

Special Article – Vitamins Deficiency

Impact of Nutrigenomics on Various Metabolic Disorders in Relation to Life Style Alteration

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Abstract

Nutrigenomics is defined as the science regarding how bioactive chemicals in food and supplements change the molecular expression and or structure of an individual's genetic makeup. Increasing excitement regarding nutrigenomics has come from the increasing awareness of the potential for modification of food or diet to support health and decrease the risk of diet related diseases. This field is emerging which has been unfolding the role of nutrition on gene expression which brings the science of bioinformatics, nutrition, molecular biology, genomics, epidemiology and molecular medicine. Development of nutrigenomics was only possible with the parallel advances in transcriptomics, genomics, proteomics and metabolomics, besides knowing the importance of food as health supplement. How a particular nutrient interacts with associated genes in a particular organ or tissue makes us understand how a person's genetic makeup respond to a particular nutrient in the sense of DNA transcribed into mRNA followed by a protein. With new knowledge regarding changes in gene expression in Diabetes Mellitus (DM) is not limited to protein kinase B, insulin receptor, glucokinase duodenal home box and thus trying to target the proteins by modifying or improving the nutritional availability or uptake, may help to devise novel foods, supplements or nutraceuticals. This article reviews role of nutrigenomics with respect to dealing with a drastic increase in diseases which have mushroomed with the changes in life style, urbanization, sedentary life habits like increasing obesity, DM, metabolic syndrome and cardiovascular diseases.

Keywords: Nutrigenomics; Transcriptomics; Nutrition; Genomics; Metabolic syndrome; Diabetes mellitus; Cardiovascular diseases; Inflammation; Nutraceutical; Food supplements

Introduction

According to WHO health is a state of complete physical, mental and social well being and not merely the absence of disease or infirmity and fundamental rights of every human being without distinction in race, religion, political, belief, socioeconomic condition [1]. Health implies a person's functional or metabolically ability of acclimatizing under different influences under different conditions. There has been a change of type of diseases' due to urbanization and change in food habit, life styles as well as environment. A marked rise in noncommunicable diseases has been occurring in countries which are rapidly evolving [2]. Genetic makeup along with availability of nutritious foods is moderate only to symbolic health status but it is much more complex interaction between individual's genome along with environmental factors which a person faces throughout life time besides the nutritional level, concentration of bioactive and their ability to influence health states and some of crucial factors needing to be addressed in studies which aim at food-nutrient-health status. Hence developing any dietary supplement, functional food, nutraceuticals for disease prevention involves a largely complex process. Changing the function of particular gene /their protein product during progression of any disease is affected by further modification in nutritional composition of food or diet [3]. The interaction between nutrients-genes-diseases is a highly complex

phenomenon. The isolation of DNA IN 1869, finding its structure in 1953 and ultimately the revelation of human genome in 2003 has helped to solve many problems. These scientific discoveries were only feasible due to simultaneous technical advances occurring in the field of Omics (transcriptomics, epigenomics, proteomics and metabolomics) along with Bioinformatics [4]. Nutrigenomics came in the post genomic era, a combination of nutrition and genomics which has brought together the science of nutrition, genomics computational biology and bioinformatics and molecular medicine to tackle chronic diseases. This makes one understand the importance of food fortification, diet supplementation, with special nutrients and its effects on human health and how it can decrease the risk of life related disease.

Metabolic diseases associated with lifestyle

Life style have become unhealthy along with living practices which are the major factors how life style results in high mortality rate diseases especially noncommunicable diseases (which have been causing major number of deaths In the past decades [5]. Lifestyle associated disease a group of disease. Resulted from exposure of human kind over longer period to unhealthy diet, lifestyle and living environment. There are similar risk factors shared by these diseases being slow in progression, non infectious, no transmissible like CVD's, nutrition induced cancers, chronic bronchitis, renal failure,

hypertension, etc.

WHO report has suggested that there is a rapid change in disease profile for past few decades from communicable to non communicable diseases irrespective of region, ethnicity, and economy [6]. 60% of deaths worldwide occurred from lifestyle associated chronic diseases double than infectious diseases [7]. In India also the NCD accounted for 53% of deaths, of which 24% alone were only due to CVD's [5]. Mainly these diseases are associated with risk factors involving mitochondrial changes, oxidative stress and inflammation etc like epidemiological characteristics. Mainly unhealthy diet lead to increase in metabolic risk factors involving mitochondrial changes, oxidative stress and inflammation etc like epidemiological characteristics. Mainly unhealthy diets \geq increase in BP, Glucose, altered lipid profile etc [8]. Also these diseases affect the inflammatory processes which are self limiting and controlled processes executed by Innate Immune Systems (IIS) needed to restrict incursion of foreign material and limit damage to the human body [9]. Inflammatory process is controlled by eicosanoids, which is a metabolite obtained from fatty acids (arachidonic acid, eicosapentaenoic acid, docosahexaenoic acid). Inflammation is supposed to be negatively affected by unhealthy diet and social environmental stress which is faced by human beings presently. Diets rich in saturated fatty acids and antinutrients (lectin, saponin), low dietary fibers, Vitamin D and K and those that are not balanced in antioxidants are supported to be having poor IIS activity [10]. Genes like plasminogen activator inhibitor1 associated with obesity in animal models showed such changes [11]. The changes in life style along with environmental change also have been associated with a change in intestinal gut micro biome affecting health [12].

It was believed that these diseases were part of developed nations was shattered as social, economical and environmental processes are more favorable in their spread in lower and middle income countries [13]. If such transition continues this will further increase the disease profile especially in developing and under developed nations.

Nutrition, Food and health interactions

Food consists of plants micro biota, animal origin having essential nutrients like carbohydrates, fats, proteins, vitamins and minerals essential for normal functioning. In lieu of nutritional properties food has health benefits. Ingredients of various foods or plants have been used medically for ages as charka samhita is a traditional Indian medicine system based on foods and herbs with medicinal properties [14]. Importance has been given for nutritionist in establishing between lifestyle associated metabolic diseases. Food as a medicine has been recommended both in health sectors and by general public for improving health [15]. Composition of food is basis for availability and amount of energy, macro and micronutrients growth promoting factors in a diet. It gives the basis of relationship between food, health and disease. There is a correlation of both the onset of chronic diseases like DM, cancer, atherosclerosis, CVD [16,17]. Deficiencies of different nutrients are associated with specific disease processes like vitamin C lack with scurvy, niacin B3 with pellagra etc [18]. Besides nutritional deficiencies other dietary compounds may help in health protection [19]. Besides that it has been seen that natural compounds like β -carotene as well as vitamin A can affect umpteen pathways in a disease [20]. Nutrients might cause varying effects like up regulation/down regulation of genes and changes in protein expression both in

fed along with fasted states [21]. Also epigenetic changes like DNA methylation and histone modification which is relevant to adult chronic disease are also possible [22]. Hence multidisciplinary effects will be required for understanding the rationale behind association between foods as medicine and improving human health.

Nutrigenomics Origin

This new science tells us what particular food tells your genes. What one eats directly determines the genetic message your body receives. These messages in turn control all the molecules which constitute your metabolism: the molecules which tell your body to burn calories or store them.; If one can learn the language of your genes and control the message and instruction they give your body and your metabolism you can radically alter how food interacts with your body, lose body weight and optimize your health [23].

The concept that diet has an influence on your health is not new Nutrigenomics includes any interactions which have been associated between food and inherited genes known as inborn errors of metabolism which have long been modulated by changing the diet. An example of this is phenylketonuria which is caused by mutation of a single gene. Those people who are afflicted should not consume the amino acid phenylalanine. Other eg's is lactose intolerance, which means that they are unable to digest milk products once the gene encoding lactase the enzyme which breaks down lactose, is normally turned off after weaning. But some 10,000-12,000 years ago a polymorphism in a single DNA nucleotide appeared among northern Europeans. This single nucleotide polymorphism resulted in the continued expression of the lactase gene into adulthood. This was advantageous as people having this SNP could make use of nutritionally rich dairy products in regions having short growing seasons and the revolutions in molecular genetics in the late 20th century, scientist set out to find out other genes having interactions with dietary components. By the 1980's companies were commercializing nutrigenomics. The human genome project of the 1990's in which entire DNA was sequenced in human genome, jumpstarted the science of nutrigenomics.

Nutrigenomics is the science of how bioactive chemicals of food supplements alter the molecular expression and or the structure of an individual genetic makeup [24]. Nutrigenomics shows the influence on gene/protein expression which are regulated at a particular time under specific environment and also generate response resulted from simultaneous functioning of gene protein networks in regulation of related human disease and nutritional alteration may be utilized to inhibit occurrence of particular diseases [24]. Nutrient –Gene Interaction in Life Style Associated Disease.

Interactions of nutrient in DM

There are 2 types of diabetes globally. Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM). Up to 8.3% population is affected globally, with 387million world population is expected to increase to 592 million by 2035 [25].

T1DM is an autoimmune disease occurring from destruction of pancreatic β islets by T lymphocytes infiltration and hence loss of β cells along with deficiency in insulin secretion. At the start of disease roughly 70% of cells are damaged [26]. Yet T2DM is the most common type of complex disease accounting for >90% diabetes cases [27]. A lot of factors like insulin resistance-cell dysfunction,

altered insulin signaling, oxidative stress associated with this disease causes various complications like neuropathy, retinopathy, nephropathy, macro and micro vascular lesions [28]. DM occurs more commonly in people between 40-59 years of age [25]. Various factors like genes and diet, metabolic profile, environmental changes and their interactions has important role in disease progression. Omics approaches have been used in studying the effect of dietary ingredients upon gene functioning. These approaches help us to find targets like gene, proteins and their interactions occur with nutrients [4]. It is important to study the nutrient-gene-interactions in the etiopathogenesis of different kinds of metabolic syndromes. Gene expression is controlled by these factors by regulating signaling molecules of complex metabolic pathways.

Dietary flavanoid interactions

Both *in vivo* as well as *in vitro* studies showed that dietary flavonoids benefit in DM. These secondary metabolites showed beta-insulin signaling as well as its secretion, carbohydrate metabolism, and glucose uptake in different insulin sensitive tissues [29]. Clinical studies have shown that anthocyanin rich foods especially from apples, blueberries, and pears were associated with a lesser risk of DM [30]. Mostly human diet containing vegetables, fruits, herbs, cocoa, tea, soya and other plant food products were found to be rich in flavonoids. Various evidences show that these metabolites exert beneficial effects in glucose homeostasis and regulate carbohydrate digestion through various insulin signaling pathways needed in the management of DM [29,30]. Epi Gallo Catechin Gallate (EGCG) is a flavanoid, which improves β -cell viability and insulin secretion by activating insulin receptor proteins (IRS2) and AMP Activated Protein Kinase (AMPK) signaling pathway in glucotoxic conditions [31]. EGCG helps in the downstream signaling of protein kinase B(Akt), Insulin Receptor (Ir), Insulin Receptor Substrate 2 (Irs2) Pancreatic Duodenal Home Box1 (Pdx), along with Fork head Box Protein O1 (Foxo1) [32]. It also improves the morphology of β -cell insulin secretion in db/db mice models. This occurred from decrease in carnitine palmitoyl transferase1 (L-Cpt1) levels which is a mitochondrial fatty acid transporter and that in response causes a decrease in fatty acids in blood circulation. Further EGCG supplementation decreases the levels of DNA-damage- inducible transcript (Ddit3), which is an endoplasmic reticulum stress marker and its downstream signaling targets like Cdkn1 and its Protein Phosphatase1, Regulatory Subunit15a (Ppp1r5a). Decreased expression of these markers improves pancreatic function and lowers insulin resistance in diabetic mouse model [33].

Use of naringin and hesperidin flavonoids in *in vivo* studies also showed antihyperglycaemic properties in C 57 BL/Ks db/db mice. Raised levels of Glucose Transporter Type4 (Glut4) and glucokinase was seen in adipocytes which activates Peroxisome Proliferator Activated Receptors PPAR's [34]. Anthocyanin has anti diabetic properties by improving insulin resistance and hyperglycemia in T2DM. It down regulated the levels of gluconeogenic enzymes like PEPCK and G-6-Pase while at same time up regulating PAPR α , Glut4, LCpt1 and aconitase expression in liver tissue [35]. Quercetin is one of the most abundant flavonoids distributed in plant kingdom. It also can down regulate expression of Cdkn1a, a cell cycle regulator and nitric oxide Inducible (Inos2) genes in liver and pancreas of the streptozotocin induced diabetic mice models [36]. These studies

suggest that flavonoids present in diet have significant anti diabetic potential as seen from gene expression in liver, pancreas and skeletal muscles. Thus these metabolites possibly have a regulatory role in nutrient induced responses like release of insulin from β -cells, sensitivity in insulin responding tissues, proliferation along with regeneration of β -islets and their survival.

Vitamin interactions

Vitamins belong to a class of nutrients which exert their protective effect by action as antioxidants. The antioxidant properties are directly related to reduce lipid per oxidation, decreased DNA damage or by inhibiting various *in vitro* malignancies and degenerative diseases [37]. *In vivo* experiments show that VitD can preserve β -cell function during insulinitis by causing down regulation of inflammatory mediators such as interleukins (IL-1, IL-15) and interferon γ -Inducible Protein 10 (IP10) in obese diabetic mice model during insulinitis [38]. Biotin (vitamin H), which is an activator of carboxyl's enzymes, was seen to modify gene expression both transcription ally as well as at posttranscriptional level. Supplementation with biotin markedly increases glucose induced insulin secretion along with β -islets functioning in mice models. Expression levels of insulin, alpha ID subunit (Casma Id) Fork Head Box A2 (Foxa2), Acetyl-Co-A Carboxylase (Acac), Hepatocyte Nuclear Factor 4 A (Hnf4- α), Pdx1, Gk, and calcium channel also get raised by biotin [39,27]. Another vitamin, riboflavin, which is a cofactor of FAD and FMN markedly down regulated cytokine induced raised expression of IL-6 mRNA in NIT1 insulinoma cells as well as in cultured islets [40].

Dietary fat interactions

It has been shown that dietary fats, which are a major macro energy nutrient, maintain the balance between lipogenesis and fatty acid oxidation in human body. Some fatty acids also affect cell metabolism and gene expression in different metabolic disorders. But high fat diet intake is associated with a greater risk of DM [41]. Increased levels of palmitate were found to inhibit glucose induced insulin gene expression as demonstrated by Hageman et al. in 2005. This occurred by decreasing the binding of transcription factors like Pancreatic Duodenal Homeobox1 (Pdx1) and Mammalian Homologue Of Avian (MafA) to the insulin promoters \geq reduced secretion of insulin from rat islets [42].

α -Lipoic acid improves glucose metabolism in T2DM. It decreases the blood glucose levels and increases the insulin stimulated glucose uptake by muscles via Glut4 receptors [43]. Also lipoic acid prevents the increased NADPH oxidase subunit p22 (phox), glucose-6-phosphatase (G6pc2), Gk, Fructokinase (Frk) gene expression in high fructose diet fed diabetic rats [44].

Nutrient –Gene –Interactions in CVD's

In CVD there are intimal lesions because of lipid deposition, inflammatory response, fibrosis and cell death in blood vessels [45]. CVD is a major cause of death as per WHO report [46]. Global evaluation shows that it contributes to 17.5million deaths in 2012, which is a part of 31% of all global deaths [47]. Nutrition has an important role in preventing CVD's as well as their management [48]. Genes helping in both biosynthesis along with metabolism of lipids constitute Arachidonate5lipoxygenase (ALOX5), Fatty Acid Synthase (FASN), Apolipoprotein E(APOE), Lipo Protein Lipase (LPL), Peroxisome Proliferator Activated Receptors (PPAR's) etc

which can be modulated by taking a healthy diet [49].

Polyunsaturated fatty acids

Apolipoprotein A 1 (APOA1): APOA1 belongs to a 28.1Kda protein which is very important constituent of HDL needed for excretion from body [50]. This gene is used for prediction of CVD's and Myocardial infarction as a biomarker [51]. Hence the clearance of HDL is essential by intake of low fat diet. PUFA plays an important role in modulating expression of factors having an important role in carbohydrate metabolism and lipids. Thus intake of these essential fatty acids decreased the LDL cholesterol levels in patients [52].

Lipoxygenase: ALOX5 gene is an important enzyme that regulates leukotriene synthesis along with cytokines and chemokines [53]. Levels are increased in atherosclerotic lesions, hence mobilizing more inflammatory cells APOE^{-/-}, 5LO^{-/-} and LDLR^{-/-} 5LO^{-/-} mice models showed the role of 5LOX as a candidate gene for the progression of atherosclerosis [54]. Omega 3 PUFA diet is shown to block the release of leukotriene production by affecting eicosanoid biosynthesis [55]. *In vivo* studies showed that omega 3 fatty acids gave protection to mice model of retinopathy because of oxidation of 4 Hydroxy Docosa Hexaenoic Acid (4HDHA), which inhibits angiogenesis acting directly on PPAR α and endothelial cell proliferation [56].

Endothelial Nitric Oxide Synthase (eNOS): eNOS generates Nitric Oxide (NO) from L-Arginine in blood vessels. On production, NO diffuses to vascular smooth muscle cells, which causes dilation of blood vessels by the stimulation of guanylyl cyclase receptor and increasing concentration of cGMP. It also inhibits platelet and leukotriene aggregation, helping in the risk of adhesion of WBC's and atherosclerosis. Raised eNOS production correlates with increased H₂O₂ production, causing endothelial dysfunction which further leads to CVD [57]. L-Arginine has been found to benefit in hypercholesterolemia in animals along with humans [58]. n3 PUFA's improve eNOS expression, causing vasorelaxation and also lowers circulating markers like E-Selectin, Intercellular (ICAM) and Vascular Cell Adhesion Molecule1 (VCAM1). Peroxisome Proliferator Activated Receptors (PPAR's) are a part of nuclear receptor proteins, which play a role in cellular metabolism and development. It is made up of 3 isoforms PPAR α , PPAR β / δ , PPAR γ , having variation in tissue distribution [59]. PPAR's can be activated by long chain fatty acids or thiazolidinediones (PPAR γ) ligand. Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Investigation revealed that PPAR α activating drugs caused a reduction in CVD as well as MI [60]. Mechanism of action is by decreasing infiltration and production of pro inflammatory mediators (IL-6, IFN γ , CRP etc [61] PPAR β / δ is suggested to activate fatty acid oxidation in heart and muscle. It also raises HDL cholesterol, thereby reducing fat deposits aiding in management of CVD [62,63]. PPAR γ agonists showed beneficial effect by activating PPAR γ , causing a reduction of matrix metalloproteinase 9, CD40, plasma IL-6, IL8 [64]. Gene expression is controlled by PUFA either by generation of alternative ligand or by changing membrane fluidity [65]. Above discussion indicates as per a person's genotype, dietary actions may be utilized for managing CVD.

Expression of VCAM1 and Cholesterol

VCAM1 has an important role in endothelium and leukocytes

interaction. Atherosclerosis onset binds monocytes to T lymphocytes by VCAM1, which \geq plaque formation [66]. Yet oxidized lipid is needed for VCAM1 expression are induced through inflammatory pathway which involves pro inflammatory cytokines like TNF α and IL1 [67].

Isoflavones-Interventions in the Progression of CVD

Isoflavones are a subclass of flavonoids having antioxidant properties. Some of them being Diadzen, genistein, and glycitein are shown to modulate expression of pro inflammatory cytokines, including improvement in vascular reactivity and inhibition of platelet aggregation [68]. They control the expression of different biomarkers like Inducible Nitric Oxide Synthase (iNOS), inflammatory cytokines like TNF α , Cell Adhesion Molecules (VCAM1, ICAM1, E-Selectin and cyclooxygenase [69,70].

Role of diet in inflammation

Nutritional composition of diets control inflammatory processes due to changes in gene expression in response to immune response modulation, either by changing gene expression or interfering with the signaling cascade.

Inflammation refers to a biological response of human body to prevent any invasion or injuries which may lead to acute (self healing) or chronic condition, lasting for a longtime, needing medication. Different inflammatory types can remain for years and ultimately proceed to occurrence of different diseases in the form of some cancers, allergies of intestine, atherosclerosis. Variety of nutrients and food products has been shown to regulate inflammation. Inflammatory process is regulated by immune system where different immunological mediators play important role [71].

Turmeric or curcumin long a, the golden spice has long been known to be used in Ayurveda against inflammatory processes. It is made up of a number of bioactive products, however curcumin is a major metabolite which accounts for numerous pharmacological activities like antioxidant, antimicrobial and strong inflammatory properties. Curcumin is a pleiotropic molecule having capacity to act with molecule with capacity to act with molecular target of inflammation. It is an important therapeutic agent both for inflammatory conditions, along with different types of cancers [72]. In rat model it has a preventive along with healing effect in gastric ulcers disease by acting as a strong inhibitor of H+K+ATPase gene [73]. Curcumin prevents Lipopolysaccharide (LPS) induced inflammatory mediators like IL-6, TNF α and COX2 mRNA's in macrophages by controlling the expression of Suppressor of Cytosine Signaling1 and 3(SOCS1&SOCS3) and p38 MAPK suppressors, further on trolling SOCS 1&3 expression and activation of p38MAPK kinase [74]. *In vivo* and *in vitro* clinical investigations in humans on curcumin (diferuloylmethane), oral bioavailability and safety showed that it inhibits TNF α action and its production [75]. Also curcumin shows important role in the prevention of Helicobacter pylori induced inflammation. H. pylori infection activates a sequence of gastric changes with induction of gastric mucosal inflammation, which may shift to gastric cancer development sometime. Also anti inflammatory effects of curcumin may be influenced by altering the expression of Toll Like Receptors (TLR's) and Myeloid Differentiation primary response gene 88 (MyD88) [76]. Thus it may be an important approach by which nutritional challenge can be used for prevention

of H. Pylori induced inflammation. Vitamin A addition provided beneficial effect against multiple skin related disorders which are inflammatory along with different precancerous and cancerous states [77,78]. A Vit A derivative is retinoid which can inhibit neoplasm and improve immune system. Because of retinoic acid treatment, a marked rise in TLR4 gene with reduced levels of IL-1b, in mammary glands and NFkB DNA binding was seen in LPS induced mastitis in rat model and mammary epithelial primary cell cultures [79]. It was concluded that retinoic acid because of suppression of TLR4/NFkB signaling alternated the LPS induced inflammatory response. Various evidences are seen showing inflammations role in CVD or atherogenesis. VitE and its isoforms have potent antioxidant and anti inflammatory properties. Tocopherol (alpha T) supplementation was found, responsible for decreasing CRP, IL-8 and Plasminogen Activator Inhibitor (PAI-1), levels in animal subjects. Isoform α T was effective in reducing reactive N2 species and have anti inflammatory properties [79]. Using experimental mice in *in vitro* studies showed that sesame oil, having seamol as the active ingredient is used as an alternative treatment for atherosclerosis. Diets containing sesame oil markedly decreases atherosclerotic conditions, plasma cholesterol, LDL cholesterol and triglyceride levels in LDLR mice models. Marked decrease in plasma cytokines which are inflammatory like IL-6, IL-1 α , Regulated Activation, Normal T Cell Expressed and Secreted (RANTES), Monocyte Chemo Attractant Protein1 (MCP1), and Chemokine (CXC motif) ligand 16 (CXCL-16) suggested sesame oil has anti inflammatory properties. Similarly gene array studies showed that sesame oil could \geq induction of ATB Binding Cassette Transporter (ABCA1) & ABCA2, Lecithin Cholesterolacetyl Transferase (LCAT), APOE and cholesterol 7 α hydroxylase (CYP7A1), which are involved in cholesterol metabolism, reverse cholesterol transporter [80]. Though VIT6 deficiency is not very prevalent, it can increase risk of inflammation related diseases in certain populations [81]. A bioactive derivative of Vit B6 i.e Pyridoxal -5phosphate (PLP) acts as a cofactor in various biochemical reactions. Plasma concentration of PLP found inversely related to CRP, which is an inflammatory marker and low PLP associated with inflammatory conditions like Inflammatory Bowel Disease (IBD). Both low and high PLP plasma concentration was seen to be significantly associated with suppression of colon specific molecular inflammation (TNF α , IL-6, IFN γ , COX2 and I NOS expression along with histological markers. Hence supplementation with vit6 may help in IBD management [82].

Dietary treatment of metabolic disorders

A lot of work has been done regarding nutrigenomics research and role of nutritious foods on metabolic diseases related to lifestyle changes. Importance of food supplementation in trying to avoid or managing lifestyle related diseases is discussed.

Functional foods

Functional foods is defined as any food or component of food which may give a health benefit beyond the traditional nutrients it contains as per the Institute of Medicine Food and Nutrition Board. These functional foods which get derived from plants are flavanoids, dietary fibres, antioxidants, omega 3 fatty acids, proteins, vitamins, probiotics, which are found to be of use in managing diseases related to lifestyle like congestive heart failure, hypertension, arrhythmias, angina and hyperlipidemia [83]. Examples of functional foods are green tea, having catechins [84], flaxseed containing lignans [85].

fenugreek containing saponins [86], banana leaves extract with components like corosolic acid. Ellagittannins [87], soyproteins with phytoestrogens, genistein, and deidzein [88], grapes and its products with anthocyanadin, flavan-3-ols, flavonols [89], curcumin long a having curcumin [90,91], fruits and vegetables having dietary fibres [92], red wines berries, peers apples having proanthocyanidine [93]. Curcumin which is a dietary flavanoid showed adipogenic effects in both human as well as murine adipocytes [94]. Ciardi et al found that adipocytes which were incubated with curcumin exhibited a dose dependent reduction in lipopolysaccharide induced IL-6 secretion [95]. Curcumin decreased hyperglycaemia and improved insulin sensitivity in male sprague dawley rats in which T2DM had been induced, besides simultaneous reduction of TNF α [96]. Giving Trigonella foenum graecum seed extracts orally to streptozocin induced diabetic rats showed lowered blood glucose levels, total cholesterol, triglycerides, simultaneously increasing HDL cholesterol in a dose dependent manner [97]. The glucose lowering property of Trigonella foenum graecum(fenugreek) seed powder is mainly caused by the bio active compound like 4 hydroxy isoleucine(amino acid)and steroid saponin trigonelline. In a clinical trial 24 adults having T2DM received hot water soaked fenugreek seeds for 8 weeks [98]. The results showed a marked reduction in fasting blood sugar, triglycerides and VLDL. In another human clinical trial done on 56 healthy men and women was done to study the effect of soyprotein 25g/d with various isoflavone concentrations. It was found that there was dose dependent decrease in total and LDL cholesterol levels but did not show any effects on the concentration of HDL and triglycerides [99]. Besides the plant functional ingredients different bioactive components of animal products also have positive role in managing lifestyle related disorders. Also omega 3 fatty acids (docosa hexaenoic acid and eicosa pentaenoic acid) derived from fish oil play an important role in different conditions like cancer and CVD [100,101]. A conjugated fatty acid namely linoleic acid derived from grilled beef was found to have anti cancerous activity [102]. Conjugated Linoleic Acid (CLA) also possess strong antiobesitic and hypolipidaemic effect. Linoleic acid treatment was found to increase the body protein concentration while simultaneously decreasing the fat deposition [103]. Probiotics are health promoting fermented food products. There are reports which show that Lactobacillusacidophilus causes hypocholesterolemic effects by inhibiting 3hydroxy 3 methyl glutaryl CoA reductase activity, an enzyme vital in cholesterol biosynthesis [104,105].

Nutraceuticals

In the last few decades marked improvement has occurred in life styles of human beings, but simultaneously it has been associated with the introduction of lifestyle associated metabolic disorders. Bad food habits are the main cause of present health related diseases. Stefen Defelice defined Nutraceuticals in 1989 as any substance which is a food or part of a food and provides medical health benefits which include the prevention and treatment of disease [106]. Main types of Nutraceuticals are dietary phytochemicals like antioxidants, flavonoids, glycosinolates, phytoestrogen, dietary fibres and carotenoids. Dietary phyto chemicals refers to naturally occurring bioactive plant derived compounds like anthocyanine in blue berries, flavanols in green tea, lycopene in tomatoes and rasveratrol in grape seeds which have a positive effect on health. Flavonoids show

inverse relationship between dietary ingestion and risk of both DM, as well as CVD [107,108]. Green tea, flavanol, Epigallo Catechin-3-O-Gallate (EGCG) lowered the VCAM1 and ICAM1 genes expression by inhibiting the protein and mRNA in Human Umbilicalvein Endothelial Cells (HUVEC) (10 to 50 μ M) [109]. Also there was a significant correlation found with consumption of flavan-3-ols in lowering risk of CHD mortality [110]. Dehydrochalcone, phloridzin, also showed a role in management of post prandial hyperglycemia. Dihydrochalcone given at various oral doses like 5,10,20,40 mg/kg body wt were shown to decrease blood glucose levels and improve dyslipidemia in streptozotocin induced diabetic rats [111]. Quercetin (0.08%) supplemented diet x6wks given to T2DM increased HDL Cholesterol, while lowering total cholesterol in another study. Also dietary quercetin addition also lowered the increased activity of Super Oxide Dismutase (SOD), Catalase (CAT) and Glutathione Peroxidase (GSH-Px) antioxidant enzymes in liver tissues [112]. In addition to decreasing liver fat accumulation in mice fed on western diet, quercetin addition also improved hyperglycemia, hyperinsulinemia and dyslipidemia by decreasing the expression of PPAR α [113]. In another study addition of naringin-7-O-glucoside in a dose dependent manner (10, 20, and 40 μ M) show marked improvement in proliferation of rat cardiac H9C2 cellline [114]. The proliferation of cells was thought to be due to increased caspase3 and caspase 9mRNA besides elevated HO1 mRNA expression. Polyphenols which are present in lemon like flavonone exhibited protective effects against high fat diet induced obesity in micemodel. Giving obese mice lemon polyphenols like eriocitrin, hesperidin and naringin etc) caused increased expression of PPARs and acyl CoA Oxidase, besides causing reduction in body weight [115]. The diet supplemented improved insulin resistance in experimental model by adjusting serum insulin and glucose levels. Giving citrus polyphenol hesperidin 500mg/dx3wk to 24 volunteers having metabolic syndrome in a randomized placebo controlled, double blind cross over trial found to improve endothelial dysfunction with simultaneous decreasing circulating inflammatory biomarkers like CRP and serum amyloid A protein and soluble E selectin [116]. Thus citrus polyphenols caused vasculo protective actions which might highlight its positive CVS effects. Oral hesperidin and naringin 50mg/kg body wt x 30 days to high fat fed streptozotocin induced T2DM rats showed anti hyperglycaemic and anti dyslipidemic effects [117]. These animals displayed better glucose and serum amino transferase, lactate dehydrogenase and creatine kinase although serum insulin and muscle glycogen content were reduced. Thus besides nutrient supply nutraceuticals also have capacity to manage and or prevent nutrient linked diseases.

Dietary supplements

They are anything which aids in supplementing human diet and are not meant for preventing any disease. They may be any pills, tablets, capsules and meant to meet needs of specific nutrient, fitness, optimal physical health or improve total well being and health [118]. Mostly DS are made up of biologically active crude or purified primary or secondary metabolites. They can be classified according to dietary fiber supplement and mineral supplements, supplements for weight loss, colds, ageing population, brain bone health, immune system, heart health GIT health etc [119]. In a study done on approximately 40,000 volunteers around 40-75yrs age showed that vitamin E helps decreasing CHD risk. ≥ 60 vit EIU/day lowered the

CHD risk by 36% than in those men who took <7.5 iu/day [120]. In another study carried out on approximately 87,245 female nurses, it was shown that vitamin E supplementation for ≥ 2 yrs of the subjects resulted in decreasing risk of coronary disease damage by 41% [121]. Also arginine ingestion gave protective effects against CVS diseases. In a study involving 15 patients who received arginine hydrochloride supplementation at different concentrations 6-12.6g/d x6wk demonstrated markedly $>$ blood flow from 5.1 \pm 2.8 to 6.6 \pm 3.4ml/min/Dl in forearm [122]. Secondary metabolites like hydroxy citric acid, conjugated linoleic acid, flavonoids, pyruvates etc have been shown to be important component of weight loss supplement in improving fat and carbohydrate metabolism [123]. But these compounds are also related to diabetes. Luteolin (0.002 and 0.01%) supplementation of high fat diet given to male C57BL/6 mice x12wks were not only able to suppress body weight gain induced, but also helped in improving glucose intolerance and insulin sensitivity [124]. A pilot study done on 13 T1DM subjects showed that daily omega-3 fatty acid diet supplementation. 5.4g of eicosapentaenoic acid and 2.3g of docosahexaenoic acid x4wks reduced the blood glucose, triglycerides and HDL cholesterol levels [125]. Cocoa polyphenols were shown to have protective effects in management of CVS and inflammatory diseases. In a meta analysis it was also shown that cocoa supplements given to 173 hypertensive subjects x2wks marked to decreased BP [126]. In a separate study T2DM patients who were given cocoa phenolic rich chocolate showed increased level of HDL cholesterol and decreased total cholesterol and HDL cholesterol ratio [127]. EGCG supplemented diet given to pathologically affected islets showed T2DM could be prevented and showed that there was an increase in number and size of islets in db/db mice [128]. In a study conducted to find the effect of probiotics (in a dose of 200ml @4x208CFU/100ml concentration symbiotic cultures of Lactobacillus and Bifidobacterium bifidum) in T2DM Patients showed a reduction in total cholesterol and triglycerides along with HDL cholesterol levels [129]. In a randomized double blind controlled clinical study, which was carried out to study the effect of probiotic yogurt given Lactobacillus acidophilus La5 and Bifidobacterium lactis Bb12; 300g/dx6wks in T2DM patients. This supplementation \geq decreased levels of fasting glucose and HbA1C though antioxidant activity, erythrocyte SOD and GSH-PX activities were found to rise [130]. In an *in vivo* study where male albino wistar rats were fed a high fructose diet supplemented with dahi (milk based food) showed improve men in blood glucose level, dyslipidaemia, oxidative damage and insulin secretion. They hence advocated dahi (milk ferment mixed cultures of L. acidophilus, L. casei, and L. lactis) as probiotic supplement in management of T2DM [131].

Ethical considerations

Before it becomes a part of routine treatment nutrigenomics has to show its efficacy. There are various opinions as far as the claims exist of predictive type of studies which nutritional genomic studies are [25,132,133]. Therefore there are some doubts regarding outcomes, or that products of nutrigenomics are obvious as far as their acceptability are across different regions, age group, ethnicity, gender [134]. Who should be distributing nutrigenomic products and services, whether it should be public or private means or for that matter via health practitioners are also debatable [135]. The benefits on health of any food constituents, DS, functional foods,

nutraceuticals are based on a person's genetic variations and lifestyle environment against a particular disease [136]. Even in this case one can look into pharmacogenomic models where human subjects are being utilized to answer scientific questions through long term clinical trials [137]. One can follow the guidelines which are settled for the conventional nutritional research as it also involves human model for sample collection or information from such models [138]. But in nutrigenomics problem lies with the type of data to be collected and information generated like diet-gene interaction, genotype characterization, and reusability of data stored in bio banks and showing this information along boundaries [139]. Thus different sets of socio ethical guidelines and regulatory systems might be required for assessing nutrigenomic product. Hence NuGO got established by European Union (EU), with the idea of moving nutrigenomics studies and since 2010 one has started to look for bigger role globally. This is an association of different institutions involved in nutritional genomics R&D activities around Europe. NuGO was developed from EU Sixth framework Network of Excellence with a main objective of laying guideline procedures of carrying all nutrigenomic studies [138].

Also in Canada, in University of Montreal there is Omics-Ethics Research Group looking into these ethical issues like ethnicity, regional specificity, age, gender, exaggerated claim etc of studies including nutrigenomics which apply omics associated technology. This group lays emphasis to develop evidence based system by which one can validate socio-ethical issues in relation to omics technology and study how they can be used for developing guidelines for conducting R&D in this field of nutritional genomics [140].

Conclusion

Changes in eating habits, availability of Fast foods, better living environment and work standard, easier lifestyle with limited walking, better economic status, and urbanization are some examples of current life style. This shift has improved present human living standards but has taken a toll on health status as shown by marked increase in mortality rates in last decade by non communicable diseases. Also luckily there has been a greater invention in past decade regarding knowledge of human genome, besides various transcriptomics, genomics, metabolomics and other omics which has added nutritional and medical science researchers to counter the posed challenges. Nutrigenomics has become important both for unhealthy as well as healthy people to improve health using modification of diet. Multiple *in vitro*, *in vivo* studies along with clinical studies have been carried over worldwide that have increased chances of healthy living using dietary intervention. However important is need of high integrity and use of regulatory mechanisms with ethical means to further nutrigenomics research.

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