NFI BULLETIN

Bulletin of the Nutrition Foundation of India

Volume 31 Number 4 October 2010

New Areas of Nutrition Research

B.Sesikeran, K.Polasa, A.Vajreswari, M.Raghunath, K.M.Nair, R.Hemalatha, K.V.Radhakrishna, Sudip Ghosh, V.Sudarshan Rao, S.Vazir, Fernandez, S., P.Raghu

Introduction

India is a vast and varied subcontinent; with 2.4% of global landmass it is supporting over one-sixth of the world's population. As a developing country with high population density, India's planners recognized that optimal nutrition and health are prerequisites for human development. Article 47 of the Constitution of India states that, "the State shall regard raising the level of nutrition and standard of living of its people and improvement in public health among it's primary duties". Green revolution ensured that the country became self sufficient in food production and public distribution system (PDS) led to improvement in access to food. Clinical and community research played an important role in identifying interventions to improve nutritional status of vulnerable segments of population. Based on these research studies multisectoral health and nutrition interventions were initiated; as a result of all these, there has been substantial reduction in severe grades of undernutrition in children and some improvement in the nutritional status of all the segments of population. However, mild and moderate degrees of undernutrition, micronutrient deficiencies and food safety related problems continue to be common. Rapid advances in technology during the last two decades have enabled scientists to undertake basic research studies to unravel the factors responsible for common nutritional disorders and assist evolution of appropriate interventions. Some of the major advances in research tools to explore nutrition and food safety are reviewed in this article.

Research on micronutrient deficiencies

The National Nutrition Policy (1993), had identified iron deficiency anaemia, iodine deficiency disorders and vitamin A deficiency among children as major preventable health problems in India and suggested strategies to control them[1]. Micronutrient survey conducted by the National Nutrition Monitoring Bureau (NNMB) has shown that there has not been any reduction in nutritional anaemia[2]. The 11th Five Year Plan and the draft National Health Research Policy (2010)[4] have identified micronutrient deficiencies as major public health problems[3]. The following are some of the new areas that can be taken up specifically to address micronutrient deficiency in our country.

Biomarkers of micronutrient status:

Currently, either the direct measurement of nutrient levels or of their related proteins in blood, plasma or urine, are being used as biomarkers of sub-clinical nutritional deficiencies. A biomarker that reflects changes in micronutrient status can facilitate a better understanding of the relationships between the dietary intake of the micronutrient, its status and function. Also, the focus should shift from the measurement of single nutrient status to identification of complex and dynamic biomarker patterns. This will enable to instill greater realism into efforts aimed at answering questions relating to aetiology, progression of disease states, and the effects of micronutrient status on a range of functional outcomes[5,6].

The development of field-friendly methods of biological sample collection and simultaneous measurement of multiple biomarkers for multiple micronutrients (e.g. in a single dried blood sample) are major technological challenges. There is no biomarker for zinc nutriture. It is extremely important to have a sound understanding of the basic mechanisms and expression of the two families of mammalian zinc transporters, ZnT and ZIP. A very interesting function of ZIP4 lies in the response of this protein to inflammation. Hypoferrimia and hypozincemia are among the classical changes observed across species during the acute phase response[7].

Hepcidin, as a regulator of iron trafficking:

The existing evidence suggests that hepcidin is a negative regulator of iron transport in the small intestine; it effectively reduces the intestinal iron absorption and increases the macrophage retention, thereby leading to reduced availability of systemic iron[8]. Hepcidin has also been demonstrated to

CONTENTS

bind to several transitional metal ions including zinc. But the mechanisms and physiological significance of such interactions, particularly the interaction of hepcidin with ferroportin (FPN-1), need to be investigated further[9].

Updating of RDA requires establishing accurate methods of measuring absorption:

Absorption of micronutrients is influenced by food composition and physiological status. This entails generating population-specific absorption values for establishing RDA. Absorption studies using radioisotopic techniques are very useful in obtaining absorption values of nutrients but there are hazards associated with the use of these techniques. Moreover, the use of isotopes in vulnerable segments of the population (children, adolescent girls, pregnant and lactating and non-lactating women) is discouraged. Recently, radioisotopes have been replaced by stable isotopes for these techniques, because the latter have a number of advantages. Multiple stable isotopes of one mineral or isotopes of multiple minerals can be administered simultaneously or sequentially[10].

Nanotechnology is an emerging field and there is scope for development and delivery of micronutrients as nano-nutrients[11]. With advancements in the understanding of absorption, action and interaction at cellular level, it is possible to target micronutrients to the intracellular compartments or to the site of action. There are several avenues of investigation that need to be explored, for example, the solubility of iron and its inability to effectively escape the duodenal pH for presentation at the absorptive surface, transferrin receptor(s), ferritin as a nano particle, and interactions with transporters and phytates and other minerals. Nanodetectors can be tested in ELISA systems for developing field-friendly methods of detection of micronutrient status. In epidemiological surveys such sensors will be of great help.

Evidence-based micronutrient supplementation models for replication:

Coexistence of multiple micronutrient deficiencies has been reported from developing countries, and these deficiencies appear to work complementarily. Either the absence or overabundance of any micronutrient may result in deficiencies in one or more micronutrients[12,13]. Therefore, there is a need to evolve evidence-based multiple micronutrient supplementation (fortification) models that can be replicated throughout the country[14]. Malabsorption of micronutrients due to disorders of the stomach and intestine can cause anaemia. *Helicobacter pylori* seems to be involved in the causation of anaemia, and this area needs further research[15,16].

Biofortification:

The long-term goal of controlling micronutrient deficiency is possible to achieve only through a substantial improvement in dietary quality and diversification of diets. Breeding staple foods that are dense in minerals and vitamins provide a low-cost, sustainable strategy for reducing levels of micronutrient deficiency. Biofortification is an emerging area, and is accomplished through a process of selection of new varieties that are rich in micronutrients through conventional plant breeding and marker-assisted breeding techniques[17].

Innovative strategies - single vs multiple:

Although strong evidence exists for the benefits of food fortification in alleviating micronutrient deficiencies, designing appropriate intervention strategies requires further basic and applied research. A food-based strategy is a promising public nutrition approach. However, it requires a holistic environment, if it is to be effective[18].

Food safety

Salt reduction:
The consumption of excess of sodium has been cited as a primary cause of hypertension and cardiovascular diseases. Hence, the WHO as well as the National Institute of Nutrition have issued dietary guidelines, advising people to reduce their salt intake. However, reduction of salt in processed foods may pose food safety concerns[19].

Newer methods of food safety assessment:

Targeted compositional analysis is today a key component of the food safety assessment paradigm in which known nutrients, anti-nutrients, toxicants, allergens, and other molecules of potential biological importance to humans or animals are quantitatively analyzed. This allows safety assessors to compare the composition and safety of one food with those of closely related counterparts. Newer technologies measure many analytes, some of which are unidentified, but the analysis often sacrifices one or more of the characteristics of validated analytical methods currently used for food analysis. Data bases that would allow the safety assessor to interpret differences are not currently available. The regulation of transgenic crops is far more rigorous than is justified, since they present no new risks compared with traditional breeding methods, and are more precisely defined and better understood than their non-transgenic equivalents.[20].

Food, nutrition, obesity, physical activity and cellular processes linked to cancer

The process of a normal cell turning into a malignant/cancer cell involves several steps. With the advent of reliable assessment tools of DNA polymorphisms (genomics), DNA expression (epigenomics), RNA transcription (transcriptomics), changes in protein structure (proteomics) and metabolite evaluation (metabolomics), it can be demonstrated that nutrients play a major role at every stage of development of a cancer cell.

Nutrigenetics: nutrient-gene interactions / lipidomics/genomics / proteomics.

Nutrient-gene interactions form the basis for genome-wide association studies to unravel the new source of genetic variability associated with the risk of chronic degenerative disease, especially that of cardiovascular disease (CVD). It is difficult to establish gene-nutrient interaction for clinical end points of myocardial infarction (MI) or atherosclerosis. However, recently, AA-derived pro-inflammatory 5-lipo-oxygenase (LO) pathways have been implicated in the risk of atherosclerosis in humans. In a US study and in a population study in Costa Rica, a 5-LO promoter polymorphism was shown to be associated with atherosclerotic lesions and interactions with fatty acids[21]. Many studies have also established the existence of fatty acid gene interactions with PPAR variants, especially PPAR which regulates glucose and lipid metabolism. N-3 PUFAs are also known for their hypotriglyceridemic effect, and the individual variability in this response is also related to genetic variability[22-24].

CD36, a fatty acid transporter belonging to the scavenger receptor class B1 family is known to interact with a variety of ligands including long-chain fatty acids and oxidized and modified LDL particles, and is also implicated in atherosclerotic risk and insulin resistance.

The apoE genotype is another widely studied SNP in relation to risk of CVD. There are three variants of apoE (e2,e3, e4). ApoE4 carriers exhibit 40-50% higher risk of CVD; this has been attributed to moderately elevated plasma cholesterol and triglyceride levels. Further, the role of macrophage-derived apoE in vascular health and atherogenesis is also recognized[25]. Decrease in fat intake may serve as a means of reducing the increased CVD risk associated with an apoE4 genotype.

Scavenger receptor class B type I in cholesterol homeostasis and fatty acid metabolism.

SR-B1 is a multiligand receptor with multiple physiological functions[26]. It was the first molecularly well characterised HDL receptor that was discovered to have physiological significance. It is involved in the regulation of plasma HDL-C levels through reverse cholesterol transport (RCT), a process by which cholesterol is removed from peripheral cells and transported via plasma lipoproteins (such as HDL) into the liver for either recycling (VLDL formation) or excretion from the body in bile (bile acid synthesis and biliary secretion). SR-BI is predominantly expressed in macrophage foam cells, hepatocytes and steroidogenic organs such as the adrenals and gonads. In macrophages, it promotes cholesterol efflux to mature HDL. In the liver, SR-BI is involved in selective HDL-cholesterol uptake, and its capability to mediate the hepatic uptake and biliary secretion of HDL cholesterol leads to increased reverse cholesterol transport, thereby suppressing atherosclerosis[26]. CD36 (human homologue to murine fatty acid translocase, FAT) is a close relative of hSR-BI. CD36 is involved in the regulation of the overall metabolic activity of mitochondria in adipocytes[27,28]. There have been very few studies focusing on the regulation of SR-BI. Fatty acids, polyunsaturated fats, cholesterol, estradiol, vitamin E and vitamin A have also been shown to play important roles in bringing about differential expression of the SR-B1 receptor[29] possibly affecting CD36 expression due to their sequence-homology. Thus, dietary interventions involving these transporters are particularly important.

Emerging areas of research in diabetes: endoplasmic reticulum (ER) stress

The endoplasmic reticulum (ER) is the prime site of folding and maturation of trans-membrane, secretary and ER-resident proteins. Proteins must be correctly folded and assembled prior to their transit to the intracellular organelles or cell surfaces, or secretion. Under normal physiological conditions, a quality control mechanism conformationally sorts out the unfolded proteins from the folded ones and retains the unfolded protein in the ER while deploying the correctly folded protein out of its lumen[30]. The misfolded proteins are then removed from the ER to the cytosol where they are degraded by proteasomes[31]. However, when the assembly line in the ER is overwhelmed under certain pathophysioloical conditions, an emergency mechanism becomes activated as a survival strategy. To cope with the ER stress, the cells evoke an 'unfolded protein response' (UPR) pathway, an integrated signaling pathway that transmits information about the folding status in the ER lumen to the cytoplasm and the nucleus[32]. Various studies in the past decade have indicated that obesity is associated with chronic inflammatory response, characterized by the production of various pro-inflammatory cytokines and the activation of inflammatory signalling pathways[33]. An interesting feature of the inflammatory response in obesity is that it appears to be triggered by and resides predominantly within the adipose tissue[34]. Work carried out by Ozcan *et al.*[35], attributed ER stress to the development of insulin resistance during obesity.

Folic acid and B12: obesity and risk of chronic disease

Besides the known problem of neural tube defects associated with folic acid deficiency, current research is also focused on the role of folic acid and vitamin B_{12} in the causation of obesity and chronic diseases. In addition to the earlier recognized role of folic acid and vitamin B_{12} in erythropoiesis, Yajnik *et al.* have also demonstrated the presence of hyperhomocysteinemia (which is a recognized cardiovascular risk factor) in these subjects. Yajnik *et al.* have demonstrated that women who eat green leafy vegetables (GLVs) at least every alternate day gave birth to infants that were almost 200 g heavier than the infants of women who never ate GLVs, and that their odds ratio (OR) for low birth weight was 0.43. Higher intake of GLV at 28 wk of gestation was also associated with higher maternal fasting plasma insulin and triglyceride concentrations and lower albumin concentrations, all of which were related to increase in the size of the neonate[36].

Vitamin D status, birth weight, immune status and infections

Recent studies have concentrated on the extra-skeletal benefits of vitamin D. A study carried out in Lucknow has shown vitamin D deficiency to be widely prevalent. In this study 84% of women (84.3% of urban and 83.6% of rural women) and 95.7% of neonates were found to have hypovitaminosis D[37]. A recently concluded study carried out at NIN has shown a significant positive association between maternal and cord blood vitamin D levels (19.9 and 11.3 ng/ml, respectively). Only 10 newborns out of 98 had vitamin D levels of >20ng/ml in cord blood. When analyzed on the basis of vitamin D levels (>20 vs <20) in cord blood, the group with vitamin D levels >20 ng/ml had a significantly higher mean birth weight relative to the other group (2895 gms vs 2636 gms, p=<0.05). Vitamin D is known to be a powerful immune system modulator, and also has antimicrobial properties. A study carried out in India demonstrated that vitamin D levels are inversely associated with lower respiratory tract infection (LRTI) and wheezing in children[38]. Vitamin D receptors are present in a wide variety of tissues right from early placenta, but their role is not well understood. Some studies have demonstrated the association of vitamin D with insulin sensitivity/diabetes, lipid profile, hypertension, certain cancers, chronic diseases and all-cause mortality[39]. Future research should focus on functional parameters. Well designed studies should address all these issues, with special reference to micronutrients such as folic acid, vitamin B_{12}, vitamin D, iron and zinc.

Improving infant and young childfeeding practices

Findings from a recent study indicate that formative research as a precursor to the development of intervention content and delivery of messages can achieve behavioural change as regards infant and young child feeding practices[40]. The intervention messages in this study were based on international recommendations, but were also culturally appropriate and sensitive to local practices. The results demonstrated improved dietary intake, growth and development among the study groups that received interventions as compared to the controls who received the standard ICDS inputs.

Adolescent diets and behaviour-prevention of chronic diseases

The "obesogenic" environment is the most logical starting point for preventive measures. Modern-day urban consumerism is directed largely at the adolescent market, making healthy choices difficult for them. At the same time, exercise patterns have changed and considerable time is spent sitting, at school, are in front of the television or computer at home. Unhealthy dietary habits such as excessive intake of saturated fats, salt, sugary soft drinks and ready-to-eat junk foods, and inadequate intake of fibre, contribute to the increase in prevalence of overweight and obesity. Physical inactivity and smoking/ tobacco chewing have been found to be independent predictors of CHD and stroke in later life. Studies are currently underway, aimed at behaviour change among children and adolescents in schools. These involve the co-operation of the teachers so as to provide a facilitating environment and stimulate interest in physical activities. A study is also being carried out to investigate the adverse effects of soft drink consumption on cognitive ability[41].

Health and nutrition in the elderly

This field of research has been among the most neglected. With advances in medical intervention techniques, larger segments of the Indian population are elderly. The nutritional needs of the elderly require special attention, not only in terms of quantity but also of quality and texture, in view of the reduced ability of elderly persons to chew and digest food. Depression and anxiety are common among the elderly, and lack of attention from their families can aggravate the situation, often leading to reduced intake of food and impacting their quality of life and their health. This area of research is still in the planning stage.

Omega-3 fatty acids - DHA

Although, it is well established that omega-3 fatty acids are important for optimal brain function during infancy, data regarding the persistence of these neuro-developmental effects into childhood and/or adulthood are just beginning to emerge in the literature. Studies using functional MRI (fMRI) brain scans have just begun to explore whether and how dietary omega-3s especially DHA affect activity in regions of the human brain. The fMRI scans taken during attention tests showed that DHA groups showed significant activity increases in dorso-lateral prefrontal cortex which is associated with working memory[42]. DHA has recently been found to be efficacious in improving cognition and memory even in middle-aged persons and, in fact, throughout the lifespan. The Alzheimer's Association, in its 2009 International Conference in Vienna[43], reported some benefits of DHA.

Epigenetics

Epigenetics may be defined as the study of heritable changes in gene expression that operate outside of DNA. It is a mechanism by which genes are switched on or off. The epigenome is controlled by nutritional status, stress, infection and inflammation. The epigenetic mechanisms basically include DNA methylation and histone modifications (acylation, acetylation and deacetylation of histone proteins)[44]. DNA methylation is covalent addition of CH_3 to 5th position of cytosine. The reaction is catalysed by DNA methyl transferases. DNA methylation is confined largely to CpG dinucleotides in CpG islands. CpG islands are regions of CG content (500 bp) specially found in promoter regions of genes. Of the CpG sites in human DNA, 70-80% are methylated. Methylation is also believed to be associated with gene silencing. Disruption of methylation reactivates gene expression at silent loci.

Histone modifications is a process when DNA wraps around core histones H2A, H2B, H3 and H4, forming nucleosomes. Their N- terminal tails protrude from this structure and are the potential sites for modifications. Acetylation of Lys, methylation of Lys and Arg, phosphorylation of Ser and Thr, ubiquitination of Lys and ADP-ribosylation of Glu etc., bring about histone modification. Acylation of histones is associated with active chromatin and gene expression. Dietary components such as vitamins, minerals and aminoacids affect DNA methylation. S-Adenosyl methionine (SAM) (formed by methionine cycle) is a common co-substrate involved in methyl group transfers. It is made from adenosine triphosphate (ATP) and methionine by methionine adenosyltransferase. More than 40 metabolic reactions involve the transfer of a methyl group from SAM to various substrates such as nucleic acids, proteins and lipids. SAM is also known to regulate IGF2 methylation and thereby foetal growth and development. The literature supports the hypothesis that methyl donor supplementation prevents trangenerational obesity and regulates the amplification of body weight. The effects of maternal food restriction or exercise on birth weight last for more than one generation[45]. In conclusion, nutrition (methyl donors)/ hypoxia/ infection induce epigenetic alterations. However the role of these methyl donors in bringing about intra-uterine growth retardation (IUGR) is still to be studied.

Inflammation and inflammatory cytokines associated with foetal growth and nutritional status

Over the past decade, it has come to be realized that inflammation has a prominent role in the pathogenesis of many diseases[46-48]. There are studies providing insights into the role of inflammation in causing stunting and poor growth in children. Paradoxically, metabolic syndrome, a disease of affluence, is also linked with inflammation[48]. A study on IUGR and histological chorioamnionitis, and local cytokine (IL8, TNF) levels from chorioamnion undertaken in NIN showed increased inflammatory response in women at term. Of the 180 women studied, 29% had chorioamnionitis (CHA), a marker of intrauterine infection, and the mean concentration of IL8 was > 2000pg, indicative of inflammation[49]. Babies born to mothers with chorioamnionitis had lower birth weight, and significantly lower crown heel length (CHL) and head circumference (HC) as compared to those born to mothers without chorioamnionitis.

Conclusion

Technological advances have enabled scientists to undertakebasic research studies exploring mechanisms by which nutrient deficiencies modulate changes leading to deficiency diseases and illnesses. These advances, together with a better understanding of the mechanisms of nutrient action should, in the next few years, provide better strategies and perhaps even throw light on the causes for the failures reported in many international studies.

The authors are from National Institute of Nutrition, Indian Council of Medical Research, Hyderaba

References

1. National Nutrition Policy. Government of India, Department of Women and Child development, Ministry of Human Resource Development, New Delhi, http://wed.nic.in/nnp.pdf. 1993.

2. NNMB Technical Report No 22 Prevalence of micronutrient deficiencies http://www.nnmbindia.org/NNMB%20MND%20REPORT%202004-Web.pdf

3. 11th Five-year plan (2007-2012) report of the working group on integrating nutrition with health http://motherchildnutrition.org/india/pdf/mcn-integrating-nutrition-with-health.pdf, 2007.

4. Draft National Health Research Policy Department of Health Research, Ministry of Health & Family Welfare, Government of India New Delhi, March 2010

5. Hooper L, Ashton K, Harvey LJ, Decsi T, Fairweather-Tait SJ. Assessing potential biomarkers of micronutrient status by using a systematic review methodology: methods *Am J Clin Nutr* 89: 1953S-1959S, 2009.

6. Background material: Biomarkers of Nutrition for Development (BOND): Building a Consensus. Organized in collaboration with the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH),U.S. Department of Health and Human Services (DHHS), held at International Atomic Energy Agency, Vienna, Austria , *February 8-10, 2010.*

7. Litchen LA, Cousins RL. Mammalian zinc transporters: Nutritional and physiologic regulation. Ann Recv. Nutr 29: 153-76, 2009.

8. Fleming RE, Bacon BR. Orchestration of Iron Homeostasis. New Engl J Med. 352; 1741-44, 2005.

9. Haase H, Rink L. Functional significance of zinc related signaling pathways in immune cells Ann Recv. Nutr 29: 133-152, 2009.

10. Stable isotopes in human nutrition. Laboratory methods and research applications. Abrams SA and Wong WW (Eds). CABI Publishing, Wallingford, UK 2003.

11. Nano. The essentials. Understanding nanoscience and nanotechnology. T.Predeep (Ed), The Mcgraw-Hill Publishing Company Ltd, New Delhi, 2007.

12. Winichagoon P. Coexistence of micronutrient malnutrition: implication for nutrition policy and programs in Asia. Asia Pac J Clin Nutr. 17 Suppl 1:346-8, 2008.

13. Kraemer K, Stoecklin E, Badham J. Chapter 22, Conclusions and research agenda In Nutritional anemia, Kraemer K and Zimmermann MB (Eds) Sight and Life Press, Switzerland, pp 383-388, 2007.

14. Gera T, Sachdev HPS, Nestel P. Effect of combining multiple micronutrients with iron supplementation on Hb response in children: systemic review of randomized controlled trials. Public Health Nutr. 21: 1-18, 2008.

15. Lynch S. Chapter 6, Iron metabolism. In Nutritional anemia, Kraemer K and Zimmermann MB (Eds) Sight and Life Press, Switzerland, pp59-76, 2007.

16. Nair KM, Iyengar V. Iron content, bioavailability and factors affecting iron status of Indians. Indian J Med Res, 130:P 634-645, 2009.
17. Symposium: Plant Breeding: A New Tool for Fighting Micronutrient Malnutrition Plant Breeding: A New Tool for Fighting Micronutrient Malnutrition. Bouis HE J. Nutr. 132:491S-494S, 2002.
18. Allen LH. To what extent can food-based approaches improve micronutrient status? Asia Pac J Clin Nutr. 8; 17 Suppl 1:103-5, 2008..

19. Peter J. Taormina. Critical Reviews in Food Science and Nutrition 50(3): C209-227, 2010.

20. Chassy BM. Regul Toxicol Pharmacol, 2010.

21. Dwyer JH, Allayee H, Dwyer KM, *et al*. Arachidonate 5-lipooxygenase promoter genotype, dietary arachidonic acid, and atherosclerosis. N Engl J Med. 350:29-37, 2004.

22. Tai ES, Corella D, Demissie S, *et al*. Polyunsaturated fatty afids interact with the PPARA-L162V polymorphism to affect plasma triglyceride and apolipoprotein C-III concentrations in the Framingham Heart Study. J Nutr. 135: 397-403, 2005.

23. Volcik KA, Nettleton JA, Ballantyne CM, *et al*. Peroxisome proliferators-activated receptor [alpha] genetic variation interacts with n-6 and long-chain n-3 fatty acid intake to affect total cholesterol and LDL-cholesterol concentrations in the Atherosclerosis Risk in Communities Study. Am J Clin Nutr. 87: 1926-1931, 2008.

24. Ma X, Bacci S, Miynarski W, *et al*. A common polymorphism haplotype at the CD36 locus is associated with high free fatty acid levels and increased cardiovascular risk in Caucasians. Hum Mol Gen. 13: 2197-2205, 2004.

25. Jofre-Monseny L, de Pascual-Teresa S, Plonka E, *et al*. Differential effects of apolipoprotein E3 and E4 on markers of oxidative status in macrophages. B J Nutr. 97: 864-871, 2007.

26. Krieger, M. Scavenger receptor class B type I is a multiligand HDL receptor that influences diverse physiologic systems. J. Clin. Invest. 108, 793797, 2001.

27. Bonen A, Campbell SE, Benton CR. Regulation of fatty acid transport by fatty acid translocase/CD36. Proc Nutr Soc. 63: 245-249, 2004.

28. Brahimi A, Abumrad NA. Role of CD36 in membrane transport of long-chain fatty acids. Curr Opin Clin Nutr Metab Care. 5:139-145, 2002.

29. Jeyakumar, SM, Vajreswari A. and Giridharan NV . Impact of Vitamin A on High-Density Lipoprotein-Cholesterol and Scavenger Receptor Class BI in the Obese Rat. Obesity. 15: 322-329, 2007.

30. Ellgaard L, Helenius A. Quality control in the endoplasmic reticulum. Nat Rev Mol Cell Biol. 4(3):181-91, 2003.

31. Plemper RK, Wolf DH. Endoplasmic reticulum degradation. Reverse protein transport and its end in the proteasome. MolBiol Rep. 26(1-2):125-30, 1999.

32. Liu CY, Kaufman RJ. The unfolded protein response. J Cell Sci. 116(Pt 10):1861-2, 2003.
33. Hotamisligil GS. Inflammatory pathways and insulin action. Int J ObesRelatMetabDisord. Suppl 3:S53-5, 2003.

34. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. J Clin Invest. 115(5):1111-9, 2005.

35. Ozcan U, Cao Q, Yilmaz E et al. Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. Science 306(5695):457-61, 2004.

36. Caroline H.D. Fall, Chittaranjan S. Yajnik, Shobha Rao et al. Micronutrients and fetal growth, J. Nutr. 133: 1747S1756S, 2003.

37. Alok Sachan, Renu Gupta, Vinita Das et al. High prevalence of vitamin D deficiency among pregnant women and their newborns in northern India. *Am J Clin Nutr.* 81:10604, 2005.

38. Wayse, V., Yousafzai, A, Mogale, K. et al. Association of subclinical vitamin D deficiency with severe acute lower respiratory infection in Indian children under 5 y. Eur J Clin Nutr. 58: 563-567, 2004.

39. Michael F. Holick. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Am J Clin Nutr. 79:36271, 2004.

40. Vazir S, Bentley M, Engle P,.Balakrishna N et al. A Home-based educational intervention to caregivers in South India to improve complementary and responsive feeding, and psychosocial stimulation improves dietary intake, growth and development of infants. Abstract accepted for presentation at Experimental Biology Conference, 2010.

41. Laxmaiah A, et al. Assessment of effects of consumption of carbonated water beverages and soft drinks on health of adolescents and young adults. (personal communication)

42. McNamara RK, Able J, Jandacek R, Rider T, et al. "Docosahexaenoic acid supplementation increases prefrontal cortex activation during sustained attention in healthy boys: a placebo-controlled, dose-ranging, functional magnetic resonance imaging study" American Journal of Clinical Nutrition Published online ahead of print, doi:10.3945/ Am. J. Clin. Nutr. 28549, 2009.

43. Jeffrey S. DHA Supplements Show Some Benefit in Cognitive Decline but Not Alzheimer's Disease. International Conference on Alzheimer's Disease (ICAD), 2009.

44. Rudolh Jacnisch & Adrian Bird. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Natuare Genetics. 33: 245-254, 2003.

45. Singh AS, Muldu C, Twisk JWR et al. Tracking of childhood overweight into adulthood a systematic review of the literature. Obesity Reviews. Vol. 9. Issue 5, pp. 474-488, 2008.

46. Kuhns JG, Swaim LT. Disturbances in growth in chronic arthritis in children. *Am. J. Dis. Child.* 43:11801183, 1932.

47. De Benedetti F, Alonzi T, Moretta A, Lazzaro D. Interleukin 6 Causes Growth Impairment in Transgenic Mice through a Decrease in Insulin-like Growth Factor-I A Model for Stunted Growth in Children with Chronic Inflammation. etal. J. Clin. Invest. 99:643650, 1997.

48. Monteiro R, Azevedo I. Review Article. Chronic Inflammation in Obesity and the Metabolic Syndrome. Mediators of Inflammation. Article ID 289645, 10 pages, 2010.

49. Hemalatha R, Ramalakshmi BA, Quadri SSYH et al. Intrauterine Growth Restriction in Term Women with Histologic Chorioamnionitis. Research Journal of Obstetrics and Gynecology 10. 3923. 18-24, 2008.