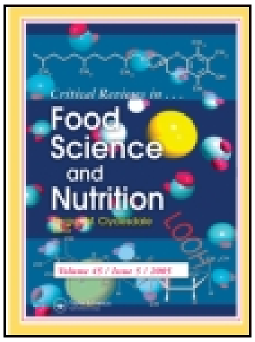

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A Question Mark on Zinc Deficiency in 185 Million People in Pakistan—Possible Way Out

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This paper reviews research published in recent years concerning the effects of zinc deficiency, its consequences, and possible solutions. Zinc is an essential trace element necessary for over 300 zinc metalloenzymes and required for normal nucleic acid, protein, and membrane metabolism. Zinc deficiency is one of the ten biggest factors contributing to burden of disease in developing countries. Populations in South Asia, South East Asia, and sub-Saharan Africa are at greatest risk of zinc deficiency. Zinc intakes are inadequate for about a third of the population and stunting affects 40% of preschool children. In Pakistan, zinc deficiency is an emerging health problem as about 20.6% children are found in the levels of zinc, below 60 μg/dL. Signs and symptoms caused by zinc deficiency are poor appetite, weight loss, and poor growth in childhood, delayed healing of wounds, taste abnormalities, and mental lethargy. As body stores of zinc decline, these symptoms worsen and are accompanied by diarrhea, recurrent infection, and dermatitis. Daily zinc requirements for an adult are 12–16 mg/day. Iron, calcium and phytates inhibit the absorption of zinc therefore simultaneous administration should not be prescribed. Zinc deficiency and its effects are well known but the ways it can help in treatment of different diseases is yet to be discovered. Improving zinc intakes through dietary improvements is a complex task that requires considerable time and effort. The use of zinc supplements, dietary modification, and fortifying foods with zinc are the best techniques to combat its deficiency.

Keywords Zinc, zinc deficiency, symptoms, recommended intake, Pakistan, government policies, possible solutions

BACKGROUND

Population of developing countries is on peak than world's average population growth rate of 1.8% (Population Division, 2009). There is a need of real hard effort and food revolution in poor and developing countries to solve food scarcity (Huang et al., 2002) but it require consistent and determined efforts. In comparison of total population, about 65% of world's total population is starving (Food Security Statistics, 2008) and lives below poverty line. Malnutrition and under nutrition are found among people where food supply and diet diversification are lacking. Right now in 21st century developing world is under severe threat of micronutrient malnutrition, because of consumption of cereals that are rich in phytates and these limits bioavailability of essential nutrients (Hussain et al., 2010).

The deficiency of essential vitamins and minerals are regarded as "hidden hunger" and it affects more than one-third of the world's population, threaten women and children, resulting devastating consequences for public health, social development, and future of country. It is estimated that as many as two billion people are at risk of zinc deficiency in this world so called as "Global Village." Zinc and other micronutrient deficiencies (MNDs) contribute significantly to the burden of disease and linked to adverse functional outcomes such as stunting, wasting, increased susceptibility to infections during pregnancy, decreased IQ level, cognitive losses, blindness, and premature mortality. Literature reviews estimates that 20% of the world's population may be at risk of inadequate dietary intake of zinc and the populations at highest risk are located in South and Southeast Asia, Sub-Saharan Africa, Central America, and the Andean region. Premature and small-for-gestational-age infants,

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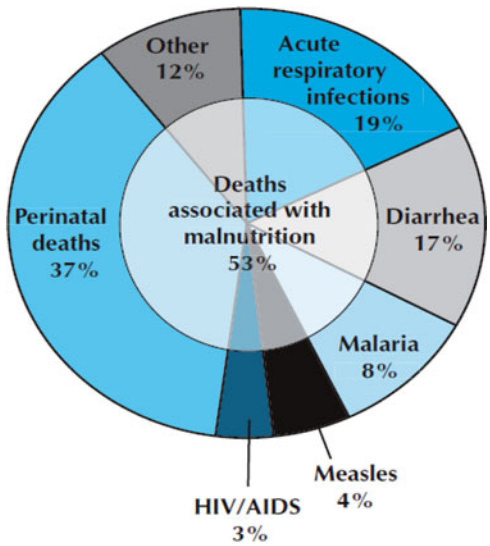

Figure 1 Causes of death among children less than five years of age worldwide (Black et al., 2003; Muller and Krawinkle, 2005). (Color figure available online.)

and preschool children, mostly in between 6 and 23 months of age comes in most vulnerable list and need extreme attention from Non-governmental Organizations (NGOs) and Government bodies (Boy et al., 2009).

Specialists have divided Malnutrition into protein energy malnutrition (PEM) and MNDs; these two constitute to be the majority of health burden in all developing countries covering from Asia to Africa. Malnutrition typically result in inadequate diet, and is easily diagnosable in children living in sub-Saharan Africa and south Asia (Manary and Sandige, 2008). These deficiencies covers whole developing world and creates an alarming situation in whole world. In developing world, people's diet lack both micronutrients (minerals, vitamin, and electrolytes) and macronutrients (proteins, carbohydrates, and fats) resulting in malnutrition and burden of diseases (Millward and Jackson, 2004; Muller and Krawinkle, 2005). Figure. 1 and Table 1 point the threats of malnutrition in children of developing world and confirm the degree of correlation among malnutrition and rate of death in developing countries (Fernandez et al., 2002; Black et al., 2003; FAO, 2004).

Pakistan is a developing country and since its birth malnutrition has recognized as a key factor that significantly affecting infants, children, and women. Malnutrition affects the physical growth in terms of body development, physical work capacity,

Table 1 Prevalence's of protein–energy malnutrition among children under 5 years of age in developing countries (FAO, 2004), *(NNS, 2002).

Region	Stunting (%)	Underweight (%)	Wasting (%)
Africa	39	28	8
Asia	41	35	10
Latin America and Caribbean	18	10	3
Oceania	31	23	5
Pakistan*	36.8	38	13.2

and producing risk for several chronic diseases in children. In South-East Asia, it was estimated at 43% whereas in Pakistan 50% of children fewer than five were stunted, 40% were under weight and 9% were wasted (Bellamy, 2000). This situation has not changed much in the region; recent reports showed that stunting is 37%, underweight 38%, while wasting is progressively increased to 13%, indicating lack of proper nutritional and health interventions at national level (Diaz et al., 2003). Pakistan is suffering from high rate of childhood malnutrition and has made little progress in the past 20 years due to bad governess and less attention paid by NGOs. The burden of child malnutrition in South Asia (India, Bangladesh, and Nepal) is considered much higher than most of the countries in sub-Sahara Africa. The situation is more serious in Pakistan that has long been considered as self-sufficient in diverse agriculture produce and refined foods. But lack of political commitment to systematically address the malnutrition, minimal investments in nutrition interventions, and lack of clear, focused, and practical strategy are some of the factors that contribute to the persistence of high levels of child malnutrition (Ahmed and Farooq, 2010).

Pakistan is a developing country and the deficiencies of micronutrients exist in various segments of the population. Half of its children aged five years or less are stunted, over a one third is underweight, and a quarter of all births are low birth weight (Bhutta, 2000). Iron, vitamin A and Zinc deficiency are prevalent among infants, school going children, females, and especially pregnant women indicated by several regional and national surveys. The last National Nutrition Survey (National Nutrition Survey, 2004) conducted in (2001–02), pointed out that 37% of 0–5 year olds were found to be zinc deficient. Among pregnant women, 45% had zinc deficiency. In calculation, more than 50% people in Pakistan suffer from micronutrient deficiencies that gives alarming call for urgent attention of Government, but still is a question mark.

MNDs, like Zinc and vitamin A are responsible for 0.4 million and 0.6 million deaths, respectively, in children with less than five years of age whereas iron deficiency anemia is found in 40–50% of infant and children (Black et al., 2008). It is interesting to note 50% of vitamin A deficiency cases are found in South Asia, including India (35.5 million), Indonesia (12.6 million), and (11.4 million) China (Diaz et al., 2003). In these countries, ample amount of leafy vegetables are available that could be utilized in a better way to eradicate this vitamin and other micronutrients deficiencies. According to World Bank suggestion that the cost of MNDs forces country 5% gross national product (GNP) whereas intervention and strategies might only cost 0.3% of the GNP (Hill et al., 2005). Zinc and Calcium deficiencies are also related to growth failure and increasing number of patients with osteoporosis. Co-existing nutritional interventions can prevent stunting by 36% and plummeting MNDs by about 25% (Bhutta et al., 2008). Human Zn deficiency is the fifth major cause of diseases and deaths in developing countries (WHO, 2002). Around the world, 2.7 billion people are Zn deficient (WHO, 2002; Muller and Krawinkle, 2005). About 50% of world's population is under risk of Zn deficiency and prevalence

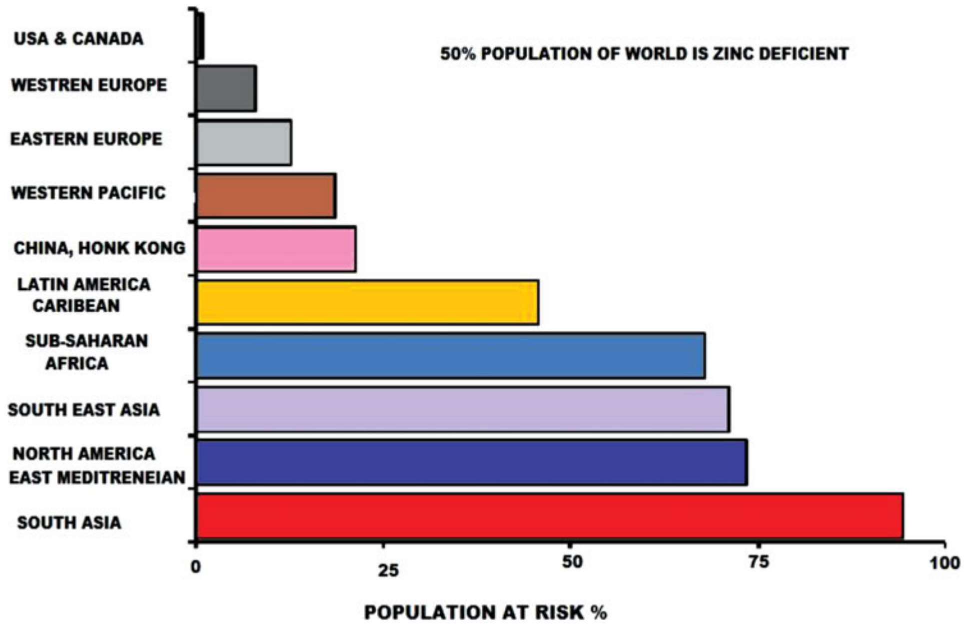

Figure 2 World population (%) deficient in zinc (Brown et al., 2001; Hussian et al., 2010). (Color figure available online.)

is more in developing countries of Asia and Africa (Fig 2). In Pakistan, every third child and 40% mothers are suffering from Zn deficiency (Bhutta et al., 2007).

ZINC AS AN IMPORTANT NUTRIENT FOR SUSTAINING LIFE

Zinc is an essential nutrient having a complex biological role, including neuropsychological aspects. The human body contains approximately 2 g zinc in total, with 60% found in skeletal muscle and 30% in bone mass, although it is found in all body tissues and fluids (Wahlqvist, 1997). Mostly, it is 10 mg Zn per day for adult women and 12 mg Zn per day for adult men. Women in pregnancy and lactation require up to 14 mg Zn per day. These intake levels are generally not fulfilled in developing countries due to diet rich in phytates and less calorie intake from cereals and other staple food (Bouis, 2002; Beers and Berkow, 2003; Hussain et al., 2010). Lean body mass and tissues contain approximately 30 μg/g of total available zinc. Plasma zinc has a rapid turnover rate and it represents only about 0.1% of total body zinc content. Higher concentrations of zinc are found in the choroid of the eye 274 μg/g (Hambidge, 1987).

ZINC METABOLISM AND HOMEOSTASIS

Zinc absorption is influenced by many factors and adequate dietary intake does not necessarily correlate with adequate zinc status. High phytate content significantly reduce zinc absorption due to the formation of strong and insoluble complexes (Lonnerdal, 2000). Concerns have also been raised over the calcium, iron, copper, and cadmium to reduce zinc absorption. The amount of animal protein in a meal positively correlates to zinc absorption and the amino acids histidine and methionine, and various organic acids present in foods, such as citric, malic, and lactic acids, can also increase absorption (King, 2003). Under normal circumstances, the absorption of zinc occurs through small intestine, but the up take process is not fully saturated. Zinc administered in aqueous solutions is considered to be efficiently absorbed up to 60–70%, but absorption from solid diets is less efficient and varies depending on zinc content and diet composition (Sandström, 1997). Zinc is lost from the body through the kidneys, skin, and intestine (King and Turnlund, 1989). The endogenous intestinal losses can vary from 70.5 mg/day to more than 3 mg/day, depending on zinc intake. Starvation and muscle catabolism increase zinc losses in urine. Strenuous exercise and elevated ambient temperatures could also lead to losses by perspiration (King and Turnlund, 1989). The utilization of zinc depends on the overall composition of the diet. Experimental studies have identified a number of dietary factors as potential promoters or antagonists of zinc absorption (Sandström and Lönnerdal, 1989). Soluble low-molecular-weight organic substances, such as amino and hydroxy acids, facilitate zinc absorption. In contrast, organic compounds forming stable and poorly soluble complexes with zinc can impair absorption (Sandström and Lönnerdal, 1989). Isotopic studies with humans identified two factors which together with the total zinc content of the diet are major determinants of absorption and utilization of dietary zinc in human body. The first is the content of inositol hexaphosphate (phytate) and the second is the level and source of dietary protein. Phytates are present in whole-grain cereals and legumes and in smaller amounts in other vegetables. They have a strong potential for binding divalent cations and their depressive effect on zinc absorption has been demonstrated in humans (Sandström and Lönnerdal, 1989).

Zinc in Biochemical Reactions

Metalloenzymes

At the cellular level, the function of zinc can be divided into three categories: catalytic, structural, and regulatory (King, 2003). As a constituent of over 300 metalloenzymes, zinc is involved in numerous chemical reactions that are important for normal body functioning, such as carbohydrate metabolism, protein and DNA synthesis, protein digestion, bone metabolism, and endogenous antioxidant systems (Wardlaw et al., 1994; Wahlqvist, 1997; Beers and Berkow, 2003).

Maintenance of Biomembranes and Immunological Functions

Zinc is important for the formation of biomembranes and zinc finger motifs found in DNA transcription factors (Semrad, 1999). Zinc is involved in many aspects of immunological functions. It is essential for the normal development and function of cells, mediating nonspecific immunity such as neutrophils and natural killer cells and affecting development of acquired immunity and T-lymphocyte function. Its deficiency rapidly diminishes antibody and cell-mediated responses in both humans and animals, leading to increases in opportunistic infections and mortality rates (Fraker et al., 2000). Animal models have shown that suboptimal intake of zinc over 30 days can lead to 30–80% loss in defense capacity. Investigation using a human model has demonstrated that even mild deficiency in humans adversely affects T-cell functions (Prasad, 1998). Conversely, high-dose zinc supplementation (20-fold RDI) can also produce immune dysfunction.

Controlling Body Coordination System

Zinc ions are unevenly distributed in the CNS, acting as neuro secretory products or cofactors. Zinc is highly concentrated in the synaptic vesicles of specific neurons, known as "zinc-containing" neurons. Zinc containing neurons are a subset of glutamatergic neurons and mostly located in the telencephalon. Zinc is released from zinc-containing neurons in a calcium- and impulse-dependent manner, producing a broad spectrum of neuromodulatory effects. Additionally, zinc appears to stabilize the storage of certain macromolecules in presynaptic vesicles (Frederickson and Danscher, 1990; Frederickson and Moncrieff, 1994; Frederickson, 2000).

Functions in Reproductive System

In humans, zinc is necessary for the formation and maturation of spermatozoa, for ovulation, and for fertilization (Favier, 1992). Zinc has multiple actions on the metabolism of androgen hormones, oestrogen, and progesterone, and these, together with the prostaglandins and nuclear receptors for steroids are all zinc finger proteins. In adult males, zinc content is high in the testis and prostate, which have the highest concentration of zinc of any organ in the body (Bedwal and Bahuguna, 1994). In women, zinc deficiency during pregnancy has been associated with increased maternal morbidity, increased risk of abortion, stillbirth, teratogenicity, and other unwanted outcomes (Bedwal and Bahuguna, 1994).

Zinc as an Antioxidant Agent

Zinc limits oxidant-induced damage in a number of indirect ways, such as protecting against vitamin E depletion, controlling vitamin A release, contributing to the structure of the antioxidant enzyme extracellular superoxide dismutase, restricting endogenous free radical production, maintaining tissue concentrations of metallothionein, a possible scavenger of free radicals, and stabilizing membrane structure (DiSilvestro, 2000). Furthermore, it was observed to decrease lipid peroxidation, and protect mononuclear cells from TNF-alpha induced NF-kappa-B activation associated with oxidative stress (Prasad, 2004).

One of the in vivo features of zinc is its insulin-like function, which is mediated via inhibition of endogenous GSK-3 (Ilouz, 2002). This is important because GSK-3 inhibition appears essential for normal function of the insulin-activated signaling pathway.

DIETARY SOURCES OF ZINC

Nature has put solution for all types of deficiencies. The solution of zinc can be found in all sectors of food choices ranging from lean red meat, whole-grain cereals, pulses, and legumes. All these products provide the highest concentrations of zinc 25–50 mg/kg raw weight. As a common perception that processing decrease the nutritional quality, similarly processed cereals has low extraction rates, polished rice, and lean meat or meat with high fat content have a moderate zinc content 10–25 mg/kg (fish, roots and tubers, green leafy vegetables, and fruits are only modest sources of zinc $<$10 mg/kg (Sandström and Lönnerdal, 1989). Saturated fats, sugar, and alcohol have very low zinc content.

ZINC REQUIREMENTS AND RECOMMENDED INTAKE

There is no specific index for zinc status limits for evaluating zinc requirements. Zinc requirements were estimated by using factorial techniques (adding the requirements for tissue growth, maintenance, metabolism, and endogenous losses) (AO/IAEA/WHO, 1996; WHO/FAO, 2001). Experimental zinc repletion studies with low zinc intakes have clearly demonstrated that the body has a pronounced ability to adapt to different levels of zinc intakes by changing the endogenous zinc losses through the kidneys, intestine, and skin (Milne et al., 1983; Lukaski et al., 1984; Taylor et al., 1991). The normative requirement for absorbed zinc was defined as the obligatory loss during the early phase of zinc depletion before adaptive reductions in excretion take place and was set at 1.4 mg/day for men and 1.0 mg/day for women. In growing individuals, the rate of accumulation and zinc content of newly formed tissues were used to obtain the data required for tissue growth. Similarly, the retention of zinc during pregnancy and the zinc concentration in milk at different stages of lactation were used to estimate the physiologic requirements in pregnancy and lactation (AO/IAEA/WHO, 1996; WHO/FAO, 2001).

Infants, Children, and Adolescents

Endogenous losses of zinc in human-milk-fed infants were assumed to be 20 μg/kg/day whereas 40 μg/kg/day was assumed for infants fed formula or weaning foods (AO/IAEA/WHO, 1996; WHO/FAO, 2001). Estimated zinc increases for infant growth were set at 120 and 140 μg/kg/day for female and male infants, respectively, for the first three months (AO/IAEA/WHO, 1996; WHO/FAO, 2001). These values decrease to 33 μg/kg/day for ages 6–12 months. For ages 1–10 years, the requirements for growth were based on the assumption that new tissue contains 30 μg/g (AO/IAEA/WHO, 1996; WHO/FAO, 2001). For adolescent growth, a zinc content of 23 μg/g increase in body weight was assumed. Growth of adolescent males corresponds to an increase in body zinc requirement of about 0.5 mg/day (AO/IAEA/WHO, 1996; WHO/FAO, 2001).

Pregnancy

The total amount of zinc retained during pregnancy has been estimated to be 100 mg (Swanson and King, 1987). During the third trimester, the physiologic requirement of zinc is approximately twice as high as that in women who are not pregnant (AO/IAEA/WHO, 1996; WHO/FAO, 2001).

Lactation

Zinc concentrations in human milk are high in early lactation, 2–3 mg/L in the first month, and fall to 0.9 mg/L after three months (WHO, 1998). From data on maternal milk volume and zinc content, it was estimated that the daily output of zinc in milk during the first three months of lactation could amount to 1.4 mg/day, which would theoretically triple the physiologic zinc requirements in lactating women compared with non-lactating, nonpregnant women. In setting the estimated requirements for early lactation, it was assumed that part of this requirement was covered by postnatal involution of the uterus and from skeletal resorption (AO/IAEA/WHO, 1996; WHO/FAO, 2001).

Recommended Intake

The studies of (Hess et al., 1977; Milne et al., 1983; Baer and King, 1984; Milne et al., 1987; Johnson et al., 1993) on factorial technique have considered a relatively small number of subjects and do not allow any estimate of inter-individual variations in obligatory losses of zinc at different intakes. The reason is that zinc requirements are related to tissue turnover rate and growth, it is reasonable to assume that variations in physiologic zinc requirements are of the same magnitude as variations in protein requirements (FAO/WHO/UNU, 1985). From the available data from zinc absorption studies (Nävert et al., 1985; Sandström and Lönnerdal, 1989; Sandström and Sandberg, 1992; Hunt et al., 1995; Knudsen et al., 1995; Sian et al., 1996), it is suggested that the variation in dietary zinc requirements, which covers variation in requirement for absorbed zinc (variations in metabolism and turnover rate of zinc) and variation in absorptive efficiency, corresponds to a coefficient of variance of 25%. The recommended nutrient intakes derived from the estimates of average individual dietary requirements are presented in Table 2.

Table 2 Recommended intake of zinc among different age groups

	Dietary Zn bioavailability (mg/day)		
Population and age (years)	High	Medium	Low
Infants			
0–0.5[a]	—	—	—
0.5–1	3.3	5.6	11.1
Children			
1–3	3.3	5.5	11
3–6	3.9	6.5	12.9
6–10	4.5	7.5	15
Males			
10–12	5.6	9.3	18.7
12–15	7.3	12.1	24.3
15–18	7.8	13.1	26.2
18–60	5.6	9.4	18.7
Females			
10–12	5	8.4	16.8
12–15	6.1	10.3	20.6
15–18	6.2	10.2	20.6
18–60	4.0	6.5	13.1
Pregnant women[b]	6.0	10.0	20.0
lactating women (0–5 months)	7.3	12.2	24.3
Lactating women (>6 months)	5.8	9.6	19.2

[a]Exclusive breastfeeding is recommended.
[b]Mean for all trimesters.
Source: (WHO, 2001 and Brown et al., 2001).

SIGNS AND SYMPTOMS OF DEFICIENCY

Zinc deficiency is an important factor contributing to increased morbidity, mortality, and impaired development of children in underprivileged settings. Zinc deficiency is now widely recognized as a leading risk factor for morbidity and mortality and is estimated to be responsible for approximately 800,000 excess deaths annually among children fewer than five years of age (Haider and Bhutta, 2009). Two types of zinc deficiencies are found, i.e., primary and secondary deficiency. Primary deficiency can result from inadequate dietary intake of zinc; however, inhibition of zinc absorption is a common causative factor (Lonnerdal, 2000). Strict vegetarians are at risk of deficiency if their major food staples are grains and legumes because the phytic acid in these foods will impair dietary zinc absorption. Zinc chelating compounds have been identified in coffee (Wen et al., 2005; Higdon and Frei, 2006) and coffee has been found to inhibit the bioavailability of zinc in vitro by 21–32% (Van Dyck et al., 1996; Higdon and Frei, 2006). Secondary deficiency develops in some people with cirrhosis, mal-absorption syndromes, sickle cell anemia, conditions of increased zinc loss, such as severe burns or major surgery, chronic diarrhea or diabetes, HIV and AIDS, and during prolonged parenteral nutrition (Prasad, 1999). Additionally, strenuous exercise and elevated ambient temperatures increase zinc losses through perspiration. A congenital disorder known as acrodermatitis enteropathica causes severe zinc deficiency.

Zinc deficiency is also associated with impaired glucose tolerance. It is assumed that zinc may interact with the hormone insulin in a way that influences the uptake of glucose by adipocytes (Ganapathy and Volpe, 1999). In addition to this interaction with insulin, zinc is known to interact with a number of other hormones, including growth hormone, various sex hormones, thyroid hormones, prolactin, and corticosteroids (Guthrie and Picciano, 1995). The interactions between zinc and hormones are double-edged because, where zinc influences the synthesis and activities of hormones, various hormones also influence the absorption and metabolism of zinc. Zinc appears to be required for the normal development and maintenance of the immune system. An adequate intake of zinc helps the body resist infection (Fraker et al., 1986; Keen and Gershwin, 1990; Ganapathy and Volpe, 1999).

The major signs and symptoms of zinc deficiency are, Anorexia and impaired sense of taste, slowed growth and development, and delayed sexual maturation. More pronounced are delayed sexual maturation, hypogonadism and hypospermia, and menstrual problems. Skin rashes, alopecia, chronic and severe diarrhea, immune system deficiencies, and increased susceptibility to infection are also of major concern. Other problems include impaired wound healing due to decreased collagen synthesis, night blindness; swelling and clouding of the corneas, behavioral disturbances such as mental fatigue and depression (King, 2003). Zinc deficiency during pregnancy is associated with the defects like increased maternal morbidity, preeclampsia and toxemia, prolonged gestation, inefficient labor, atonic bleeding, increased risk of abortion, and stillbirths. Teratogenicity, low birth weight infants, diminished attention in the newborn, and poorer motor function at six months are also reported (Bedwal and Bahuguna, 1994; Prasad, 1996; Higdon, 2003).

ZINC DEFICIENCY IN PAKISTAN

In Pakistan, despite an increase in per capita food availability and resultant rise in per capita calorie and protein intake, the prevalence of malnutrition has not improved over last 20 years (Pakistan Demographic and Health Survey, 2007). At the time of the on-set of the Ninth Plan, i.e., 1997–98, the estimated number of malnourished children was about eight million. Nearly half of the children under five years of age were found underweight of age at a level that corresponds to general malnutrition of PEM. Approximately 5% of these were severely underweight and 10% were moderately underweight. Recent studies show that Pakistan is lacking to achieve its Millennium targets goal to reduce malnutrition and it is clearly depicted from Figure 3.

Table 3 Nutrition indicators of Pakistan

Nutrition indicators of Pakistan	
Deficiencies	
Vitamin A	
(Indirect estimates)	12.50%
Bitot's spot	1.20%
Low serum retinol	12%
Zinc	37%
IDD (iodine deficiency disorder)	
Prevalence of clinical Goiter	6.50%
Biochemical Iodine Deficiency	
Moderate	17%
Severe	22.90%
Iron	45%

Source: National Nutrition Program, 2011.

The nutritional and demographic surveys, conducted during last two decades, indicate extremely poor state of female and child nutrition. According to the National Nutrition Survey (National Nutrition Survey, 1988), nearly 65% of the young children and 45% of pregnant and lactating women suffered from anemia due to iron deficiency. Nearly 28% of pregnant and 46% of lactating women consumed less than 70% of recommended daily allowance (RDA) of calories. This proportion has not changed much in 1995 (Pakistan Demographic and Health Survey, 2007). The NNS (National Nutrition Survey, 1988) observed a high incidence of malnutrition among children under five years of age. About 52% of children were found to have low weight for age (underweight); 42% had low height for their age (stunted); and 11% had low weight for height (wasted). In recent years, the proportion of children stunted declined to 36%, while the proportion of children wasted increased to 14% during 1990–94 NHS (Pakistan Demographic and Health Survey, 2007). NNS (National Nutrition Survey, 1988) also observed low consumption of protein, calories and iron among children. Almost 10–20% children of age under five years, received less than 70% of the RDA of protein, nearly 30–40% received less than 70% of the RDA for calories and 25% children of the age group 4–5 years received less than 70% of the RDA for iron. An overview of Pakistan nutrition indicators are presented in Table 3.

Despite widespread stunting and the high dietary phytate content in the average diet, there are few data on the prevalence of Zn deficiency in Pakistan. In this country, zinc deficiency has been found in malnourished children and children suffering from persistent diarrhea. The zinc deficiency has been reported in 54.2% preschool children (Paracha and Jamil, 2000). The zinc deficiency and sub-clinical infections in Pakistani preschool children have been found alarmingly high and proper intervention to

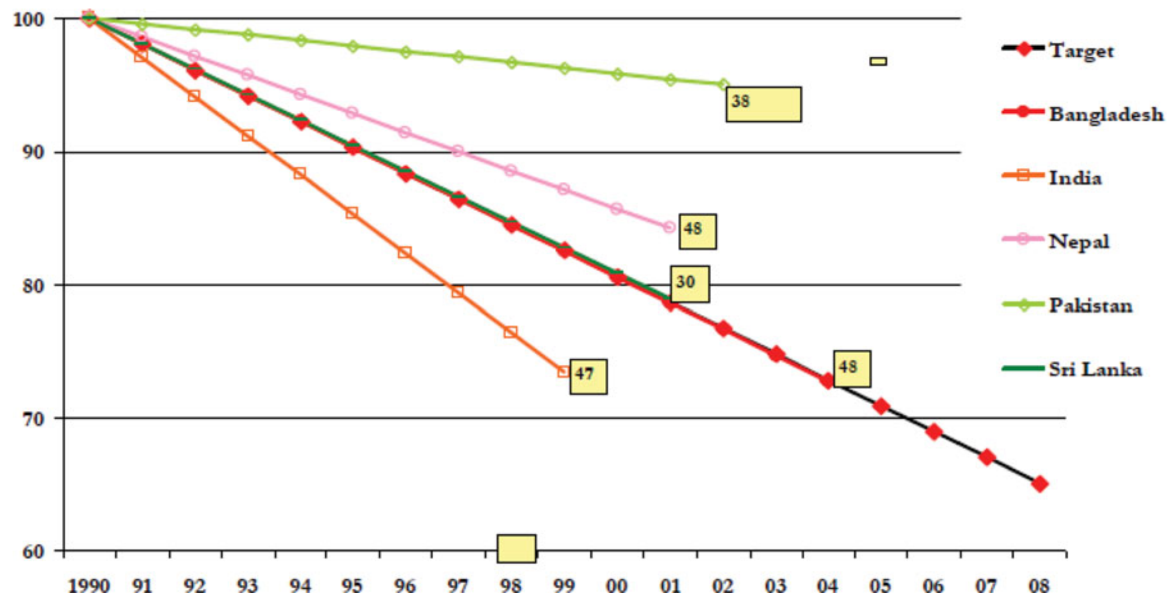

Figure 3 Millennium target goal (MDG) on reduction in malnutrition (weight for age) (1990 = 100%, target reduction to 50% of 1990 level by 2015). Source: WDI 2006 & UNDP 2006. (Color figure available online.)

reduce zinc deficiency and sub-clinical infection in vulnerable group of population is urgently required.

Bhutta (2007) evaluated serum-Zn concentrations on a nationally representative sample of 5800 women of reproductive age and children (age group: <5 years). The assessment revealed that almost a third of children and 40% of mothers had serum-Zn concentration below 60 μg/dL, and the prevalence was greater in rural populations. Bhutta et al. (2000) evaluated prospectively risk factors for Zn deficiency in two urban and rural cohorts of weaned infants. Quantitative assessment of intake of Fe and Zn from commonly consumed weaning diets indicated that dietary Zn and Fe intakes were very low (1.2 mg/day in young infants, 1.9 mg/day in older infants). These values are below the RDAs and are accompanied by a high phytate content of the diet and high burdens of diarrhea and respiratory infections.

The zinc deficiency in humans in general is a serious global issue particularly in the developing nations. In Pakistan, 54.2% preschool children of KPK (Khyber Pakhtunkhwa) province were reported to be zinc deficient (Paracha and Jamil, 2000). Similarly in a population based study in urban and rural Sindh, 54% of all pregnant women were observed to be zinc deficient (Bhutta, 2000). A comparable rate of sub-clinical zinc deficiency was seen among adolescent girls and boys in upper Sindh province. The National Nutritional Survey 2001–02 has indicated that 37.1% preschool children and 41.4% mothers of children under five years had sub-clinical zinc deficiency with serum concentrations below 60 μg/dL. Approximately 61% of people in developing countries are at risk of low dietary zinc intake (Brown and Wuehler, 2000). Bhutta et al. (2007) reported several traditional foods consumed by infants in Pakistan like Khitchri (rice + lentil), Sago Dana (sabo grain), Kheer (rice pudding), Suji Kheer (suji and milk), Suji Halwa (suji + sugar and water), Banana Kheer (banana + milk and sugar), Potato Kheer (potato + milk and sugar), and Mixed Diet (potato, lentils, spinach, and oil). They reported a significant variation in average daily intake and absorption of zinc from commonly consumed complementary foods by young infants and envisaged that absorption of zinc was more in infants of age group 9–12 months as compared to infants of 6–8 months. The most common complementary food consumed in Pakistan by Infants (6–12 months) and uptake of iron and zinc form these complementary foods are represented in Table 4. The higher Zn deficiency in Pakistani infants occurs because of incomplete beast feeding practices. The recent Pakistan demographic health survey indicates that only 23% people practice exclusive breastfeeding up to six month of age (Global breastfeeding week, 2011). Figure. 4 clearly shows that Pakistan and South Asia still follows one of the world lowest breastfeeding practices in the world (UNICEF, 2011).

The recent WHO/UNICEF review on complementary feeding in developing countries confirmed that iron and zinc requirement may be difficult to meet from nonfortified complementary foods (WHO, 1998). Diarrheal illness and helminthiasis problem in Pakistan increases micronutrients requirements. Mothers in Pakistan have very low iron and zinc status, hence delivering low birth weight babies that are more prone toward different diseases (Bhutta, 2007). A study conducted to check the plasma levels for retinol-binding protein and zinc among young infants presenting with diarrhea by Bhutta (2007) in Karachi and he concluded that the plasma zinc concentration was significant lower among those having low birth weight. The other reasons for having low zinc concentration is low rate of exclusive breastfeeding and delayed introduction of suitable complementary food (Kilbride et al., 1999).

The cereal flours are currently the most frequently used vehicles for calcium, iron, and zinc fortification in many advanced countries of the world. Unfortunately, the calcium, iron, and zinc

Table 4 Average complementary foods of Pakistani infants (modified from Bhutta, 2000)

Iron and zinc content of complementary foods in Pakistani infants (6–12 months of age)						
Content per 100 g	Energy density	Zinc (mg)	Iron (mg)	Phytate (mg)	Phytate/Zn Molar ratio	Phytate/Fe Molar ratio
Khitchri (rice-lentils)	1.2	1.9	2.8	291	15.08	8.81
Sago dana (sabo grains)	0.6	0.2	0.3	54	26.5	15.27
Dallia (wheat porridge)	0.9	0.3	0.7	61	20.0	7.39
Kheer or firni (rice porridge)	0.7	0.3	0.3	81	26.59	22.90
Suji kheer (suji and milk)	0.6	0.1	0.4	14	13.78	2.96
Suji halwa (suji, sugar, and oil)	1.8	0.4	0.6	46	11.32	6.50
Banana kheer (milk-based)	0.5	0.1	0.3	7	6.89	1.97
Potato kheer (milk-based)	0.6	0.1	0.3	16	15.75	4.52
Mixed diet (potato, lentils, spinach, and oil)	0.7	1.2	1.8	77	6.31	3.62

in cereal based foods are poorly bioavailable due to presence of antinutritional factors like phytic acid that reduces their intestinal absorption, resulting in high rates of iron and zinc deficiency, especially in infants, children, and women of child-bearing age (Sandstead, 2000). Several investigators reported that calcium may interfere with the absorption of iron and zinc (Hallberg et al., 1993). These elements can interact with each other, with one element inhibiting the absorption of the other (Lonnerdal, 2000). The postabsorptive interactions between calcium, iron, and zinc are yet not much known. There is need to understand the interactions of these nutrients for assessing the effects of iron or zinc supplementation on the nutritional status of the other nutrient. The information regarding micronutrient bioavailability is vital for the planning of appropriate intervention strategies to overcome the MNDs.

STRATEGIES AND SOLUTIONS TO COMBAT THE DEFICIENCY

Foods with a high content of absorbable micronutrients are considered the best means for preventing MNDs (Gibson and Ferguson, 1998; IZiNCG, 2004). In countries like Africa where supplies of such foods a^{++}re unavailable, specific preventive and healing interventions are needed (Adamson, 2003; Holmes and Toole, 2005). There are few countries including Pakistan that have adopted zinc supplementation (Fig. 5) as there national policy. Recently, it has been clearly understood that three main factors are responsible for zinc deficiency in developing world these includes, inadequate dietary consumption due to the intake of largely plant-based diets, or suboptimal breastfeeding practices; disease states that either disrupt zinc utilization or induce excessive losses; and physiological stressors that elevate zinc requirements, such as rapid growth during childhood and pregnancy (Hess et al., 2009). Three major nutrition-related strategies have been proposed to control zinc deficiency (Table 5). These include supplementation, fortification, and dietary diversification/modification. Right now there is growing consensus on the importance of multiple micronutrient interventions in populations with a high prevalence of malnutrition (Tontisirin et al., 2002; Shrimpton et al., 2005). For the formulation of multiple micronutrient food strict synergistic and antagonistic interactions between micronutrients have to be considered (Hurrell et al., 2004; Shrimpton et al., 2005).

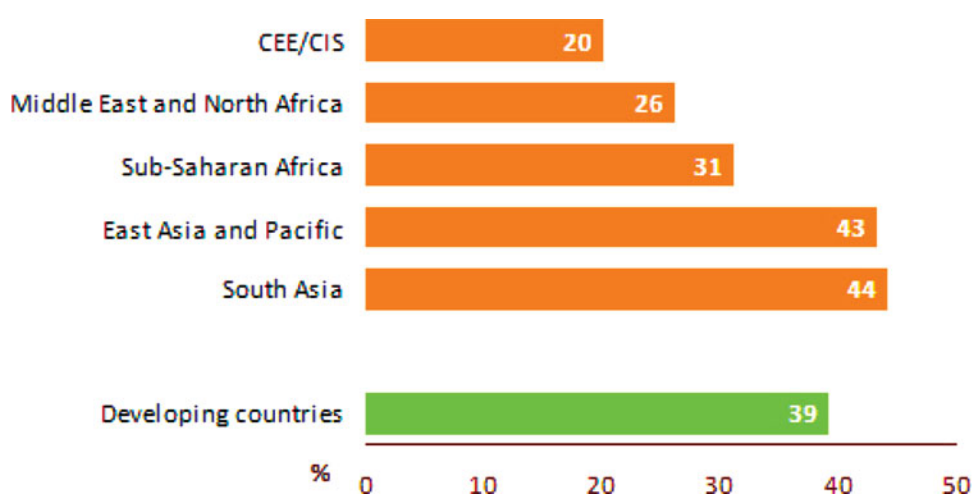

Figure 4 Percentage of infants (0–5 months) exclusively breastfed, by region (2000–2007). Source: UNICEF Global Database, 2011. (Color figure available online.)

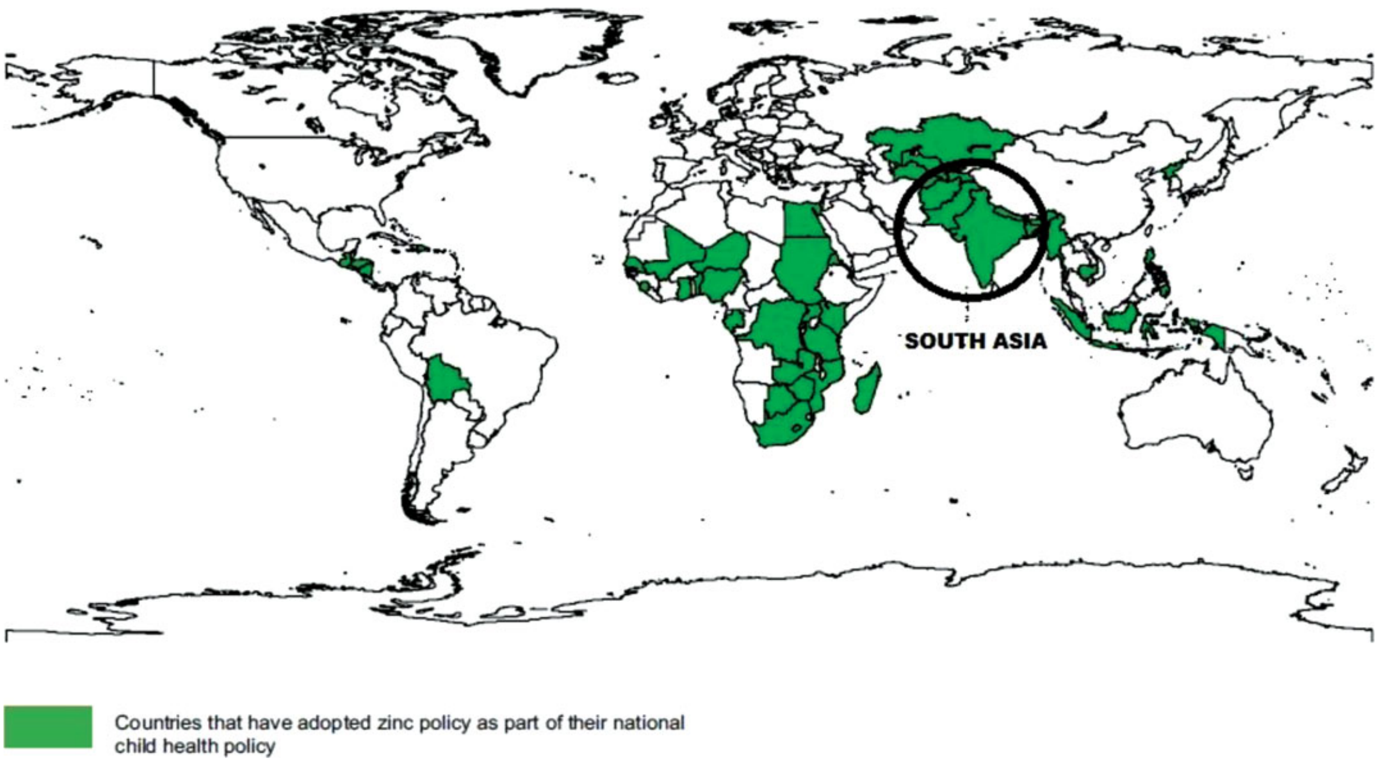

Figure 5 Countries that have adopted zinc policy on zinc supplementation (zinc task force, data from UNICEF, WHO, and USAID). (Color figure available online.)

Zinc Supplementation

Supplementation can be further divided into preventive supplementation and therapeutic supplementation for treatment of diarrhea and possibly other infections. According to WHO, supplementation refers to the provision of additional nutrients, usually in the form of some chemical or pharmaceutical compounds usually in the form of pills, capsules, and syrups, rather than in food (WHO/FAO, 2006) but these supplements are highly absorbable. Zinc supplementation has proven beneficial in the treatment of acute child diarrhea and appears to enhance linear growth (Louise and Villamor, 2010) and in fact zinc supplementation has been studied most extensively with reference to reducing diarrheal morbidity in young children. According to Zinc Investigators' Collaborative Group (IZiNCG), children with acute diarrhea supplemented with zinc, results in 15% lower probability of continuing diarrhea when compared to the controlled group (Bhutta, 2000; Scrimgeour et al., 2011) and recent meta-analysis studies supports their finding (Patro et al., 2008). Supplementation programs are particularly useful for targeting vulnerable population subgroups whose nutritional status needs to be improved within a relatively short time period. For this reason, such programs are often viewed as short-term strategies. Most of the existing experience with zinc supplementation

Table 5 Possible solutions of combating zinc deficiency in world and in Pakistan (FAO/WHO, 1998; White and Broadley, 2005; Stein et al., 2007; Bouis and Welch, 2010; Hussain et al., 2010; Scrimgeour et al., 2011)

Interventions and strategies	Coverage	Importance and economical aspects
Supplementation: include both preventive and therapeutic strategy by giving minerals as drugs in acute form.	This strategy covers from pregnancy to initial developments of children up to 5 years.	Active response and immunity development but costly.
Fortification: both single and multiple fortification method including particular element of interest (Zn and iron).	To all segments of population, but has disadvantages like limits to urban areas and disliking among people in term of color and taste.	Initial uneconomical and difficult to lunge but give valuable aspects.
Food diversification and modification: change eating habits and utilization of highly nutritious food.	Only developed societies of countries and where selection of food is available.	Economically feasible but less important only concentrated to developed world.
Biofortification: increasing the bioavailable micronutrients through plant breeding and agronomic practices.	Especially in rural area, where food modification is difficult and people reject fortification techniques.	Economically feasible and have value importance deficiency.

is derived from research trials. Issues that must be considered in the development of supplementation programs include (1) the physical and chemical forms of the zinc compound; (2) the dosage level and frequency of administration; (3) the possible inclusion of other micronutrients in the supplement; (4) the administration of supplements with or without foods; (5) the packaging and distribution system; and (6) any possible risk of toxicity.

Preventive Supplementation

Preventive zinc supplementation reduces the incidence of diarrhea by approximately 27% among young children over 12 months of age and decreases the incidence of acute lower respiratory tract infections by approximately 15%. Zinc supplementation reduces child mortality by approximately 6% (Brown and Baker, 2009). Preventive zinc supplementation also increases linear growth and weight gain of young children, hence reduced rates of stunting and underweight. The current evidence on the functional benefits of zinc is based mainly on findings from preventive zinc supplementation trials (Baqui et al., 2002; Brown et al., 2002; Brooks et al., 2005). Almost all preventive zinc intervention trials are conducted by a randomized, placebo-controlled efficacy trial design (Brown et al., 2002), and little is known about the effectiveness of preventive zinc supplementation when it is delivered under realistic program conditions. All of these trails clearly demonstrated the effective of preventive supplementation. For instance, of 12 studies that examined the effect of zinc supplementation on acute diarrhea, 11 demonstrated a reduction in diarrhea duration, with eight showing statistically significant reductions. Moreover, the published information on zinc intervention trials completed among children 6–35 months of age was derived from studies that used a single daily dose of zinc, ranging from 3 to 20 mg/day in individual studies, and mostly failed to monitor the possible adverse effects. Only one study compared daily versus weekly zinc supplementation and hardly any results are available from dose-response studies. Thus, more information is needed on optimal dosing regimens and duration of zinc supplementation. IZiNCG recommends daily intake of 3–5 mg of dietary zinc for children of ages up to 6–47 months depending upon the usual staple diet (IZiNCG, 2004). From all these frequent trails and findings in May 2004, UNICEF and WHO issued a joint statement recommending the use of zinc with oral rehydration therapy to treat diarrhea in children. Twenty milligrams of zinc are recommended for 10–14 days in children 12–59 months of age; and 10 mg of zinc for infants less than six months of age (WHO and UNICEF, 2004). It has been estimated that implementing zinc supplementation as an adjunct treatment with oral rehydration therapy to combat diarrhea, could prevent 88% of deaths attributable to diarrhea (Jones et al., 2003).

A number of studies have examined the effects of zinc on iron absorption and vice versa, using both tracer methods and biochemical and functional responses to longer term supplementation. Longer term studies suggest that each mineral reduces the magnitude of the biochemical response observed with single nutrient supplementation (Dijkhuizen et al., 2001; Berger et al., 2006), although nutritional status is still enhanced to a considerable extent despite the nutrient–nutrient interactions. Findings regarding the impact of zinc supplementation with or without iron on functional outcomes are less consistent. Simultaneous delivery of iron and zinc may undermine the growth-enhancing effect of zinc and possibly the benefits of zinc for reducing morbidity and the benefits of iron for psychomotor development. In contrast, positive effects on the incidence and duration of diarrhea in infants and young children have been found with concomitant iron and zinc supplementation compared with iron supplementation alone (Rosado et al., 1997; Baqui et al., 2002). However, studies of combined multiple micronutrient supplementation (including iron and zinc as well as other micronutrients) in Peru (Penny et al., 2004) and Bangladesh (Baqui et al., 2002) failed to detect the morbidity reduction that was observed when zinc alone was provided.

Bhutta et al. (2008) study the effect of zinc supplementation in malnourished children with persistent diarrhea in Pakistan and concluded that Supplemented children had a significant improvement in plasma zinc levels and serum alkaline phosphatase after 14 days of therapy in comparison with controls. Similarly, Fischer Walker et al. (2006) conduct randomized, placebo-controlled trial in three countries (Pakistan, India, and Ethiopia) to assess the safety and efficacy of 10 mg zinc supplementation for the treatment of acute diarrhea in infants younger than six months and they concluded that there was no significant difference of zinc supplementation in young infants for treatment of diarrhea The importance of oral rehydration solution (ORS) and continued breastfeeding for the treatment of diarrhea, should continue in young infants where zinc may not be as effective as in older children. The current WHO/UNICEF recommendations for the treatment of diarrhea suggest zinc supplementation in addition to ORS and continued feeding for all children younger than 5 years (WHO and UNICEF, 2004). Their finding suggests that WHO should consider reevaluating this policy for infants younger than six months. Yakoob et al. (2011) carried a detail review to optimize the performance of zinc supplementation in developing countries and concluded that zinc supplementation results in reduction in diarrhea and pneumonia mortality. Imdad and Bhutta (2011), used meta-analysis tool to check the effect of preventive zinc supplementation on linear growth in children especially under five years of age and they comes with a positive result that Zinc supplementation has a significant positive effect on linear growth, especially when administered alone, and this strategy should be included in national programs to reduce stunting in children <5 years of age in developing countries.

The challenges of zinc supplementation programs include product availability, coverage, training, endorsement, and treatment compliance (Scrimgeour et al., 2011). Zinc sulfate tablets have most commonly been used in supplementation programs because they are inexpensive, easy to transport and accepted by mothers and children; however, for program sustainability, local production or technology transfer is needed.

Therapeutic Supplementation

Many studies have evaluated the therapeutic effects of zinc supplementation during acute or persistent diarrhea. In studies conducted by Black (1998) on acute diarrhea, the illness duration has found to be 9–23% shorter in zinc supplemented than in controlled children, same case is for the persistent diarrhea but the results was less significant the reason behind this was less number of children participate in studies. Therapeutic zinc supplementation has been evaluated for the treatment of respiratory infections and malaria. There is insufficient and inconsistent information on the effect of zinc supplementation on the severity and duration of acute lower respiratory tract infections, and the data are inconsistent with regard to upper respiratory tract infections (Hulisz, 2004). There is little information on zinc as a component of the therapeutic regimen for tuberculosis, and there is no apparent benefit of zinc supplementation for the treatment of malaria. Dietary supplementation with zinc and other micronutrients for primary prevention of multiple MNDs that are known to result from therapies used in the treatment of gastrointestinal inflammatory disorders (Scrimgeour and Condlin, 2009). WHO and UNICEF also recommended zinc regarding the appropriate clinical management of acute diarrhea, which urges the provision of ORS and home-available fluids, breastfeeding, continued feeding of other foods, selective use of antibiotics, and the administration of zinc supplements (20 mg/day for children >12 months of age and 10 mg/day for infants) for 10–14 days with each episode of diarrhea. The significant heterogeneity of responses to zinc suggests the need to revisit the strategy of universal zinc supplementation in the treatment children with acute diarrhea in developing countries (Patel et al., 2010). Following the publication of these recommendations by WHO and UNICEF, several lower income countries have begun incorporating zinc supplementation in their therapeutic regimen for diarrhea.

According to International Zinc Nutrition Consultative Group (IZiNCG, 2004) adequate zinc nutrition is necessary for optimal child health, physical growth, and normal pregnancy outcomes. Systematic trials have found that zinc supplementation decreases rates of diarrhea and acute lower respiratory infections among young children, two of the most important causes of child mortality in lower income countries. Several studies have detected significantly reduced death rates among children who receive supplemental zinc (Brooks et al., 2005) and zinc supplements increased the linear growth and weight gain of stunted or underweight children (Brown et al., 2002).

FORTIFICATION

Food fortification is a medium- to long-term solution to alleviate specific nutrient deficiencies in a population. Its method involves the addition of measured amounts of a nutrient-rich "premix," which contains the required vitamins and minerals, to commonly eaten foods during processing. Within an integrated approach, micronutrient fortification of foods and condiments allows for an inexpensive and highly cost effective strategy to improve and protect the health and nutritional status of populations. The start-up cost for food fortification is relatively inexpensive for the food industry, and recurrent costs are rapidly passed on to the consumer. The benefits of fortification can extend over the entire life cycle of humans. It can thus be one of the most cost-effective means of overcoming micronutrient malnutrition. Although it is a fact that the first reason for fortifying foods with essential vitamins and minerals is this approach is safe and effective, the economics of food fortification has played an important role in its implementation in public policy. Food fortification is defined as "the deliberate addition of one or more nutrients to particular foods so as to increase the intake of these micronutrients and correct or prevent a demonstrated deficiency and provide a health benefit" (Haider and Bhutta, 2009; Scrimgeour et al., 2011). The WHO's dietary goal of fortification is defined as "the provision of most (97.5%) individuals in the population group(s) at greatest risk of deficiency with an adequate intake of specific micronutrients, without causing a risk of excessive intakes in these or other groups" (WHO/FAO, 2006). Food fortification most often involves the addition of nutrients to food at the point of food processing or production; however, fortification may also occur at the community or household level (Hess and Brown, 2009). The WHO distinguishes three possible approaches to food fortification: mass, targeted, and market driven fortification (WHO/FAO, 2006). Mass fortification is the addition of micronutrients to foods consumed routinely by the general population. Common mass fortification vehicles include cereal flours, vegetable oils and fats, milk, and condiments. Targeted fortification is intended to reach a specific population subgroup that have an identified risk of deficiency, such as complementary foods for young children or rations for internally displaced populations, when normal food distribution channels have been disrupted. Finally, market driven fortification is fortification of processed foods, initiated by a food manufacturers (WHO/FAO, 2006; Scrimgeour et al., 2011).

Food fortification, especially multiple micronutrient fortification, is often considered the most cost-effective approach to address deficiencies if the following conditions exist: appropriate carrier foods are available; the food industry can produce and distribute fortified carrier foods; and those subgroups identified as at risk of MND have access to adequate amounts of these foods (Gibson and Ferguson, 1998; Hess and Brown, 2009; Scrimgeour et al., 2011). Fortification may be considered a more appealing option than supplementation as it does not require the population to alter existing food beliefs and practices and therefore may result in less disruption to the health sector. Furthermore, since food fortification costs are supported by industry and the consumer, the cost burden to governments are usually low. Many countries are now recommending fortification programs as a national policy (Figure 6). Therefore,

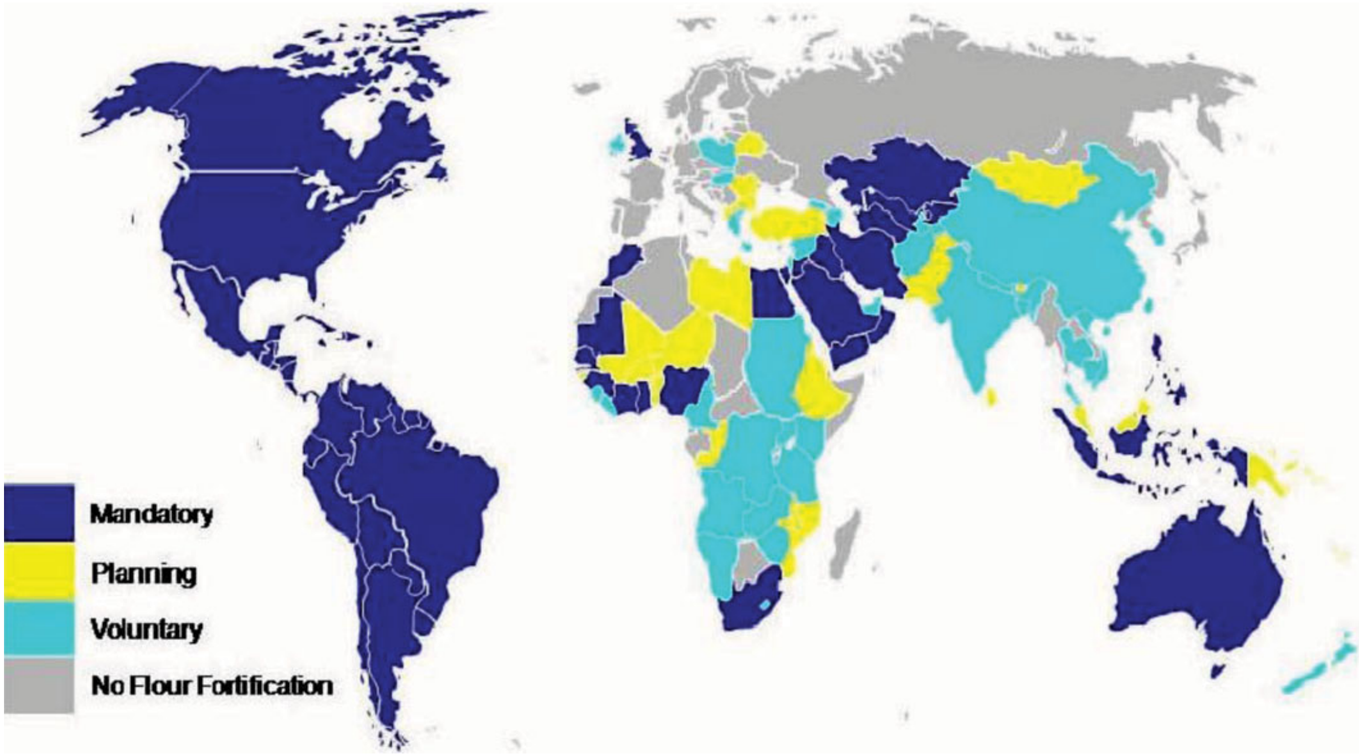

Figure 6 Fortification status in world till March, 2011 (FFI, 2011). (Color figure available online.)

fortification programs have become more common in lower income countries (Gibson and Ferguson, 1998; Hess and Brown, 2009; Scrimgeour et al., 2011). Several zinc compounds are approved for human consumption and may be used as food fortificants including the sulfate, chloride, gluconate, oxide, and stearate salts (WHO/FAO, 2006). The preferred choices are zinc oxide or zinc sulfate (Table 6), the two cheapest forms of zinc that are generally recognized as safe (GRAS) for human consumption (WHO/FAO, 2006; Hess and Brown, 2009; Scrimgeour et al., 2011). Tracer studies of foods fortified with either zinc oxide or sulfate showed that there was no difference in zinc absorption by school children or adults when either compound was used to fortify common cereal staples.

The available studies clearly show that zinc fortification can increase total daily zinc absorption, it is reasonable to say that individuals at risk of zinc deficiency who consume zinc fortified foods will have enhanced zinc status. Most absorption studies also show that adding zinc to food does not adversely affect the absorption of other minerals, like iron. Despite the known positive impact of zinc fortification on total zinc absorption, studies available regarding young children have not shown a positive effect of zinc fortified complementary foods on indicators of young children's zinc status, growth or other zinc-related functional responses.The zinc compound used should meet the purity requirements of the Food Chemicals Codex and, must have a status of GRAS. It is noticed that although a number of studies have been carried out with zinc acetate, it is not GRAS and therefore cannot be used in food fortification in the United States and as well as other counties. Zinc acetate is reported to have an offensive taste when not diluted with sugar and a high

Table 6 Common zinc salts used for fortification in different countries

Zinc compound	Common zinc salts and their properties used as fortificants				
	Status[a]	Solubility	Zn (%)	Cost (US$/kg)	Cost (US$/kg Zn
Acetate	No	Water soluble	29	5.60	19.30
Chloride	Yes	High water solubility	48	20.74	43.20
Gluconate	Yes	Water soluble	14	5.00	35.70
Oxide	Yes	Not soluble[b]	80	2.33	2.33
Stereate	Yes	Insoluble	10	—	—
Dried sulfate	Yes	Water soluble	36	3.74	10.40
Hydrated sulfate	Yes	Water soluble	23	3.15	13.70

[a]Generally recognized as safe (GRAS).
[b]Soluble in dilute acid or alkali (adopted from Ranum, 2001).

reactivity in foods. For these reasons, zinc acetate has not been used in commercial food fortification, and this lack of use has prevented it from receiving GRAS status. All of the zinc sources are white, so the color is not a problem; the potential problem is that some of the more soluble sources cause color changes in certain food ingredients, such as chocolate. Also, some zinc salts may impart undesirable flavors. For example, zinc oxide has a bitter taste, and zinc sulfate is very astringent. Zinc acetate has a slight odor of acetic acid, whereas the other salts are odorless. The most important difference between the zinc sources is their solubility, because it relates to both bioavailability and effects on food quality. Zinc oxide is not soluble in water but soluble in dilute acid. This implies that it will be inert in dry foods but that it should be available for absorption after exposure to stomach acid. Zinc acetate, zinc gluconate, and zinc sulfate are soluble in water, and zinc chloride is very soluble. Zinc oxide is the most commonly used zinc source for the fortification of cereal-based foods, followed by zinc sulfate and, to a very small extent, zinc gluconate. Zinc sulfate is specified for use in the corn-soy blend (USDA, 1998) and the wheat-soy blend produced for the US Food for Peace Program. Zinc acetate and zinc gluconate find use in dietary supplements and some weaning foods. Pakistan has launched national wheat fortification program assisted by Global Alliance for Improved Nutrition (MIH, 2011) and micronutrient initiative (MI) (MIH, 2011), it's a three year program executed by Nutrition Wing of the Ministry of Health, from this program it is estimated that 48 million (32% of Pakistan's population) get benefit. Total budget for the program is US $3.4 million (MIH, 2011).

Bioavailability of Different Zinc Salts

The bioavailability status reviewed by Davidsson (1999) gives perfect idea about the nature of different salts. There have been very few studies on zinc absorption from fortified cereals. One study on rats by Ranhotra et al. (1977) at the American Institute of Baking showed little difference in absorption of the different sources when they were added to bread. Absorption of zinc carbonate was poor, but absorption of zinc oxide was nearly as good as that of the more soluble forms. No adverse effects on bread quality were found by Ranhotra et al. (1977). In a chick feeding study (Sandoval et al., 1997) with a corn and soybean meal, the bioavailability of two commercial forms of zinc sulfate was 99% and 81%, whereas that of two sources of zinc oxide was 78% and 54%. A second experiment found a bioavailability of 94% for zinc sulfate and 74% for zinc oxide. Studies in Turkey (Saldamli et al., 1996) reported that bread fortified with zinc acetate had an acceptable quality and was effective in preventing zinc deficiency in children. It appears that zinc fortification has little detrimental effect on flour and bread quality. One study, in which levels up to 500 ppm of zinc were added as zinc chloride, even showed a beneficial effect of this addition on baking (Vadlamani and Seib, 1999). The differences in the availability of zinc from different compounds as mentioned earlier are largely a function of their solubility, which is dependent on pH, both in the food and in the stomach. In one study Henderson et al. (1995) compared the absorption of zinc from zinc acetate and zinc oxide in humans with gastric pH of low ($\leq$3) and high ($\geq$5). They concluded that absorption was higher from the acetate than from the oxide in subjects with high gastric pH (low gastric acid production), but the absorption was similar when gastric acid production was normal. Absorption of both forms of zinc was greater at low gastric pH than at high gastric pH. These results suggest that although the oxide may have sufficient bioavailability for a normal population, it might not be suitable for malnourished children whose stomach pH is higher because of reduced ability to produce stomach acid, and that therefore it should not be used in therapeutic supplementation programs.

Level of Zinc in Different Cereals

Zinc fortification of cereal flour is a safe and appropriate strategy for enhancing the zinc status of population subgroups who consume adequate amounts of fortified cereal flour (Brown et al., 2010). The levels of micronutrients added to cereals are based on restoring the levels in refined cereals back to the level contained in the whole grain product. Drake et al. (1989) demonstrated that the levels of zinc in the three main cereal staples before and after milling. They found that after milling of rice, zinc decreases from 20 to 11 ppm, in wheat 29 to 7 ppm, and in maize 18 to 7 ppm. The addition of 20 ppm zinc to white wheat flour would nearly replace the zinc lost to milling. Higher levels of zinc might be added to obtain a greater benefit, particularly when the intake of the cereal is not high. Higher zinc addition rates are often used in the special complementary foods and in branded ready-to-eat cereals. For example, 40 ppm zinc is added to the corn-soy blend and 50 ppm to the World Food Program's version of the corn-soy blend (Ranum, 1999). Even at the lower levels of 20–30 ppm of added zinc, the impact on meeting dietary requirements would be significant. At a reasonable daily intake of 100 g of cereal enriched with 20 ppm zinc, children would receive 20% of their daily zinc requirement. Such fortification levels would not present a safety hazard. At the likely upper limit of a sustained intake of 500 g of cereal per day, which would supply over 1800 kcal/day of energy, the maximum amount of zinc added to the diet would be 15 mg/day, or 100% of the adult recommended daily intake, if all cereals were fortified with 30 ppm zinc. The proper level of zinc for mass fortification programs is that which would increase the intake of zinc by the targeted individuals, without imposing a risk of excessive intake on the rest of the population. International Zinc Nutrition Consultative Group recommends a total zinc intake of no more than 40 mg/day by adults. To determine the appropriate level of fortification, it is necessary to measure or estimate the amount of the food vehicle being consumed by different segments of the population. International Zinc Nutrition Consultative Group concluded that the appropriate levels of zinc fortification of cereal staples used for mass fortification programs is generally between 30 and 70 mg Zn per kg of flour depending on the range of usual flour consumption (Brown et al., 2010). Higher levels may be desirable for foods targeted to young children.

There are several zinc compounds that are available for fortification (IZiNCG, 2004). Many compounds are listed by the USDA as GRAS, there is no consensus as to which of the GRAS compounds is most appropriate for fortification programs. Zinc sulfate and zinc oxide are the GRAS salts that are least expensive and most commonly used by the food industry. Despite theoretical considerations that suggest that zinc may be better absorbed from water soluble compounds, like zinc sulfate, several studies indicate that zinc is equally well absorbed from cereal products fortified with either zinc sulfate or zinc oxide (Brown et al., 2002).

Biofortification

This refers to the breeding of staple crops for higher levels of vitamins and minerals that are essential for human nutrition and health (Bouis, 2002); this approach contrasts with industrial fortification efforts that focus on processed food items. Biofortification involves breeding staple food crops, such as rice, wheat, maize, and pearl millet both for higher yields and higher nutrient content (Bouis, 2002; Welch and Graham, 2004; Scrimgeour et al., 2011). This method has multiple advantages, including the fact that it capitalizes on the regular daily intake of a consistent amount of food staple by all family members, and, because staple foods predominate in the diets of the poor, this strategy implicitly targets low-income households (Nestel et al., 2006; Rosado et al., 2009; Scrimgeour et al., 2011) specifically, zinc biofortification could provide both a feasible means of reaching zinc-deficient populations in relatively remote, or rural areas, and it could deliver fortified foods to people with limited access to commercially marketed fortified foods that are more readily available in urban areas (Nestel et al., 2006; Rosado et al., 2009; Scrimgeour et al., 2011). Recently, a zinc-biofortification study, conducted in Mexico (Rosado et al., 2009) they reported that absorption of zinc was greater from the zinc bio-fortified wheat than from control wheat when fed to adult women as their primary source of energy and nutrients. The results of their study confirmed that zinc absorption from the same quantities of wheat flour was greater from the zinc biofortified wheat than from wheat with a more typical zinc concentration. Though substantial quantities of zinc were lost with moderate extraction (80%), absorption of zinc from the zinc biofortified wheat remained significantly higher than that from the control wheat. Indeed, the quantity of zinc absorbed from zinc fortified 80% extracted wheat was similar to that from the 95%-extracted wheat because of the simultaneous reduction in phytate. The findings are of practical interest because it indicates that the benefits of the zinc-biofortified wheat are not lost with a moderate degree of milling. Follow-up long-term feeding studies are needed to verify the efficacy of zinc biofortified wheat.

Biofortification in Pakistan Staple Food Wheat

Wheat is the staple food of Pakistan. Wheat is consumed all over world as a major source of food. Wheat contains higher content of phytates and these hinder with absorption of Zn and iron, so biofortification is one of recommended method to over comes the problem of bioavailability. Wheat flour fortification program has been successfully implemented in Pakistan to reduce the prevalence of micronutrients deficiency. Bread wheat (*Triticum aestivum* L.) and tetraploid or durum wheat (*Triticum durum* L.) are the wheat genotypes that are grown on large scale to feed millions of people all around the world (Saldamli et al., 1996; Hussain et al., 2010). Wheat is a major source of calorie intake in central and western and South Asia (Fig 7). It is grown on very poor soils like alkaline calcareous soils of semi arid regions. These anthropogenic and climatic factors lead to decreased availability of soil Zn (IZA, 2009). Wheat is highly susceptible to Zn deficiency in such conditions and produces low grain yield with low levels of grain Zn concentration. Wheat grains contain about 25–30 μg Zn per gram dry weight, while for a measurable impact of Zn biofortification on human health, desired wheat grain Zn concentration should be >50 μg per gram of dry weight (Cakmak et al., 1998). There is a possibility to fortify wheat flour for micronutrients as adopted by Government of Pakistan for Iron and recently MI launch different programs to fortify food with Zn salts. Genetic engineering, breeding, and agronomic approaches are important tools of biofortification (Zimmermann and Hurrell, 2002; Cakmak, 2008). Increased grain Zn concentration is an important quality parameter of food. The biofortification approach relies on crop management and improvement strategies for higher grain Zn. The absorption of dietary Zn is mainly limited by high phytate in our food. Phytate:Zinc molar ratio >15 reduces Zn absorbance to only 15% (White and Broadley, 2005; Brown et al., 2001).

Zinc Wheat for Pakistan

Scientists are trying to develop zinc wheat for the Pakistan especially in Punjab province where per capita wheat consumption averages about 350 g per day. The people in Pakistan especially in villages much prefer to consume whole wheat rather wheat flour in refined form. Farmers replicates seeds only from fewer varieties that gives them good yield, hence only few modern varieties are found among them, these must be replaced periodically with modern varieties, as they lose their resistance to new evolving strains of disease. The main strategy of HarvestPlus is to incorporate high zinc and iron traits into new wheat varieties that are resistant to new strains of yellow and stem rust. HarvestPlus estimates, under an optimistic scenario, that high zinc

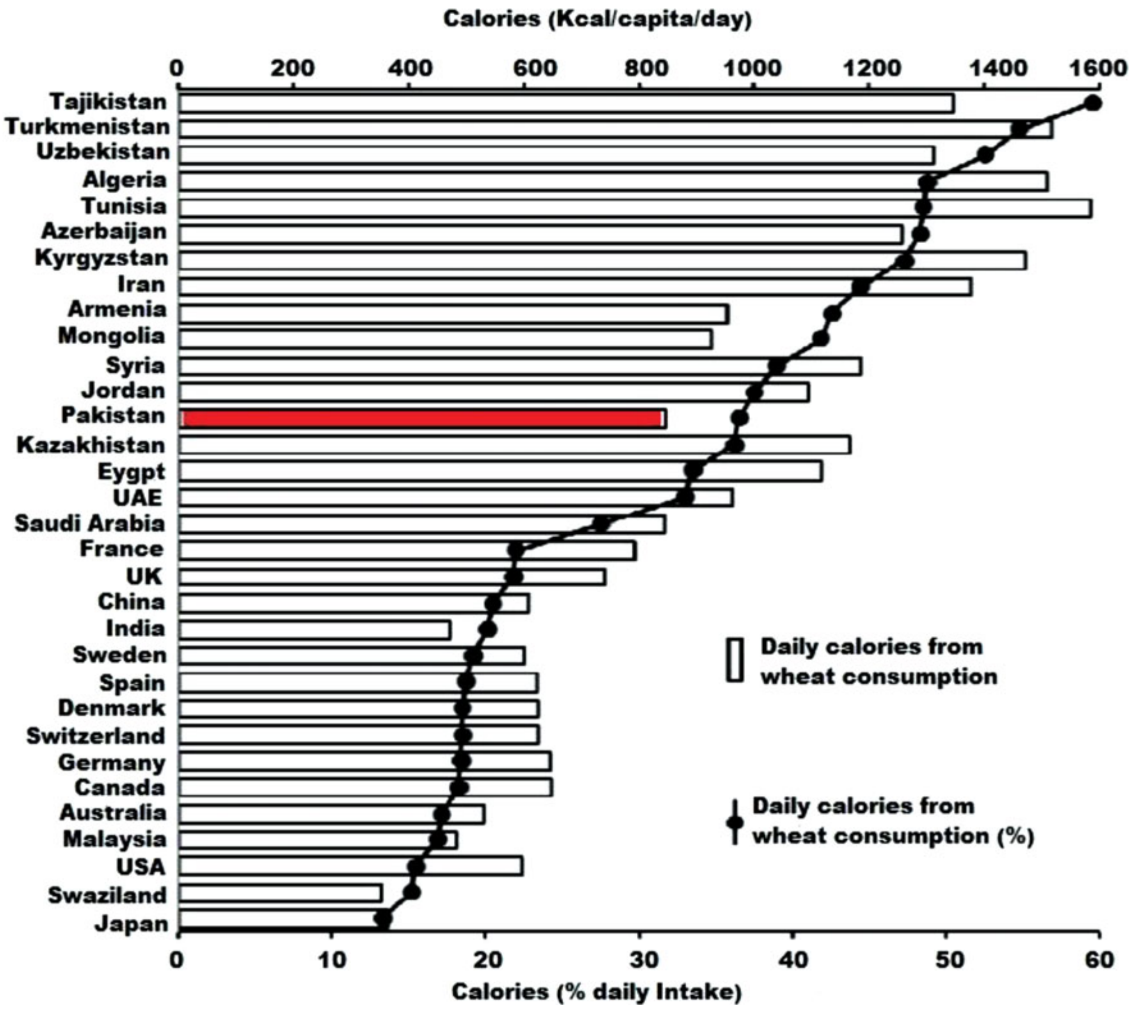

Figure 7 Daily calorie intake of wheat in different countries of world (modified from Hussian et al., 2010). (Color figure available online.)

wheat varieties would be consumed by "100 million Pakistanis" 10 years after release (HarvestPlus, 2011).

DIETARY DIVERSIFICATION/ MODIFICATION

To make food with a higher content of absorbable zinc and better bioavailability is the main aim of dietary diversification (Gibson and Anderson, 2009) and it is not an easy task. In terms of dietary diversification, three main strategies are adopted all around the world with certain modification. These strategies include complementary food enhancement or enrichment, agricultural interventions, and behavioral change (Gibson and Anderson, 2009). All of these techniques must be applied in Pakistan in order to elevate Zn deficiency. The main focus of agricultural interventions is to increase productivity of local crops that are utilized as staple food; like wheat, rice, maize, sorghum, and millet. During agricultural intervention main attention will be paid upon macro and micronutrient status. Many researchers have proven that higher intake of zinc are positively correlated with higher intakes of iron and protein (Galal et al., 1987). Agricultural interventions in Pakistan include research on development of new varieties of wheat breed with higher concentration of Zinc. These new techniques are ongoing with cooperation of HarvestPlus group (HarvestPlus, 2011). Intervention of new varieties that are lower in phytate content (Khan et al., 2007) and have higher bioavailability is also on it way and Pakistan Agricultural Research Board has funded 27.288 million Rupees for development of wheat varieties having higher zinc and iron content (Baig, 2011). Similarly, by modification of agronomic practices like utilization of Zinc fertilizers is another intervention (Kanwal et al., 2010). Other interventions include increased utilization of leafy vegetables and consuming higher vitamin A content foods (Gibson and Anderson, 2009). It is also recommended to increase utilization of animal's foods (meat and fish) as regular part of diet beside milk and vegetables because it increases the intake bioavailable zinc especially for infants and school-age children. Recent studies have proven that there are some indigenous fish species in Cambodia and Bangladesh that are rich sources of Iron, vitamin A and Zinc (Roos et al., 2003). Many scientists have concluded that both short-term measures (supplementation and fortification) and long-term solutions (dietary diversification or modification and biofortification) can be used to alleviate zinc deficiency in developing countries especially Asia and Africa (Gibson, 2006).

Dietary diversification or modification includes some technological perspectives at lower level and changing diet patterns (Gibson and Anderson, 2009). Both of these are prime important in developing countries where diet are basically from plant-based and consumption of animal-source foods, such as meat, poultry, and fish, is limited because of economic, cultural, and religious constraints. As a result, the zinc content of low income countries diets is low and the efficiency of absorption is limited. Dietary inadequacy is probably the primary cause of zinc deficiency (Gibson and Anderson, 2009). Promotion of house based livestock husbandry, aquaculture, and production of zinc-rich food besides leafy vegetables can increase zinc content of diet. Technological perspectives include reduction of phytates in diet at household level by simple techniques like germination, microbial fermentation, and soaking to activate phytase, which is present naturally in cereals and legumes (Gibson et al., 2006). Similarly, use of ascorbic acid containing fruits to destroy antinutritional factors like thiaminases and disruption of carotenoid-protein complexes is also recommended (Gibson et al., 2006).

This combination of two dietary strategies suggested by Gibson and Anderson (2009) that involving increased consumption of animal-source foods and phytate reduction is considered as the best to enhance both the content and bioavailability of zinc in the diets of rural households in low income countries (Gibson, 2006). Utilization of animal foods in combination of vegetables have the added advantage of simultaneously improving the content and bioavailability of iron, zinc, calcium, and essential vitamins like B12 and A, and as well as enhancing protein quality and better digestibility (Gibson et al., 2003).

To increase the zinc content of plant-based materials, several strategies can be utilized. These include art of plant breeding, the use of zinc fertilizers, and genetic modification techniques like marker assisted technology. All of these methods are promising, but research is needed to evaluate their economic, environmental, and health effects. Promoting programs of exclusive breast feeding up to six months of age is also considered as zinc intervention programs. Complementary feeding programs should be implemented in a better way with diversity of nutrients and consideration of their positive and negative impacts. These interventions if properly implemented would result in increase uptake of zinc leading towards a better society with improve nutrient status and positive development of a developing country.

CONCLUSION

It is common saying, "health people make a healthy and progressive country." Pakistan is still a developing country, and it is mandatory for Government to provide safe and nutritious food to 185 million people, so to make Pakistan a healthy and developed country. Zn and Iron are limiting micronutrient in all segments of population. This is not only common for Pakistan millions of people around world is unable to achieve target goals in terms of nutrition. Pakistan has agriculture based economy. Fortification and biofortification are best recommended method to solve this hidden hunger. Zinc supplementation must be incorporated as national vaccination program, if to achieve millennium target goals. But it remains a question mark on policy maker and Government?

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