very important for cell functions at biological, chemical and molecular levels. These elements mediate vital biochemical reactions by acting as cofactors for many enzymes, as well as act as centers for stabilizing structures of enzymes and proteins. Some of the trace elements control important biological processes by binding to molecules on the receptor site of cell membrane or by alternating the structure of membrane to prevent entry of specific molecules into the cell. The functions of trace elements have a dual role. In normal levels, they are important for stabilization of the cellular structures, but in deficiency states may stimulate alternate pathways and cause diseases. These trace elements have clinical significance and these can be estimated using different analytical method.

Introduction

Macronutrients (fat, protein, carbohydrates) deliver energy and important material to ensure the entire body composition. Micronutrients are needed to keep this process of continuous construction and re-construction running. Consequently, the requirement for micronutrients will differ depending on the individual need which is related to the different metabolic conditions within the life cycle. Within the first 1000 days of life, from conception to the end of the second year of life the requirement for micronutrients is high and if the supply is inadequate that might have consequences for physical and at least cognitive development. In particular, iron, iodine, are micronutrients which might become critical during that period. Due to the fact that clinical symptoms of deficiencies develop late, but inadequate supply of one or more micronutrients may have consequences for health the term hidden hunger has been introduced to describe that situation. In particular the time period of pregnancy and early childhood is critical and hidden hunger is a worldwide problem, affecting>2 billion people, primarily females and children. The importance of different requirements during the life cycle is usually not considered. In addition, we do not really know what the individual requirement is. The estimation of the requirement is based on studies calculating the supply of a micronutrient to avoid a deficiency disease within a healthy population and is not based on sound scientific methodology or data. We need to consider

that at different moments in the life cycle the supply might become critical in particular in case of a disease or sudden increase of metabolic turnover (Biesalski et al., 2018).

Elements such as iron, zinc, and selenium are essential components of enzymes where they attract or subtract molecules and facilitate their conversion to specific end products. Few elements donate or accept electrons in redox reactions, which results in generation and utilization of metabolic energy and have an impact on the structural stability and to import certain biological molecules. Iron is involved in the binding, transporting, and release of oxygen in higher animals. Some of the trace elements control important biological processes by facilitating the binding of molecules to their receptor sites on cell membrane, by alternating the structures or ionic nature of membrane to prevent or allow specific molecules to enter or leave a cell and in inducing gene expression resulting in the formation of protein involved in life processes.

Essential elements for human body

• Four organic basic elements: H, C, N, O

• Quantity elements — Na, Mg, K, Ca, P, S, Cl.

• Essential trace elements — Mn, Fe, Co, Ni, Cu, Zn, Mo, Se, I.

• Function suggested from active handling in humans, but no specific identified biochemical functions — Li, V, Cr, B, F, Si, As.

Biological Classification of Trace Elements

Various classifications have been proposed by so many authors on elements — both major as well as the trace elements, considered as essential for the normal development and growth. Classification proposed by Frieden (1981) which divided the elements into micro, trace, and ultra-trace elements based on the amount found in tissues.

1. Essential trace elements: Boron, cobalt, copper, iodine, iron, manganese, molybdenum, and zinc.
2. Probable essential trace elements: Chromium, fluorine, nickel, selenium, and vanadium.
3. Physically promotive trace elements: Bromine, lithium, silicon, tin, and titanium.

Categorical Classification of Trace Elements

It is observed that there are at least 29 different types of elements including metal and nonmetals in an adult human body. These 29 elements can be broadly classified into five major groups they are as follows:

- **Group I:** These elements are the basic components of macromolecules such as carbohydrates, proteins, and lipids. The elements belonging to these groups are carbon, hydrogen, oxygen, and nitrogen.
- **Group II:** These are nutritionally important minerals. They are also called as principal elements or macro elements. Their daily requirement for an adult human is above 100 mg/day. The deficiency of such elements usually proves fatal unless intervened properly. The elements belonging to this group are sodium, potassium, chloride, calcium, phosphorous, magnesium, sulfur.
- **Group III:** There are the essential trace elements. An element is called as trace elements when their requirement per day is below 100 mg and deficiency leads to disorders and may prove fatal. The elements belonging to this group are copper, iron, zinc, chromium, cobalt, iodine, molybdenum, and selenium. Of these, iodine is a nonmetal, while others are metals.
- **Group IV:** They are additional trace elements. Their role is not clear and they may be essential. The elements belonging to this group are cadmium, nickel, silica, tin, vanadium, and aluminum.
- **Group V:** This group of metals is not essential their presence may produce toxicity. They have no known function in the human body. The elements belonging to this group are gold, mercury, cyanide, and lead.

The trace elements included Group III also called as minor elements. Their requirement is below 100 mg/day and their absence may not hinder normal development, but their activity may be substituted by another metal. Analytical methods are used to measure metal concentration in human tissues and body fluids.

Changing Nutrient Needs through the Life Cycle

Life Stage	Change in Nutrient Needs
Pregnancy	Increased requirements: energy, protein, essential fatty acids, vitamin A, vitamin C, B-vitamins (B1, B2, B3, B5, B6, B12, folate, choline) & calcium, phosphorus, magnesium, potassium, iron, zinc, copper, chromium, selenium, iodine, manganese, molybdenum
Lactation	Increased requirements: vitamins A, C, E, all Bvitamins, sodium, magnesium Decreased requirements: iron
Infancy, childhood	Increased requirements: energy, protein, essential fatty acids
Adolescence	Increased requirements: energy, protein, calcium, phosphorus, magnesium, zinc (females only)

Early adulthood (ages 19-50)	Increased requirements for males, compared with females: vitamins C, K; B1, B2, B3, and choline; magnesium, zinc, chromium, manganese Increased requirements for females, compared with males: iron
Middle age (ages 51-70)	Increased requirements: vitamin B6, vitamin D
Elderly (age70+)	Increased requirements: vitamin D Decreased requirements: energy; iron (females only)

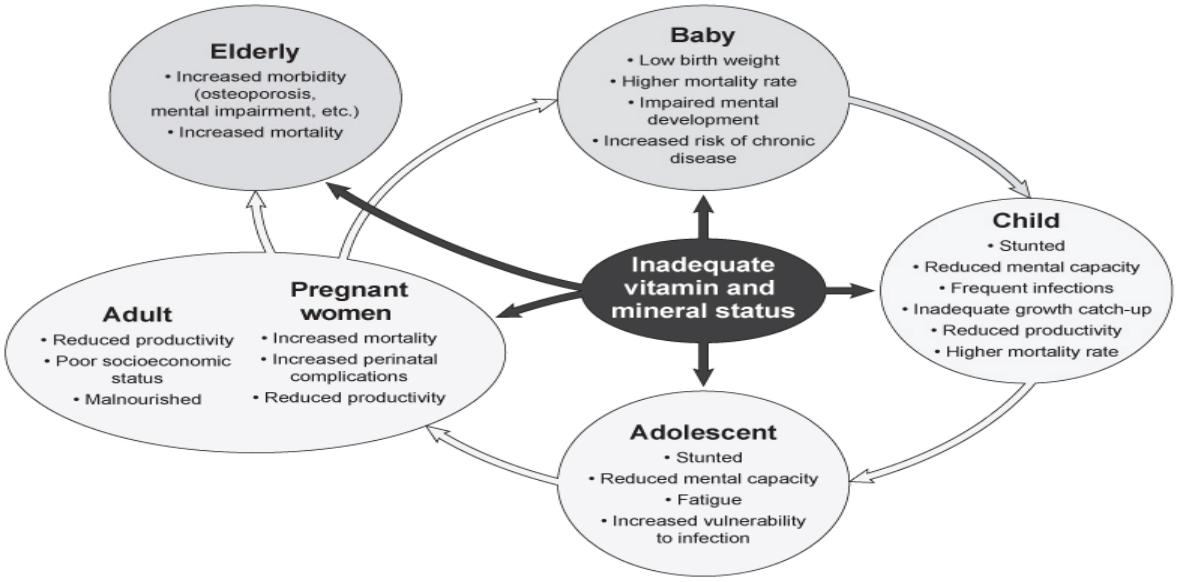

Figure 1. The cycle of micronutrient inadequacies across the life span

Brain Development in Humans

Nutrients and growth factors regulate brain development during fetal and early postnatal life. The rapidly developing brain is more vulnerable to nutrient insufficiency yet also demonstrates its greatest degree of plasticity. Certain nutrients have greater effects on brain development than do others. These include protein, energy, certain fats, iron, zinc, copper, iodine, selenium, vitamin A, choline, and folate. The effect of any nutrient deficiency or overabundance on brain development will be governed by the principle of timing, dose, and duration. The ability to detect the specific effects of nutrient deficiencies is dependent on knowing which area of the brain is preferentially affected and on having neurologic assessments that tap into the functions of those specific areas. As examples, Iron deficiency alters myelination, monoamine neurotransmitter synthesis, and hippocampal energy metabolism in the neonatal period. Assessments of these effects could include tests for speed

of processing (myelination), changes in motor and affect (monoamines), and recognition memory (hippocampus).

Brain development is a temporally extended and complex process, with different parts and functions of the brain developing at different times (Grossman et al., 2003). By 5 weeks after conception in humans, the anterior-posterior and dorsal-ventral axes of the neural tube have already developed (Levitt, 2003). The cortical plate (which is the forerunner of the cerebral cortex) and some inter-neuronal connections form from 8 to 16 weeks of gestation (Levitt, 2003). From 24 weeks of gestation until the perinatal period, the neurons in the cortical plate die and are replaced by more mature cortical neurons. During this time, significant refinement in neural connections take place. From 34 weeks post-conception until 2 years of age, peak synapse development, and significant brain growth occurs. By preschool age, synaptic density has reached the adult level. The myelination of some parts of the brain (particularly those that control higher cognitive functions, such as the frontal lobes) continues well into adolescence, whilst myelination occurs earlier in other parts of the brain that coordinate more primary functions (Toga et al., 2006). Although the gray matter (which contains the bodies of nerve cells) reaches asymptote by the age of 7–11 in different regions of the brain, it is thought that the growth of the white matter (which represents axonal nerve tracts) continues beyond 20 years of age. Studies have shown that the maturation of specific brain areas during childhood is associated with development of specific cognitive functions such as language, reading, and memory (Giedd et al., 2010). The development of the frontal lobes, which are believed to control higher cognitive functions (including planning, sequencing and self-regulation), appears to occur in growth spurts during the first 2 years of life, and then again between 7 and 9 years of age and also around 15 years of age (Bryan et al., 2004). The development of some subcortical structures including the basal ganglia, amygdala, and hippocampus (which are also centrally involved in some mediating higher cognitive functions, including memory, executive functions, and emotion) also continues until late adolescence. Since rapid brain growth occurs during the first 2 years of life (and by the age of 2 the brain reaches 80% of its adult weight), this period of life may be particularly sensitive to deficiencies in diet (Giedd, 2006). Adolescence is also a significant and sensitive developmental period, with research indicating that structural reorganization, brain and cognitive maturation and—in particular—major developments in the pre- frontal cortex take place during puberty (Blakemore et al., 2010).

Effect of Zinc on Brain Development

Zinc is an essential micronutrient, present naturally in some foods and also available as a dietary supplement. It involves in various activities of cellular metabolism and required for catalytic activity of approximately 100 enzymes (1) and play a vital role in immune function (2) and cell division (3). It is reported to support normal growth and development of fetus during pregnancy, childhood and adolescence (4). Pregnant women are at increased risk of

developing zinc deficiency due to high fetal demand for zinc and likely to suffer health consequences due to zinc deficiency.

Risk of Zinc deficiency

Zinc deficiency usually occurs due to inadequate zinc intake or absorption, increased losses of zinc from the body and increased requirements for zinc. All these conditions are obvious to pregnant women. Pregnant women are more susceptible to zinc deficiency, particularly in 2nd and 3rd trimesters. It is so because of increased volume of blood, poor bio-absorption and intake of zinc. It is also associated with iron deficiency anemia.

(a) Effect of zinc on pre-natal stage: Since zinc is important for enzymatic activity, involved in replication of cells in brain growth, zinc finger protein in brain structure and neuro transmission, it is an important element for neuro development of fetus and it is also involved in many metabolic activities like hormone transport, receptor binding and production of neuro transmitter precursor.

(b) Effect of zinc on post-natal outcomes: Problems occurred due to maternal zinc deficiency not only limited to the fetal life but also occurs in postnatal period since it is important for the transfer of many immunologic substances and vitamin A. Perinatal zinc deficiency may lead to poor development of natural immunity and decreased acquisition of antibodies from mother and adversely affect the proper development of many tissues and organ systems in the fetus. It suppresses the immune responses and also reported to decrease the size of spleen and thymus, impaired lymphocytic mitogenic responses, plaque forming activities and decreases immunoglobulin M and immunoglobulin A concentration. Since zinc is required as a cofactor for immunoglobulin transport across the placental barrier, the deficiency of zinc during pregnancy may diminish utero acquisition of antibodies by the fetus. Hence zinc deficiency may be a cause of impaired disease resistance, poor immunity and decreased efficiency for vaccine in fetus.

Effect of Zinc on Learning and Behaviour Abilities

Zinc deficiency has been studied in animals by restricting zinc intake during pregnancy or specific developmental periods. Rats have been used to examine zinc deficiency during the prenatal and infancy periods. Animals who experienced severe zinc deficiency early in their fetal development were at increased risk for abortion and fetal abnormalities. Animals who experienced zinc deficiency, after the period of organogenesis but during early development, and were refed and tested as adults had difficulty in maze-learning tasks, particularly when shock was used in the learning procedure. They responded with increased emotionality that was evidenced by their aggression, poor memory and difficulty avoiding the shock. Thus, zinc deficiency early in life appeared to have long-lasting effects on the animals' responses to stress, which interfered with performance in learning situations.

Effect of Zinc on Biochemical Parameters

The effects of Zn deficiency on some hematological parameters in rats were observed and it shows that a significant decline in Hb, total erythrocyte count and packed cell volume of both male and female rats. Reduction in Hb content may be due to increased rate of disruption or reduction in the rate of formation of erythrocyte. The decrease in packed cell volume was obviously due to the decreased cellular count in blood of rats that were Zn deficient. Researchers reported that dietary Zn deficiency in rats increased osmotic fragility of their erythrocytes and the oxidative damage was responsible for the impaired erythrocyte stability. They found that Zn deficiency reduced numbers of spleen cells.

Effect of Iron on Brain Development

One of the most common nutritional deficiencies in both developing and developed countries is iron deficiency. In some parts of the world, such as in Sub-Saharan Africa and South-East Asia, the prevalence is more than 40%. It is believed that iron is involved with different enzyme systems in the brain, including: the cytochrome c oxidase enzyme system in energy production, tyrosine hydroxylase for dopamine receptor synthesis, delta-9-desaturase for myelination, and fatty acid synthesis, and ribonu-cleotide reductase for brain growth regulation (Rioux et al., 2011). There are three time periods when children are at particular risk for iron deficiency: the fetal/neonatal period, infancy and early toddlerhood (6-24 months of age), and following the onset of menarche in girls. Brain growth and development is relatively rapid during two of these periods, while it is nearly complete during the third. This distinction allows for studying the comparative effects of a single nutrient deficiency on a growing versus a mature brain. Because of its intricate involvement in cell cycle kinetics and myelination, one would expect profound neuroanatomic changes in a brain that is still growing, but perhaps no structural effect in a relatively mature brain. Teenage iron deficiency would not be expected to affect myelination since it is largely completed by that time; however, iron deficiency prior to 3 years of age would likely result in profound and possibly permanent myelin changes. Furthermore, areas that are growing particularly rapidly might be expected to be most affected. Since the brain does not develop homogenously (i.e., not all parts mature simultaneously), iron deficiency during one growth period (e.g., fetal life) may result in very different neuroanatomic and neurobehavioral deficits than iron deficiency during another growth period (e.g., infancy). Iron also has important effects on neurochemistry and neuro metabolism through its effects on monoamine metabolism and oxidative phosphorylation. Iron deficiency may affect these chemical and metabolic aspects of brain function similarly in developing and mature brains. Therefore, neurotransmitters, such as dopamine and glutamate would be vulnerable to iron deficiency at any age.

Effect of Iron on Behaviour Abilities

Higher levels of irritability in infants of mothers with iron-deficiency anemia. In the other, poorer iron status at birth (cord blood ferritin and hemoglobin) correlated with higher levels of negative emotionality and lower levels of alertness and suitability (Wachs et al;2005).

Effect of Iron Biochemical Parameters

Accumulation of iron by the human fetus begins early in pregnancy, increases dramatically in the third trimester, and continues after birth up to 30–50 y of age. Unless maternal iron deficiency is severe, term infants are generally considered to be protected from IDA through the first few months of life, but as iron stores are used up, a sharp decline occurs in serum ferritin and the infant becomes vulnerable to deficiency if the supply of dietary iron is not adequate. Because preterm infants have only 40–70% as much total body iron at birth as do term infants, they are more vulnerable to early iron deficiency. Studies in rats indicate a similar pattern of accumulation of iron in the fetal and postnatal brain. Once in the brain, iron is sequestered, with very low turnover, in contrast with the rapid turnover of iron in plasma. Dietary iron deficiency results in biochemical changes in the blood and reduced concentrations of iron in tissues. IDA is generally considered to correspond to a degree of dietary iron deficiency sufficient to deplete ferritin stores and to decrease iron concentrations in some tissues, but not sufficient to reduce serum hemoglobin to the point of anemia. Individuals with depleted iron stores and serum hemoglobin concentrations below the 98th percentile of a normally distributed population are generally considered to be iron deficient anemic.

Effect of Iodine on Brain Development

Iodine deficiency is a significant worldwide public health issue, especially in children and during pregnancy (World Health Organization, 2004). Iodine deficiency in the soils in many countries has led to food fortification, most commonly the use of iodized salt (World Health Organization, 2004). The relationship between iodine and cognitive development is extensively researched. It is well known today that severe iodine deficiency during pregnancy may cause “cretinism” in children (Zimmermann, 2011). The clinical manifestation of cretinism depends on the severity of iodine deficiency; the features may include mental retardation, speech and hearing impairment, upper motor neuron and extrapyramidal lesions. Iodine is necessary for the production of thyroid hormones in the body; 70–80% of it is found in the thyroid gland (Melse-Boonstra and Jaiswal, 2010). Iodine deficiency manifests in hypothyroidism, causing underproduction of thyroid hormones including triiodothyronin (T3) and thyroxin (T4). Thyroid hormones play an important role in neurodevelopment and numerous neurological processes including neuronal cell differentiation, maturation and migration, myelination, neurotransmission, and synaptic plasticity (Zimmermann;2011). In

addition, in animal model's hypothyroidism alters neurogenesis and the development and functions of synapses in the hippocampus.

Effect of Selenium on Brain Development

Selenium is a micronutrient whose role in brain development is only now being elucidated. Selenium deficiency is seen in geographical regions where there are low selenium levels in the soil. Food crops and pasture grasses grown in these soils will have lower selenium content; therefore, populations who depend on local food crops and animal products are at risk for selenium deficiency. The highest rates of selenium deficiency are in communities living in several regions throughout China with low soil content (FAO/WHO, 2004). Several other regions with low soil content (e.g., Finland, New Zealand, United Kingdom) have reduced the rates of selenium deficiency due to importation of crops and animal products raised in high content regions. Finally, another population at relatively high risk of selenium deficiency is preterm infants because of their lower body stores and generally poorer antioxidant status. Although direct evidence of selemium's effect on cognitive development in humans is lacking, its role in brain thyroid and iodine metabolism, as well as its interaction with other micronutrients (e.g., iron, copper, zinc, lead) that affect brain development, is important to note. Selenium is required for the synthesis of proteins (selenoproteins) that are involved in thyroid metabolism. Thus, as with iodine, selenium deficiency can lead to hypothyroidism and cretinism.

Effect of Copper on Brain Development

Copper is an important component of proteins essential for neural functioning. However, Cu has been implicated in the pathogenesis of neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Alzheimer's disease (AD) is characterized by neuronal degeneration, increased concentrations of Cu, Fe and Zn, and increased deposits of amyloid β protein in the brain. In Alzheimer's disease, the amyloid precursor protein gene molecule, which has been directly linked to early-onset forms of the disease, contains a Cu-binding site. The binding of Cu^{2+} to amyloid precursor proteins in vitro results in the oxidation of two cysteine molecules to cystine and produced two electrons. As only one electron is needed to reduce Cu^{2+}, the remaining electron may be involved in the production of hydroxyl radicals. The binding of amyloid β protein to Cu and Zn could promote ROS generation. Atox1, a Cu transport protein, is a Cu-dependent suppressor of oxidative damage in yeast lacking SOD. Neuronal cell lines transfected with the Atox1 gene to increase the endogenous level of Atox1 expression are protected against serum starvation and oxidative stress. Thus, Atox1 may play a role in preventing neuronal cells against oxidative damage induced by Cu (Gaetke et al., 2003).

One of the first and most severely injured brain areas in AD is the hippocampus, which is associated with neurogenesis and long-term memory storage. It is also thought to be more

susceptible to metal disturbance than other brain areas. Another brain region that suffers from damage in AD due to plaque pathology is the cortex, associated with functions such as argumentation, feeling, and language. An analysis on the human brains of deceased patients with dementia concludes that defective brain regions have a very low copper content (Pickart et al., 2017). The copper content of aged human brains has a significant negative correlation with the degree of severity of amyloid plaques (Exley et al., 2012). Based on the results showing a significant reduction in copper ion in AD patients compared to controls (Giacoppo et al., 2014), it has been hypothesized that AD is a result of copper deficiency (Klevay, 2008).

Conclusion

Micronutrients are essential components of the human diet and contribute to growth, development and performance. It is known that the functions and effects of micronutrients may be different within the life cycle and should be ensured by an adequate diet. Nevertheless, different micronutrients are not adequately supplied within the life cycle according to a couple of studies and meta-analyses. This may or may not have adverse health effects, depending on the importance of the micronutrient not adequately supplied in a certain stage of the life cycle.

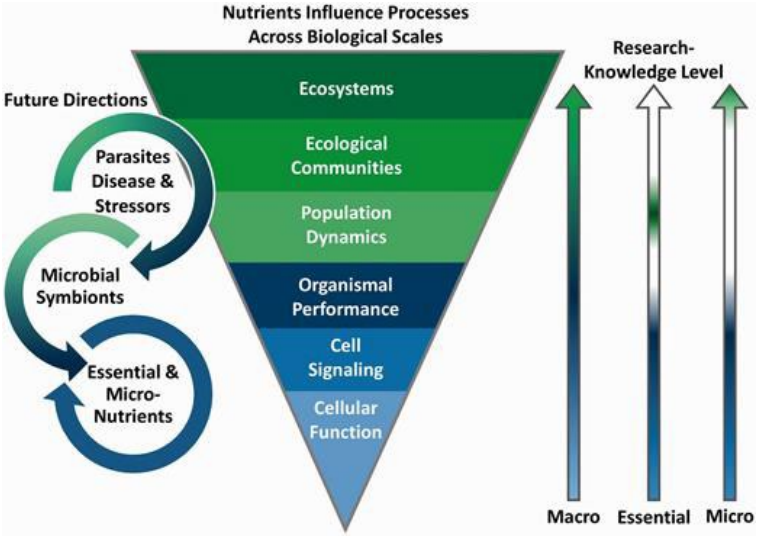

Figure 2. An estimate of the current state of knowledge (vertical arrows) of nutrients' effects across biological scales (triangle sections) is illustrated for each of the major classes of nutrients

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