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Review

Micronutrients as therapeutic tools in the management of sickle cell disease, malaria and diabetes

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The Global use of micronutrients in health care delivery has taken center stage due to the realization of their importance in disease management. Sickle cell disease, malaria and diabetes are among the diseases plaguing a good population of the developing world and the cost implication for their management is very high. Sickle cell disease and malaria have anemia as a common factor and immunological disturbances are also prevalent in these disease conditions. Free radicals are generated in sickle cell disease, malaria and diabetes so a balance between minerals and antioxidants is imperative to maintain membrane integrity and function. Protection of red cell membranes from free radical-mediated oxidative stress is crucial to their management. Minerals such as copper, iron, chromium, magnesium, selenium and vanadium as well as vitamins like A, C, E, folate and the B group have been found to relieve oxidative stress associated with them. Micronutrients and their importance in the management of sickle cell disease, malaria and diabetes is reviewed here, with emphasis on the need to harness the natural resources abundant in our environment.

Key words: Sickle cell disease, Malaria, diabetes, micronutrients, anemia oxidative stress, immune system.

INTRODUCTION

Agriculture provides the entire nutrient requirement to sustain life on earth. The farming systems of developing world cannot meet the nutritional needs of their people. Therefore, it is important to establish a relationship between agriculture, nutrition and health to find sustainable solutions to nutrient malnutrition (Welch and Graham, 2005).

Micronutrients consist of vitamins and minerals required by the body in small quantities for the normal function of cellular metabolic processes. They usually function as essential cofactors in the numerous enzyme catalyzed reactions and their absence can result in impairment of metabolic functions which can lead to serious disease conditions. Currently, attention is focused on dietary supplements as being beneficial in coronary heart disease, cancer, osteoporosis and other chronic and degenerative diseases such as diabetes, Parkinson's and Alzmeimer's (Hypponen, 2004; Mandel, 2005).

Sickle cell disease, malaria and diabetes are common diseases which plague our communities in Africa and deserve cooperation from both medical practitioners and scientists in related areas to identify rational and sustainable strategies to manage these conditions effectively. Sickle cell is a heritable disease for which no cure has yet been found. Very often in our midst, we sadly experience the tremendous suffering and helplessness of parents managing children who have sickle cell disease (SCD). Children with SCD are characteristically thin, stunted in growth, pale because of chronic hemolysis and cell death, poor fat muscle and bone mass. These characteristics are associated with increased energy demand. The red blood cell (RBC) membrane's integrity is maintained by its hydration. If the membrane becomes dehydrated, this impacts on its deformity which may lead to sickling. When the cells are

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sickled, they clog the small blood vessels so that the tissues are deprived of oxygen
and other nutrients, this leads to oxidative stress and derangement of tissue functions. Anemia is caused by fragile red cell membranes which induce premature destruction of red blood cell and sickle cell crises may be caused by blood vessel occlusion triggered by membrane deformation (Ohnishi and Ogunmola, 1999; Ohnishi et al., 2000) . It is pertinent to note that after so many years since the discovery that the sickle cell hemoglobin had abnormal eletrophoretic mobility, no substantial research work has been undertaken to understand the mechanisms of the disease (Bunn, 1997).

Presently the healthcare cost in the management of patients with sickle cell disease is disproportionately high compared with the number of people afflicted by the disease. The group most affected by this high cost is the common people in our localities who belong to the low socio-economic class. Therefore, the use of herbal mixtures and supplements has been on the increase in the management of sickle cell disease (Ajayi et al., 1993; Ballas , 2000; Wambebe et al., 2001).

It is a known fact that Malaria is the most important parasitic disease infecting people in vast areas of Africa and beyond (Greenwood et al., 2005). The causative agent and the mode of transmission are clearly understood. The devastating effects of malaria is reflected in the estimates suggesting that it directly causes about one million deaths per year or 3000 deaths per day, most of these deaths occur in African children (Greenwood et al., 2005). Recently, an initiative such as Roll Back Malaria Partnership scheme has come on board to check the increasing afflictions due to Malaria. In spite of the fact that this is a laudable programme, it is not cost effective for the rural communities who are supposed to be the important beneficiaries of the scheme. Malaria is a re- emerging disease due to drug resistance which can be as a result of gene mutations caused by the abuse of the over-the-counter drugs, compliance failure, fake and adulterated products. A common important feature of malaria is severe anemia that causes death in areas with intense malaria transmission. Currently modern pharmaceuticals are too expensive in areas where malaria is endemic therefore the use of herbal remedies is popular.

Diabetes is a complex non communicable disease characterized by elevated level of glucose in the blood and urine. Secretion of glucose in urine occurs when the blood glucose level exceeds the kidney threshold. Many factors contribute to the manifestations of clinical features described as diabetes. These include hormonal influences, genetic and many kinds of underlying molecular defects as well as components of dietary and environmental origin. It is classified as Type I or Type II depending on whether it is insulin dependent or non-insulin dependent. Type I is known as insulin-dependent diabetes (IDDM). People who suffer from this type of diabetes require regular injection of insulin to maintain life and limit the development of complications. Type II is non-insulin dependent diabetes (NIDDM). This subclass is heterogenous, with genetic, nutritional and environmental factors contributing to the deterioration of carbohydrate tolerance. The loss of water and glucose which occur in diabetes leads to many metabolic changes such as fat and protein breakdown as well as the consequent generation of ketone bodies. But these do not constitute the focus of our discussion in this review and will not be considered further.

We are concerned by the fact that diabetes is quietly taking its toll on many individuals among our populace, yet it does not seem to attract any significant attention as is the case with malaria or HIV/AIDS or even the sickle cell disease. We are alarmed by the number of people who approach us with inquiries about the use of natural products to take care of their diabetic problems. That has informed us to include this topic in this discussion.

Each of the three diseases has its unique cause or origin. Malaria is of parasitic origin, sickle cell disease is genetic, while diabetes originates from both genetic and metabolic sources as already discussed. In spite of this, they all, in their respective clinical presentations point to some common consequences –anemia which is common to the sickle cell disease and malaria, generation of free radicals in excess of what obtains under normal physiological conditions and weakening of the immune defense mechanism. In addition, the metabolic interplay that accompany the manifestation of these clinical features, result in the depletion of certain nutrient and micronutrients needed in the respective metabolic processes. There is no doubt that nutritional status influences susceptibility and immunity to various infectious and non-infectious diseases.

In this review, we wish to look at recent developments in the management of sickle cell disease, malaria and diabetes using micronutrients. We are interested in micronutrients because of the experiences from our research activities with natural products. We are convinced that with enlightenment, the debilitating effects of these aliments can be comfortably managed in the ordinary home setting. We are aware that herbs and medicinal plants are a reservoir of these essential and beneficial nutrient components. Our objectives are:

a. To identify micronutrients that have been found essential in the respective disease conditions and examine the extent to which they have been useful in the management of each case.
b. To explore the metabolic functions they carry out, which alleviate the applicable disease state.
c. Gather information and document sources of these micronutrients for the benefit of the generality of our society as a means of pointing out the need for more research into this important area that has received little attention, at least, in the sub-Saharan African region.

SICKLE CELL DISEASE (SCD)

Many metabolic changes which occur in SCD that lead to anemia include sickling, generation of reactive oxygen species and the general decrease in the rate of physical development. Anemia is a life threathening feature in SCD. There is increased turnover of hemopoietic cells due to chronic hemolysis and cell death leading to tremendous red marrow expansion. These conditions lead to hyper-metabolic rate and increases in nutrient and energy demand (Malik, 1999). Nutrient deficiency, red cell dehydration, cell fragility which induce premature destruction of red blood cells and chronic hemolysis lead to anemia.

Use of micronutrients in the management of anemia in SCD

Maintaining the membrane integrity is the bottom line in the control of anemia in SCD. Disruption of membrane integrity arises from fragility, dehydration as well as increased production of reactive oxygen species. Chronic hemolysis lead to loss of hemoglobin. These metabolic changes lead to depletion of essential nutrients and micronutrients required for proper cell function.

Some minerals and vitamins have been found beneficial in the control of anemia under this condition. These include iron (Fe), copper (Cu), zinc (Zn) and folate (Prasad, 1999). Prasad et al. (1975) first reported zinc deficiency in adult patients with sickle cell disease. Iron is very important in the synthesis of hemoglobin and Cu and Zn play very important roles in Fe metabolism (Prasad, 1999). The biological importance of iron in mammals is well known. Therefore its importance in this situation of loss of hemoglobin cannot be over emphasized considering its role in oxygen transport as well as in many metalloenzymes involved in oxidative phosphorylation.

Copper is known to be essential in the proper functioning of different metalloenzymes which include ceruloplasmin involved in iron metabolism. Deficiency of copper is known to cause anemia. The mechanism of copper deficiency-induced anemia is not understood (Das, 1990). Previous studies suggest that the copper-containing enzyme, ceruloplasmin, may have specific role, probably related to its function in mobilization of stored iron in the liver which makes iron available for hemoglobin synthesis (Das, 1990). However, it has been observed that in copper deficiency-induced anemia, in spite of elevated iron level in the liver, the rate of hemoglobin synthesis remains significantly reduced (Das, 1990).

Like copper, the mechanism through which zinc exerts its effect in correcting anemia in SCD is not understood, but it is known that the proteins making up the cytoskeleton of cell membranes acquire some abnormal configurations and often get irreversibly damaged. Zinc prevents the formation of such irreversibly damaged sickle cells (Das, 1990). Furthermore, it has been proposed that the role of zinc in the management of sickle cell anemia centers on its calcium antagonism. Zinc is known to inhibit the activity of calmodulin which activates the calcium-ATPase that controls the calcium pump system of the erythrocytes. During sickling, there is an influx of calcium into the erythrocytes and this occurs, probably, due to the fact that the calmodulin is so over-activated that the membrane is destroyed. It is suggested, therefore, that during zinc therapy, its anti-calcium action, (through its effect on calmodulin) produces anti-sickling effect (Das, 1990).

Sickling and free radical generation in SCD

The erythrocyte from individuals with SCD are fewer in number than normal and are abnormal. When hemoglobin from sickle cells is deoxygenated, it becomes insoluble and forms polymers that aggregate into tubular fibers. The insoluble fibers are responsible for the deformed sickle shape of the erythrocytes. These block the blood capillaries causing severe pain and interference with organ function. Also the red blood cell membrane integrity is maintained by its hydration, but in SCD the cells are dehydrated and this impacts on its deformability which may lead to sickling. Red cells generate super oxide species (which are also generally generated under normal physiological conditions) but which are drastically increased in SCD. Unstable hemoglobin produced under this condition generates free radicals which are more unstable and further induce RBC hemolysis (Chan, 1999).

Micronutients in the control of sickling and reactive oxygen generation in SCD

The sickle erythrocytes are fragile and dehydrated. They require a delicate balance of minerals and antioxidants to maintain hydration and membrane integrity (Malik, 1999). It has been shown that Magnesium (Mg) is effective in reducing not only the painful episode in SCD but also affects the hydration of RBC. Brugnara (1999) has reported that K-Cl cotransport is a major determinant in the dehydration of erythrocytes in SCD. Reduced erythrocyte-magnesium content with normal serum Mg is observed as a common feature of HbSS in sickle cell disease. When the internal Mg of the erythrocytes is increased, the activity of K-Cl cotransport is markedly diminished. Therefore, blockage of this pathway by intracellular Mg could result in decreased dehydration and sickling *in vivo* (Brugnara, 1999). Among the many important functions of Mg is its involvement, along with calcium, in the organization of membranes. Both cations

are known to act as bridges between the neighbouring carboxylate groups in lipoproteins and such bridges stiffen the cell membranes (Das, 1990).

The generation of reactive oxygen species which is a steady state cellular event in normal respiring cells, is exacerbated in sickle cell disease as in many other diseases. Uncontrolled production of reactive oxygen often leads to damage of cellular macromolecules such as lipids, proteins and DNA as well as other antioxidant molecules (Chan, 1999). Protection of red cell membranes from free radical-mediated oxidative stress is crucial to the successful management of the sickle cell crisis. Certain minerals, copper, iron, magnesium selenium as well as some antioxidants and vitamins, have been found to effectively relieve the oxidative stress that prevails in SCD. The vitamins include vitamins C, E, folate, vitamin B12 and B6 (Nalta et al., 1980; Whethers, 1999; Sies et al., 2005). Other nutrients include tryptophan, lipoic acid and carotenoids (Chan, 1999). Ohnishi and Ohnishi (2001) proposed that a cocktail of antioxidants would be effective in alleviating the incidence and severity of crisis in sickle cell patients.

In sickle cell anemia, these micronutrients are deficient. Some of them act as cofactors for the enzyme systems involved in reactive oxygen removal. For example, selenium is a prosthetic group of a metalloenzyme, the glutathione peroxidase which functions in the protection of hemoglobin. Copper, iron and magnesium have been discussed earlier in terms of their roles in hemoglobin synthesis. Besides, copper is a prosthetic group in ascorbate oxidase which is involved in the oxidation of ascorbic acid-an antioxidant, ceruloplasmin involved in iron metabolism as well as superoxide dismutase. Some animal studies have indicated that the limiting feature of zinc is associated with the post-translational change in plasma membrane proteins. Red cells from zinc-deficient rats showed increased osmotic fragility associated with decreased plasma membrane sulfhydryl concentration and this is readily reversed by dietary zinc supplementation (O' Dell, 2000). Further discussions on zinc supplementation in sickle cell disease will come up subsequently.

General physical development and immune system function are diminished in SCD

The diminished growth deficits in children with homozygous sickle cell disease, including low weight, reduced height velocity for age, delayed skeletal and sexual maturation and reduced fat deposits are consistent with suboptimal nutrition (Singhal, 1999). Factors that would contribute to these conditions include metabolic demands of an expanded bone marrow as well as high energy expenditure and a relatively low energy intake. According to Singhal (1999), the resting metabolic rate appears to be 16-20% greater in SS adolescents than in control subjects. Poor food availability (especially in developing countries) or appetite depression associated with a chronic low grade inflammatory process could, therefore, produce a relative energy deficiency.

Micronutrients in the improvement of physical development and immune system in SCD

Zinc is known as an important nutrient for growth and development. Its effects are evident in children with sickle cell disease, where it affects growth, sexual maturation and immune function (Zemel et al., 2002). A deficiency of zinc in patients with sickle cell disease results in growth retardation (dwarfism), hypogonadism in males, rough skin, poor appetite, mental lethargy and recurrent infections. Interleukin-2 activity is tremendously decreased if Zn is deficient. The addition of Zn will increase the production of interleukin-2. The amount of interleukin-1B, a cytotoxic cytokinine, increases if there is a deficiency in zinc (Prasad, 1999). Zinc serves as coenzyme in very many enzymes which include transcriptases, some pyrimidine nucleotide dehydrogenases, DNA polymerase and plays many fundamental roles in cell replication, gene expression and in the metabolism of nucleic acids and proteins. Zinc is also essential in the spermatogenic cycle and at the stage of maturation of spermatids to form spermatozoa (Das, 1990).

Chromium is another mineral that has been found beneficial in the management of sickle cell disease. The involvement of chromium in SCD is not clearly defined but it is known that it potentiates insulin action. It has been proposed that chromium acts as a cofactor in the initial reaction of insulin with the receptor sites of insulin-sensitive cell membrane (Das, 1990). If the effect of chromium is associated with insulin action, it is probable that its beneficial effect might be as a result of its involvement in carbohydrate metabolism which is a source of energy. The same is true of manganese (Mg) which is known to play a fundamental role in the synthesis of glycoproteins, specially involved in bone formation. It is also known to be a component of pyruvate carboxylase and acts as a cofactor in the respiratory enzymes. These metabolic processes lead to energy production which is very much in demand in the sickle cell disease. Further discussions on these micronutrients will continue as we examine the other disease conditions that feature in this review.

MALARIA

In the past few years, malaria has attracted more attention with the establishment of several new initiatives such as the Roll Back Malaria Partnership, partly

because of increasing recognition that the malaria situation in-Saharan Africa has deteriorated due to many reasons which include political instability, poverty and poor infrastructure in the development of efficient health services. This situation is aggravated by the fact that malaria and HIV interact in several ways but drug resistance poses the greatest problem (Greenwood et al., 2005). Malaria deaths are estimated at 1.5 to 2.7 million a year, most of which are children under five years and pregnant women (WHO, 1998). 90% of these deaths occur in sub-Saharan Africa (Young et al., 2000).

Micronutrients and Malaria management

Zinc, vitamins A, E, carotenoids, vitamins B, C and folic acid have been reported to have modulatory effects on the pathogenesis of malaria. These micronutrients have been found to be deficient in acute *Plasmodium falciparum* infection and we shall consider their roles subsequently. Malaria and sickle cell disease originate from different causes but they share some common clinical presentations which include anemia, impaired growth and immune function as well as generation of reactive oxygen species. As we have done in the preceding discussions on sickle cell disease, we shall examine the use of micronutrients in the control of these metabolic changes associated with malaria.

Iron and vitamin A in malaria-induced anemia

It is well established that malaria causes anemia (Nwanyanwu et al., 1996). According to young et al. (2000), the consensus statement on the relationship between iron and malaria is that a concurrent implementation of iron supplementation and malaria control activities is the ideal (INACG, 1999). Some studies have shown that oral iron therapy enhanced haematological recovery of patients with falciparum malaria treated with sulphadoxine-primethamine (SP), it also tended to prolong their parasitemia (Young et al., 2000). Another report indicates that malaria infection seriously worsens iron status and satisfactory improvement cannot be achieved by iron supplementation unless the underlying malaria is treated (Gera and Sachdev, 2002; ACC/SCN, 1997). Also low serum iron levels inhibit replication of the malaria parasite and some earlier studies have shown an increase in malaria episodes after iron deficiency has been treated (Masawe et al., 1974). This seems to be a pointer to the fact that the relationship between iron supplementation and malaria is not yet understood. Nonetheless, it has been reported that vitamin A supplementation combined with iron supplementation, is more effective in reducing anemia than iron supplementation alone (Angeles -Agdeppa,1997; Young et al., 2000; Crawley, 2003) and periodic high doses of vitamin A alone can improve iron status of a population (Bloem et al, 1989; Bloem et al, 1990; Suharno et al., 1993).

Vitamins A, C and zinc in the control of impaired growth and immune function in malaria

Vitamin A is necessary for normal immune function. Its deficiency is characterized by widespread immunological effects, including pathological alterations in mucosal surfaces, impaired antibody responses, changes in lymphocyte populations and altered T - and B-cell function, comprised function of neutrophils, macrophages and natural killer (NK) cells, altered immune responses and altered antibody responses (Semba, 1994, 1999).

There is a widespread recognition of vitamin A deficiency and malaria as two widely distributed public health problems in the developing world. In sub-Saharan Africa, vitamin A deficiency and malaria coexist, each exacerbating the health consequencies of the other (Young et al., 2000). Though there is belief that there is association between vitamin A and malaria but the specific effects of vitamin A on malaria morbidity and mortality are not understood. Some studies have shown that vitamin A potentiates host resistance to malaria (Serghides and Kain, 2002). These workers observed that 9-cis-retinoic acid, a metabolite of vitamin A increased parasite clearance and reduced proinflammatory cytokinine responses to malaria parasite infection. Therefore, immunological effects can account for, at least, part of the mechanism by which vitamin A impacts positively on malaria management.

The interaction between zinc and malaria is less well understood. In children with acute malaria infection, plasma zinc concentration has been found to be very low and inversely related to the acute phase protein, C-reactive protein (CRP) (Duggen et al., 2005; Muller et al., 2001). Rural African children who consume cereal or tuber-based diets which are low in animal products and high in phytic acid are likely to be vulnerable to zinc deficiency (Wise, 1995; Hambidge, 1997). Children appear to be more vulnerable to low zinc status, presumably, due to their high zinc requirements for growth and development (Gibson, 1994). Duggen et al. (2005) were of the opinion that in children whose age, diet, and/or nutritional status place at risk of zinc deficiency, those with low zinc levels should be supplemented with oral zinc and should be followed with clinical and/or biochemical response. They further suggested that when available, plasma zinc concentrations should be evaluated with concurrent measures of the acute phase response. Like vitamin A, zinc is known to be an immune modulating agent and is essential for normal immune function. It is known that zinc is important for cell-mediated immunity through neutrophils, macrophages and NK cells, and it affects the development of acquired immunity and antibody production, particularly immunoglobulin G (Shankar and Prasad,

1998).

Vitamin C has been suggested to play a significant role in the pathogenesis of acute falciparum infection (Garba et al., 2002). These researchers reported that vitamin C enhanced the humoral and cellular immune response to acute falciparum infection in male and female adults. Their work provides evidence that adult with falciparum malaria mobilize their tissue store of ascorbate as part of their response to infection, hence the increase in the ascorbate level observed in these patients. Apparently, this observation is not consistent with association of malaria infection with depressed immunity in children where decreased plasma ascorbate level was observed. This was attributed to the immature nature of the immune system in children who must be provided with doses of ascorbic acid supplements to protect them from oxidant compounds released from the red cell rapture during falciparum malaria infection.

Vitamin C has been shown in many studies to modulate a wide variety of cellular functions which include bone formation, folic acid metabolism, regulation of the respiratory cycle in the mitochondria and microsomes, enhancement of absorption of iron, formation and maturation of red blood cells and immune response mechanisms (Garba et al., 2002).

Vitamins A, E and the carotenoids in the management of oxidative stress in malaria

These micronutrients are well known to have antioxidant effects but not much work has been done in relation to their interaction with falciparum malaria infection. However, one study carried out in children with acute malaria infection in Kampala, Uganda, showed that the plasma level of these vitamins were depressed at enrollment and increased by day 7 (Metzger et al., 2001). The study showed that higher plasma lycopene concentrations at enrollment were associated with clearance of parasitemia between enrollment and day 3. Their study suggested that the children with acute malaria have depressed concentrations of antioxidants.

DIABETES

The classical approach to diabetic treatment depends on the cause of the disease, which could be due to insulin deficiency or dietary imbalance. If the cause is insulin deficiency, cure is via insulin therapy. This is very expensive for poor diabetics, many of whom dwell in rural communities in the developing countries. They often resort to the use of natural herbs which have not been scientifically evaluated. There is no doubt that our forests are replete with herbs with hypoglycemic properties but there is little that can be said about them scientifically, which is where the problem of the diabetics of the low socio-economic class lies. A casual survey of the incidence of diabetes in our communities revealed that it is widespread among the aging group. The question arises then as to the reason for its prevalence among the aged. The need arises then for research into the metabolic changes in glucose metabolism among the aging group. It is this curiousity that prompted this review, at least, as a starting point in looking into this problem.

Micronutrients can regulate metabolism and gene expression and influence the development and progression of many chronic diseases of which diabetes is one (O' Connell, 2001). Some of the micronutrients that have been associated with beneficial effects in diabetes include chromium, vanadium, nicotinamide, magnesium, vitamins E and B. Metabolic changes that occur in diabetes are complex and, if not properly controlled, are further complicated by secondary effects such as neuropathy, nephropathy, dyslipidemia cardiopathy and retinopathy, to mention but a few. But basically it is presented with glucose intolerance or insulin resistance which leads to hypoglycemia. Also diabetes -induced oxidative stress prevails. Subsequently, we shall examine how some of the identified micronutrients have influenced the management of these conditions.

Chromium, vanadium and magnesium in the management of hypoglycemia in diabetes

Chromium is required for normal glucose metabolism (O'Connell, 2001; Das, 1990, Anderson, 1998). According to Das (1990), chromium functions as a glucose tolerance factor but occurs in foods in varying different forms of which it is not yet clear in which form it is most effective. However, a particular form containing an organic moiety not fully characterized has been considered as the "glucose tolerance factor" (GTF). This particular form is much more effective than any other salt. Mammal are reported to have limited ability to synthesize GTF, therefore, it is important to investigate the occurrence of this form in foods instead of considering the total chromium content. For example, Das (1990) reported that chromium in beer is four times more effective in regulating glucose metabolism in rats than the chromium in lettuce, spinach or egg yolk.

Experimental chromium deficiency leads to impaired glucose intolerance which improves upon the addition of chromium to the diet (O'Connell, 2001). Numerous studies have shown that chromium improves the glycemic state in different types of diabetes as well as various aspects of dyslipidemia (O'Connell, 2001). The severe impairment in glucose metabolism of children in many cases has been dramatically improved by giving oral dose of chromium chloride. In many cases, tissue chromium level has been found to fall with increasing age in both sexes, and in women, with each pregnancy and

simultaneously their ability to metabolize sugar decreases and “maturity- onset- diabetes” develops. It is reported that in some of these cases, these conditions were improved by raising their chromium intake from 50 to 200 μg/day (Das, 1990).

Though it is well established that chromium has strong influence on glucose metabolism, its mechanism of action is not yet clearly understood. However, it is known to potentiate insulin action. According to O’Connell (2001), no chromium-containing enzyme has been discovered, and the biologically active form of chromium is still uncertain. But the actions of chromium have been attributed to an increase in the number of insulin receptors (Anderson, 1998), increased binding of insulin to the insulin receptor and increased activation of the insulin receptor in the presence of insulin (Mertz, 1998).

Vanadium

Vanadium is not known to be an essential nutrient in man but is essential to ascidans (“sea squirts”) which can concentrate the element a million-fold from the sea water (Das, 1990). In animal models, vanadium has been shown to facilitate glucose uptake and metabolism, facilitate lipid and amino acid metabolism, improve thyroid function, enhance insulin sensitivity, and negatively affect bone and tooth decay in high doses. In humans, pharmacological doses alter lipid and glucose metabolism by enhancing glucose oxidation, glycogen synthesis, and hepatic glucose output. Vanadium acts primarily as an insulinmimetic agent, although enhanced insulin activity and increased insulin sensitivity have also been reported (O’Connell, 2001; Poucheret et al., 1998; Cam et al., 2000).

Vanadium deficiency has not been documented in humans (Sarubin, 2000; Harland, 1994), but its deficiency has been reported to induce growth impairment in chicks and rats and it is specially required for the growth of feathers in chicks. Its deficiency induces impaired reproductive activity. In the absence of vanadium, tooth and bone metabolism are also affected (Das, 1990).

The chemical nature of vanadium is similar to that of phosphorus and this seems to influence its biochemical actions (O’Connell, 2001). It may act as a phosphate analogue and has been shown to alter the rate of activity of a number of adenosine triphosphatases, phosphatases and phosphotransferases (Poucheret et al., 1998).

Magnesium

Magnesium is essential to all living organisms (Das, 1990), and is an essential cofactor for more than 300 enzymes (O’Connell, 2001). It is essential for all energy-dependent transport systems, glycolysis, oxidative energy metabolism, biosynthetic reactions, normal bone metabolism, neuromuscular activity, electrolyte balance and cell membrane stabilization (De Valk, 1999). Magnesium is one of the more common micronutrient deficiencies in diabetes. Decreased magnesium levels and increased urinary magnesium losses have been documented in both Type I and Type II diabetic patients. Low dietary magnesium intake has been associated with increased incidence of Type II diabetes in some but not all studies (O’Connell, 2001). Magnesium deficiency has been associated with hypertention, insulin resistance, glucose intolerance, dyslipidemia, increased platelet aggregation, cardiovascular disease, complications of diabetes, and complications of pregnancy. But it is not clear whether poor magnesium status plays a casual role in these disorders or simply associated with them (O’Connell, 2001).

The mechanism by which magnesium affects insulin resistance, hypertention, and cardiovascular disease are unknown. However, the widespread use of magnesium in normal metabolism of macronutrients, cellular transport systems, intracellular signaling systems, platelet aggregation, vascular smooth muscle tone and contractibility, electrolyte homeostasis, and phosphorylation and dephosphorylation reactions suggests that these effects are multifactorial (O’Connell, 2001).

Nicotinamide helps to preserve B-cell function in diabetics

Nicotinamide is one of the two forms of vitamin B3 (niacin), the other form is nicotinic acid. The active forms are nicotinamide adenine dinucleotide (NAD) and the phosphate derivative (NADP). These coenzymes are essential for the function of hundreds of enzymes and normal carbohydrate, lipid and protein metabolism. Pharmacological doses of nicotinamide are being studied for their potential benefit in the prevention and treatment of diabetes (O’Connell). Animal studies suggest that nicotinamide acts by protecting pancreatic beta cells from autoimmune destruction by maintaining intracellular NAD levels and inhibiting the enzyme poly(ADP- ribose) polymerase (PARP), an enzyme involved in DNA repair. Excessive PARP induction results in depletion of cytoplasmic NAD levels, induction of immunoregulatory genes, and cellular apoptosis (programmed cell death). Nicotinamide may additionally act as a weak antioxidant of nitric oxide radicals (O’Connell, 2001).

The effects of nicotinamide supplementation have been studied in several trials focusing on the development and progression of Type I diabetes and one small trial in Type II diabetes but results have been inconsistent (O’Connell, 2001). Nicotinamide appears to be most effective in newly diagnosed diabetes and in subjects with positive islet cell antibodies but not diabetes. People who develop diabetes after puberty appear to be more responsive to

nicotinamide treatment. Evidence emerging from different studies have offered more support for the idea that nicotinamide helps to preserve beta cell function (O'Connell, 2001).

Vitamins E and B in the management of diabetes

Vitamin E is an essential fat-soluble vitamin which functions primarily as an antioxidant. Low levels of vitamin E are associated with increased incidence of diabetes (Salonen et al., 1995). Some studies suggest that people with diabetes have decreased levels of antioxidants (Polidori et al., 2000). People with diabetes may have greater antioxidant requirement because of increased free radical production with hyperglycemia. Increased levels of oxidative stress markers have been documented in people with diabetes and improvement in glycemic control decreases markers of oxidative stress as does vitamin E supplementation (O'Connell, 2001).
Vitamin E acts to neutralize free radical species produced during normal cellular metabolism, protecting cellular membranes and lipoproteins (LDL in particular) from oxidative damage. It also interacts with water-soluble antioxidants such as glutathione (O'Connell, 2001; Shils et al., 1999; Sarubin, 2000). It may play a role in preventing and treating common complications of diabetes, such as nephropathy, and neuropathy, by decreasing protein glycation, lipid oxidation, and inhibition of platelet adhesion and aggregation (O'Connell, 2001). O'Connel (2001) has documented reports from various clinical trials which investigated the effects of vitamin E on different aspects of diabetes which include diabetes prevention, insulin sensitivity, glycemic control, protein glycation and microvascular complications of diabetes.

The B vitamins

The vitamins, pyridoxine (vitamin B6), cobalamin (vitamin B12) and folate have been investigated for their effects on diabetic patients. Folate refers to a family of naturally occurring compounds. Folic acid is the synthetic form of the vitamin. Folate is an essential coenzyme for reactions involving the transfer of one carbon units in amino acid and nucleic acid synthesis. B6 acts as an essential cofactor for hundreds of enzymes and plays a role in glucose, lipid, amino acid metabolism and neurotransmitter synthesis. The active coenzyme form of the vitamin, pyridoxal 5' phosphate, in muscle tissue is closely associated with glycogen phosphorylase. The amino acid, homocysteine, can be metabolized through transulfuration or remethylation. In the transulfuration pathway, homocysteine and serine combine to form cystathionine. This reaction is catalyzed by cystathione beta-synthetase and requires B6 as a coenzyme. In the remethylation pathway, vitamin B12 acts as an essential cofactor in a reaction in which homosysteine is converted to methionine by the methionine synthetase enzyme using folate as a methyl donor (O'Connell, 2001; Shils et al., 1999; Welch and Loscalizo, 1998).

The three vitamins mentioned above are involved in homocysteine metabolism. Hyperhomocysteinemia (Hhcys) is positively correlated with coronary heart disease, cerebrovascular disease, and peripheral vascular disease (Welch and Losccalizo, 1998). It is not known whether the presence of Hhcys precedes or follows vascular disease (O'Connell, 2001). A recent prospective, population-based study found that Hhcys is a risk factor for overall mortality in Type II diabetic patients independent of other known risk factors. Hhcys was a twofold stronger risk factor for death in diabetic patients as compared to non-diabetic patients (O'Connell, 2001). For each 5 μmol/l increment of homocysteine, risk of mortality rose by 17% in non- diabetic and 60% in diabetic subjects (Hoogeveen et al., 2000).

In patients with diabetes and hyperhomocyteinemia, increased folate intake decreases and in some cases normalizes serum homocysteine levels (Aarsand and Carlsen, 1998; Baliga et al., 2000). In people with diabetes, there is an inverse relationship between serum folate and homocysteine levels in some but not all cases. the same is true for serum B12 and B6 is inversely correlated with post-methionine-load homocysteine levels (Busysschaert et al., 2000; Salardi et al., 2000; Stabler et al., 1999). O'Connell, (2001) advises that all patients with diabetes should be encouraged to consume adequate quantities of dietary folate, B12 and B6 and to modify factors such as alcohol intake and smoking, which increase homocysteine levels.

DIETARY SOURCES OF MICRONUTRIENTS

There is no doubt that in sub-Saharan Africa, ignorance, poverty and other social handicaps like political instability dispose a large population of our people to chronic energy deficiency and micronutrient malnutrition. This review is an attempt to stress the need to enlighten our people and to research into the invaluable benefits derivable in the micronutrients abundantly available in our natural resources.

In the developed world, there is dramatic increase in the use of vitamins, minerals and other complementary nutrition-based therapies in disease management. O'Connell (2001) writes "Many health-care providers are also beginning to explore the use of these therapies in their practices. For those of us who work in conventional health care settings, it is a new venture. But for many of our patients who have been self-medicating with supplements, it is not….initially, the nutrition community focused on the roles micronutrients play in preventing deficiency diseases such as scurvy, pellagra, and rickets. As our understanding of nutritional science grew, it

Table 1. Dietary sources of micronutrients.

Micronutrients	Sources	Remarks
Zinc	Beans, beef, brewer's yeast, chicken heart, egg yolk, fish, herring, lamb, legumes, liver, meats, milk, oysters, peanuts, pork, poultry, pumpkin, seeds, seafood, soybeans, sunflower seeds, turkey, heat bran, wheat germ, whole grains, and yeast.	Zinc is an animal protein compound, red meat has the highest concentration, but boiled chick pea has the highest in vegetable protein foods (Stallings, 1999). Too much zinc causes anemia, suppressed immune system and impaired copper absorption (Anderson, 1988). Shellfish, particularly, oysters, are rich in zinc and copper. But more importantly, the minerals in shellfish are readily absorbable. The body uses them easily and efficiently. Zinc deficiency can occur in populations that consume staple diets rich in phytate which binds zinc tightly.
Copper	Crab, boiled beef, dry roasted cashews, sunflower seeds, whole wheat flour, banana, avocados, bakers yeast, beans, black pepper, garlic, grapes, green leafy vegetables, oysters, peanuts, seafood, lentils, liver, lobster, mushrooms, nuts, shrimp, soybeans, walnuts, wheat bran, and wheat germ.	Too much copper produces damage to the brain, nervous system and kidneys.
Chromium	Apple peel, banana, beer, brewer's yeast, brown sugar, butter, chicken, corn, dairy products, dried beans, eggs, fish liver, meat, mushrooms, oysters, potatoes with skin, seafood, shellfish, whole grains.	Chromium is poorly absorbed (5%) bioavailability. Chromium occurs in foods to widely varying extent in different forms. The form containing an organic moiety, not yet fully characterized is known as the glucose tolerance factor (GTF), is the best absorbed.
Magnesium	Almonds, barley, brewer's yeast, cocoa, cod, cotton seed, garlic, green leafy vegetables, herring, lima beans, meat, mackerel, millet, nuts, oats, peaches, peanut butter, peas, peanuts, seafood, shrimp, snails, soybeans, sunflower seeds, wheat, wheat bran, wheat germ, and whole grains.	
Iron	Almonds, avocados, beans, brewer's yeast, broccoli, cashews, cocoa, dates, eggs, egg yolk, green leafy vegetables, spinach, heart, kidneys, legumes, lentils, liver, oysters, peaches, pears, potatoes, poultry, prunes, pumpkins, raisins, rice, seaweed, sesame seeds, soybeans, sunflower seeds, tongue, walnuts wheat bran, wheat germ, whole grains.	The absorption of iron is influenced by what we eat with it. Vitamin C will double the amount of iron absorbed in the body. Including foods rich in vitamin C will increase iron intake.

Table 1. Contd.

Manganese	Avocados, barley, beans, brown rice, chestnuts, cloves, coffee, egg yolk, ginger, grapevine, green vegetables, hazelnuts, legumes, nuts, oatmeal, peanuts, peas, pineapples, rice bran, rice polish, seaweed, seeds, spinach, walnuts, wheat bran, wheat germ, wholsse grain cereals.	It is essential for the utilization of choline, thiamine, biotin and vitamins C and E.
Selenium	Barley, beer, butter, brewer's yeast, broccoli, brown rice, cabbage, celery, cereals, chicken, cider vinegar, cinnamon, clams, crab, cucumbers, diary products, eggs, garlic, grains, green leafy vegetables, hibiscus, kidneys, lamb, liver, lobster, meats, milk, mushrooms, nutmeg, nuts, oats, onions, seafood, tuna, turnips, wheat bran, wheat germ, and wheat grains.	
Vitamin E	Vegetable oils, margarines, wheat germ, seeds, and nuts.	Vitamin E, has been shown to have anticoagulant properties. Those using medications and herbal supplements known to decrease blood clotting, e.g., warfarin, aspirin, garlic, and ginseng may be at risk for bleeding with high dose supplements (doses>800IU).
Thiamine	Whole grain, cereals, pock products, brewer's yeast, green peas, and other legumes, beef kidney, beef liver and sunflower seeds. Niacin liver, lean meats, poultry, peanut butter, beef kidney, legumes and salmon.	To maintain adequate levels of any mineral or vitamin, it is best to consume a wide variety of food in reasonable amounts from all four food groups.
Pyridoxin (B6)	Whole grain cereals, liver, beef kidney, white meat (chicken and fish), potatoes, avocados, bananas, egg yolk, and sunflower seeds.	
Cyanocobalamine(B12)	Meat, liver, kidney, milk, Swiss cheese, salmon, and eggs.	
Fotate	Wheat germ, beef, chicken heart, beef kidney, brewer's yeast, mushrooms, oranges, and orange juice, broccoli, lima beans, bananas, strawberries, sunflower seeds, cantaloupe, and some legumes.	

became clear that nutrients act in far broader ways. We now know that micro nutrients can regulate metabolism and gene expression and influence the development and progression of many chronic diseases. Eventually, we may be able to tailor nutritional recommendations to individual's unique genetic make up, thus increasing the potential benefit and positive outcomes of medical nutrition therapy".

This long quotation emphasizes our point in this review. In the traditional society, many of the diseases that

ravage a considerable percentage of our population were unknown because our ancients lived on natural resources. Here is a story of a sickle cell woman, in her sixties; we came across in the course of our research on natural products. She is not one of those who could not make it to 30 years of age. We asked her about her secret and she showed us some little plants in her garden which she has been using, particularly, a bean plant which is very familiar in the villages but which many families with sickle cell children do not know about. The plant, *Cajanus cajan*, has been reported by Iwu (1993) to have anti- sickling properties and a lot of research work is going on towards it development as an anti-sickling agent.

Today, new thinking, even in the remotest villages, about catching on with "civilization", as well as rural urban migration have led to change in lifestyle and taste. The trend is to eat refined rice, spaghetti, noodles etc, in place of our local foodstuff packed with health-enhancing micronutrients. We do not have to look hard in communities to notice the difference in the health disposition of the children of the enlightened families who understand the health implications of unbalanced diets and the children of the poor and ignorant who do not have the same understanding. The result in the later case is undernutrition/malnutrition and the consequent depression of immunity which disposes them to avoidable diseases. Common sources of the micronutrients discussed in this review are listed in Table 1.

FUTURE PERSPECTIVE

There is need to intensify research to define the status of micronutrients not only in the diseases discussed in this review but also in other diseases prevalent in sub-Saharan Africa. There is no doubt that a lot of questions remain to be answered with regards to the relationship between the micronutrients and the respective diseases as well as among the micronutrients themselves. Some diseases manifest in old age raising various questions:

1. Is it micronutrient deficiency occurring in old age that causes metabolic changes which lead to a particular disease situation or is it the disease that leads to depletion of the micronutrients which further aggravate the situation?
2. How would the different micronutrients interact with each other, with drugs and other nutrients?

Furthermore, the micronutrient distribution in the foods in the different localities may vary from place to place because of soil differences. There is need to document this information because what is available now come mainly from the developed countries of the world where basic research into topics that are taken for granted are pursued with all seriousness.

Finally, we hope that our medical practitioners will agree with their counterparts in the developed world, and embrace the concept that these essential nutrient components are abundant in our natural products and have a lot to offer in the healthcare delivery system.

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