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Epigenetics Processes And Diet

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Abstract: *Nutrients in diets interact and modulate molecular mechanisms underlying an organism's physiological functions. The dietary intake of an individual has important long-term consequences for health, therefore, nutrition is an important factor that contribute to the development and progression of degenerative chronic diseases like cardiovascular diseases, diabetes, and cancer. Epigenetics is the heritable changes in gene activities and expression that occur without changes in DNA sequence. The major epigenetic processes are DNA methylation, histone modification and non-coding microRNAs (miRNA). Gene silencing or activation basically depends on these processes. Dietary component is identified to supply the methyl and acetyl group for DNA methylation and histone acetylation respectively. DNA methylation plays an important function in maintaining cellular function, and the development of cancer and other chronic diseases could be as a result of changes in methylation patterns. Dietary components that supply methyl group for methylation include: folate, vitamin B12, vitamin B6, methionine, genistein and choline. Whereas diallylsulphide (DADS) found in garlic and sulphoraphane in broccoli provides acetyl group for histone acetylation. However, dietary components such as vitamin B12, alcohol, and selenium may modify the response to insufficient dietary folate. The diet of parents therefore can affect their offspring even to the third generation. Also, an individual's diet can determine the physiological and phenotypical characteristics, as well as susceptibility to disease.*

Keywords: *Epigenetics, Epigenetic processes, Diet, DNA methylation, Histone acetylation, disease susceptibility.*

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I. Introduction

The dietary intake of an individual at any point throughout the life cycle can have certain consequences as far as ones health in later years or decades is concerned [1]. There is a growing scientific evidence that points to the fact that, epigenetic mechanisms may initiate or mediate the effects of nutrition and hence may be a contributory factor to the development of a number of non-communicable (or chronic) diseases [1]. Epigenetics simply refers to heritable changes in gene activities and expression that occur without changes in DNA sequence [2]. It is observed that, these non-genetic alterations are critically regulated by two [2] major epigenetic modification; thus chemical modifications to the cytosine residues of DNA (DNA methylation) and histone proteins associated with DNA (histone acetylation or modification) [3].Epigenetics specifically involves alterations that live indelible marks on the genome and this phenomenon are mostly associated with cellular machinery that are copied from one cell generation to the next. It is these processes that eventually lead to alteration of gene expression, but not alteration in DNA sequence [1].

The dietary intake of an individual has important long-term consequences for health. Nutrition is an important factor that contribute to the development and progression of degenerative chronic diseases like cardiovascular diseases, diabetes, and cancer [1, 4-6]. The effects of diet on health are not limited to only the individual but also can be passed on from the parents to their children, and these changes can further be transferred from generation to generation. This phenomenon is observed in a number of scientific epidemiological studies and animal experiments. Epidemiological studies indicated a link between smaller size or low weight babies to increased incidence diabetes (type 2), coronary heart rate disease and overweight or obesity in later life [7-11].A number of nutrient substances have been linked with induction or prevention of different diseases. Thus, increased salt intake has been related to hypertension, cardiovascular events, and gastric cancer. Also it is further reported that vitamin E and selenium may prevent prostate cancer, whereas nut consumption appears to reduce the risk of coronary heart disease. In an animal model it was indicated that, prenatal undernutrition decreased the offspring's life expectancy [12]or result to poor development of the renal nephrons that subsequently precipitate chronic kidney disease in later life [9, 13].

The epigenetic processes that result in gene expression involve three distinct, but closely inter-acting mechanisms; including DNA methylation, histone modifications and non-coding microRNAs (miRNA)[14-16].

All these are implicated in the regulation of gene expression during cellular differentiation in embryonic and foetal development and also throughout the life cycle of human development [1]. The phenotypic differences that are observed in human development are probably caused by differences in long-term programming of gene function and not just solely the gene sequence, thus studies of the basis for inter individual phenotypic diversity should investigate more into epigenetic variations in addition to genetic sequence polymorphisms [17]. This review focused on diet and nutrition, including micronutrients and other dietary factors that have bearing on epigenetics. More studies have demonstrated that micronutrients can interact with the genome, modify gene expression, and alter protein and metabolite composition within the cell by affecting epigenetic states. The effects of altered dietary supply of methyl donors on DNA methylation, are plausible explanations for the observed epigenetic changes. Therefore, recognizing epigenetic changes pertaining to behavioural pathologies have implications for human health, since they are potentially reversible and amenable to therapeutic intervention [18]. However, there is little understanding about which epigenomic marks are most labile in response to dietary exposures. More research needs to further enhance the understanding of epigenetic marks and their responsiveness to dietary factors, since it has a potential for the development of epigenetic marks as biomarkers of health for use in intervention studies [1].

Therefore, when researchers are able to decipher the phenomenon through which dietary therapeutic intervention and also different environmental exposures modify the epigenetic processes, then it would serve as the surest way to design both nutrition and behavioral intervention strategies to prevent and revert dangerous environmental and unhealthy epigenetic alterations.

II. Dietary Caloric Restriction And Epigenetics

The possibility that mammalian life span could be significantly extended by diet modification was extensively demonstrated in a rodent study published by McCay and coworkers in 1935 [19]. Caloric restriction is indicated to have the tendency of extending the average life expectancy and also has the propensity of delaying the onset of age-associated unhealthy alterations in normal growth and development. This phenomenon has been demonstrated in several organisms like mammals, yeast, worms and flies [20-22]. In higher mammals, caloric restrictions(CR)delays many chronic diseases pertaining to aging, key amongst them are, cancer, diabetes, atherosclerosis, cardiovascular disease, and neurodegenerative diseases [23-26].However, several studies have demonstrated that, the effect of diet restriction on life expectancy was more pronounced in male than in female rats [19].

It is indicated from several studies, that life expectancy can be extended by diet restriction without malnutrition as compared to diet restriction involving malnutrition that can have opposite effect as opined by other scientific researches [1]. Studies by Fontana and colleagues who researched on CR, showed that long-term CR can decrease the rate of susceptibility of chronic diseases especially atherosclerosis [26]. Their observations showed that, long-term CR of the same magnitude lead to improvements in the major risk factors for coronary heart diseases (CHD) in normal-weight and overweight middle-aged adults [27]. Furthermore, it was indicated in related studies that, CR by exercise, reduces systemic oxidative stress which is reflected in a decreased DNA or RNA oxidative damage [28]. Similar results were observed in other randomized, controlled, clinical trial were CR subjects had a lower body weight, a decreased total body and visceral fat, improved fasting insulin levels, improvements in cardiovascular disease markers (LDL, total cholesterol to HDL ratio, and C-Reactive Protein (CRP)), and no change in bone density compared to controls [27, 29-32].The most common age-related changes include increased expression of genes involved in inflammation and immune responses, and reduced expression of genes involved in mitochondrial (MTH) energy metabolism and CR prevents the majority of these age associated changes in gene expression [33-34]. The health implications of CR on epigenetics and aging for that matter stems from the fact that, all the trends result to a shift from acute medical problems to chronic and age related medical complications like cardiovascular diseases, diabetes and cancer. This undoubtedly result to an increase heath costs and economic burden to the society and to the individual [4-6].

Caloric restriction therefore, will delay the progression of chronic and age-related illnesses in an individual's quality of life. There is a body of data suggesting that CR significantly reduces the rate of age-related changes in humans [25-31, 29, 35-45]. CR is the consumption of 20-40% of the normal daily calorie while maintaining an adequate intake of other nutrients [46]. In another study, CR was observed to refer to limiting calorie intake by 10– 30% [23].Hence, this has been shown to improve health at all ages and also to slow the aging process in many eukaryotes [23].

III. Dietary Folate And Epigenetics

In recent times, studies in genetics considered obesity as a heritable disease caused by gene mutations, polymorphism, and thrifty gene hypothesis [47]. This phenomenon is best explain by the epigenetic regulation of the gene expression. An adverse environment during in utero or lactation periods has been involved in the future development of obesity. The revelation suggests that, an individual mother's nutritional status or pre-

pregnancy lifestyle choices may lead to an alteration in the developmental programming of the foetus [48]. Studies on dietary influence on epigenetic patterns focused on folate effects and hence, revealing that folate is associated with birth defects[49]. Also, it is observed that folate is important for the maintenance of epigenetic patterns. When folate levels are below an optimal level, homocysteine accumulates and DNA methylation becomes impaired. Despite this important role, folates cannot be synthesized de novo by mammals and, therefore, their cellular levels depend on dietary intake [47 – 50]. Thus, changes in DNA methylation patterns could be as a result of the interplay of various dietary and environmental factors and also could be a source of inter-individual differences with respect to the susceptibility to develop obesity or other metabolic diseases. The restriction of methyl donors such as vitamins of the B complex (cobalamin and folate) or amino acids (methionine) led to DNA methylation in the pre-ovulatory oocyte and the pre-implantation embryo [49], while mice fed on a folate-deficient diet during the post-weaning period significantly increased genomic DNA methylation in rat liver, which persisted into adulthood [50].There is evidence in humans that showed the role of nutrition in epigenetic alterations in adulthood that is demonstrated from a study carried out in patients with uremia. This disorder is frequently accompanied by hyperhomocysteinemia, characterized by an increased concentration of homocysteine and its precursor, S-adenosyl homocysteine (SAH), in the organism. SAH is a powerful competitive inhibitor of methyl transferases and may, therefore, impair DNA methylation and gene expression [47 -50]. Patients with uremia have lower global levels of DNA methylation and it was correlated with defects in the expression of genes regulated by methylation. In addition, this effect was reversed by folate treatment. Because homocysteine may be methylated to methionine by transferring a methyl group from 5-methyl tetrahydrofolate, folate could decrease homocysteine levels, resulting in the restoration of DNA methylation levels and corresponding gene expression [47 -50].

Further studies indicates that, maternal supra physiological methyl group (folate, cobalamin, choline and betaine) supply [51], and a low-protein diet in rodents throughout pregnancy [52] modified DNA methylation of some key metabolic genes (agouti, glucocorticoid receptor and peroxisomal proliferator-activated receptor alpha). In addition, essential differences in choline dietary requirements can be explained by single nucleotide polymorphisms (SNPs) in genes involved in choline and folate metabolism [53].

Generally, adult recommended daily intake (RDA) of folate is approximately 400 micrograms/day. However, the recommended nutrient intake (RNI) for folate are 400, 600 and 500 micrograms/day for non-pregnant, pregnant and lactating women [54]. Thus for those women who are pregnant, meeting this recommendation daily from the diet is difficult so as part of pregnant health care services, folate supplement may be given to complement intakes to meet desired outcomes. Individuals are encouraged to increase the consumption of foods like dried beans, liver, dark green leafy and stem vegetables in other to prevent folate deficiencies [54 -55].

IV. Dietary Protein Restriction And Epigenetics

It has been shown that the methyl donor S-adenosyl methionine (SAM), and amino acid present in the diet, inhibit the demethylation reaction [56]. Data from various studies also showed that, the regulation of epigenetic mechanisms in the brain (hippocampal glucocorticoid function) by a behavioral mechanism (early life environment) that is susceptible to modulation by l-methionine (a dietary amino acid). The DNA methylation machinery in vertebrates has two main roles. Thus, it has to establish new cell-type-specific to DNA methylation patterns during development and possibly during adulthood in response to new signals. In addition, it has the tendency to maintain these patterns during downstream cell divisions and after DNA repair [3]. The different enzymes and proteins of the DNA methylation machinery must address these different tasks. The epigenome consists of the chromatin, a protein-based structure around which the DNA is wrapped, as well as a covalent modification of the DNA itself by the methylation of cytosine rings found at CpG dinucleotides [3]. Poor nutrition during pregnancy and subsequently the delivery of low birth weight baby have been related to an increase in the incidence of metabolic syndromes in adulthood, such as type 2 diabetes, hypertension and cardiovascular diseases. During foetal life, amino acids control insulin secretion by beta-pancreatic cells. Since insulin is an important foetal growth hormone, the availability of amino acids influences the rate of foetal growth. Epigenetic deregulation also seems to be involved in protein restriction (PR) during pregnancy altered epigenetic regulation of some genes in the newborns such as the glucocorticoid receptor, which appeared hypomethylated, or peroxisome proliferator activated receptor alpha (PPAR-alpha) [57].This was associated with an increased expression of target genes of these transcription factors, acyl-CoA oxidase (AOX) and phosphoenolpyruvate carboxykinase (Pepck). AOX, target gene of PPARa, is involved in peroxisomal beta-oxidation, whereas Pepck, target gene of GR, is involved in gluconeogenesis. This phenomena bring to the fore, a link between maternal protein restriction, epigenetic alterations, and metabolic effects in the offspring. The hypomethylation of the GR and PPAR-alpha persisted after weaning, despite direct influence of the maternal dietary restriction. This suggests that the expression of these transcription factors was regulated by stable epigenetic modifications [15, 16].As far as these findings are concerned, a PR diet during pregnancy induces in

the liver of the offspring an increase in gluconeogenesis and peroxisomal fatty acid beta-oxidation capacity. As the alterations leading to this phenotype are stable, it lasts until adulthood, and may lead to metabolic syndromes, such as type 2 diabetes and obesity. Thus predisposition to these diseases results from a mismatch between the diet to which offspring are exposed early in development and nutrient availability later in development and adulthood.

The consumption of adequate amount of proteins in line with the RDA is recommended. The dietary reference intake of protein is 0.8 - 1.0 g/day, thus 56 grams/day for sedentary males and 46 grams/day for average sedentary females [15]. The average adult requires about 70-80 grams of protein per day, however protein needs may be increased in times of stress or during pregnancy in women. Some foods rich in proteins are fish, eggs, meat, soya beans, cowpea, and eggs.

V. Dietary Micronutrients, Epigenetics And Cancers

The micronutrients are able to affect the genome and its expression through the synthesis of nucleotides, prevention and repair of DNA damage, or through epigenetic mechanisms including methylation of histones, proteins responsible for chromatin structure that play an important role in regulating gene expression. Epigenetic events create a memory of cell identity, maintaining genomic functions such as the maintenance of cell identity after differentiation, the propagation of essential features of chromosomal architecture and dosage compensation [58]. Epigenetic mechanisms have the ability to modulate gene expression through changes in the chromosomes structure. Chromosomes are formed from the condensation of the chromatin, which is formed by a complex of DNA, and unique proteins called histone. Examples of epigenetic mechanisms are DNA methylation and histone acetylation [59].DNA methylation occurs at the cytosine bases of eukaryotic DNA, which are converted to 5-methyl cytosine. The altered cytosine residues are usually immediately adjacent to a guanine nucleotide, resulting in two methylated cytosine residues sitting diagonally to each other on opposing DNA strands [60 -62]. DNA methylation, which modifies a cytosine base at the CpG dinucleotide residues with methyl groups, is catalyzed by DNA methyl transferases (Dnmt) and regulates gene expression patterns by altering chromatin structures [62]. DNA methylation is essential for cell differentiation and embryonic development. Moreover, in some cases, methylation has been observed to play a role in mediating gene expression. In mammals, methylation is found sparsely but globally, distributed in definite CpG sequences throughout the entire genome, with the exception of CpG islands, or certain stretches (approximately 1 kilobase in length) where high CpG contents are found. The methylation of these sequences may lead to inappropriate gene silencing, such as the silencing of tumor suppressor genes in cancer cells [18]. Tumor suppressor genes are often silenced in cancer cells due to hypermethylation. In contrast, the genomes of cancer cells have been shown to be hypomethylated overall when compared to normal cells, with the exception of hypermethylation events at genes involved in cell cycle regulation, tumor cell invasion, DNA repair, and other events in which silencing propagates metastasis. As a matter of fact, in certain cancers, such as that of the colon, hypermethylation is detectable early and might serve as a biomarker for the disease [18]. However, it is very hard to disjoint the precise effect of nutrients or bioactive food components on each epigenetic modulation and their associations with physiologic and pathologic processes in our body, because the nutrients also interact with genes, other nutrients, and other lifestyle factors. Furthermore, each epigenetic phenomenon also interacts with the others, adding to the complexity of the system [19]. There is evidence that inadequate nutrient supply can result to a considerable levels of genome mutation and alter expression of genes required for genome maintenance. Deficiencies in several micronutrients have been shown to cause DNA damage and are thought to be associated with a number of serious human diseases: folic acid, niacin, vitamin B6 and B12 deficiency may increase the risk of colon cancer, heart disease and neurological dysfunction due to chromosome breaks and disabled DNA repair [19].

Significant opportunities in nutrition and cancer prevention exist in the early stages of initiation and promotion prior to clonal expansion of heterogeneous populations. DNA methylation and histone modifications are epigenetic events that mediate heritable changes in gene expression and chromatin organization in the absence of changes in the DNA sequence. The age-increased susceptibility to cancer may derive from accumulation of epigenetic changes and represents a potential target for therapies with bioactive compounds. Factors that mediate the response to dietary factors include nuclear receptors and transcription factors, which function as sensors to dietary components and determine changes in the profile of transcripts [60, 15]. Milner and Romagnolo [19] affirm that the opportunity of targeting nutrients–gene interactions to influence the cancer process is modulated by genetic variations in human populations, epigenetic modifications that selectively and permanently alter gene expression, by complex interactions/associations among dietary components, and heterogeneity of cells within a certain tumor. Therefore, integration of information about gene polymorphisms, identification of gene targets that regulate cell and tissue specific pathways, and development of diagnostic strategies to control for clinical heterogeneity are important to understand how nutrigenomics may be used in cancer prevention.

Adequate nutrition ensures adequate intake of micronutrients throughout the life cycle of human development so as to reverse or change epigenetic phenomena such as DNAmethylation and histone modifications, thereby modifying the expression of critical genes associated with physiologic and pathologic processes, including embryonic development, aging, and carcinogenesis [21]. There should be regular consumption of fruits, vegetables, and whole grains to reduce cancer risk since, these foods are rich sources of numerous bioactive compounds [22]. Plant foods contain a variety of components, including, but not limited to, essential nutrients, polyunsaturated fatty acids, and phytochemicals such as glucosinolates and flavonoids, many of which can inhibit cell proliferation and induce apoptosis, and which may act additively or synergistically when combined in the human diet. Polyphenols are common constituents of foods of plant origin and major antioxidants of our diet. The main dietary sources of polyphenols are fruits and beverages. Fruits like apple, grape, pear, cherry, and various berries contain up to 200–300 mg polyphenols per 100 g fresh weight [23]. The changes in the DNA by a deficiency of some micronutrients (folic acid, vitamin B12, vitamin B6, niacin, vitamin C, vitamin E, iron and zinc) are considered as the most likely cause of some types of cancer [24]. Carotenoids are the pigments that give fruits and vegetables such as carrots, cantaloupe, sweet potato, and kale their vibrant orange, yellow, and green colors. Beta-carotene, lycopene, and lutein are all different varieties of carotenoids. They all act as antioxidants with strong cancer fighting properties. On the other hand, evidence indicates that vitamin C supplements do not reduce cancer risk [25]. Carbohydrates should be consumed in the form of whole grain cereals – wheat bread and brown rice. The addition of fats should be in the form of fats dehydrogenated [25].

Some vitamins, such as the antioxidant Vitamins A, E, and C, have anti-inflammatory factors that provide protective effects [55]. The daily consumption of antioxidants has the potential of not only protecting against cancer, but also cardiovascular disorders and neurological degenerative diseases [55]. Essential nutrients that have anti-oxidative properties such as vitamin E, vitamin C, vitamin A, and Beta-carotene are involved in detoxification of the Reactive oxygen species (ROS). Vitamin E, A, and Beta-carotene are lipophilic antioxidants whereas vitamin C is hydrophilic antioxidant. Vitamin E function as a free radical chain breaker particularly, it interferes with the propagation step of lipid peroxidation. Vitamin A and Beta carotene have actions by terminating both singlet oxygen and other free radicals generated by photochemical reactions [55, 28].

Table 1: Food components and their Epigenetic role

FOOD	CHEMICAL	EPIGENETIC ROLE
Sesame Seeds	Methionine	Methylates DNA (gene silencing)
Nuts	Folic Acid	Methylates DNA (gene silencing)
Sunflower Seeds	Folic Acid	Methylates DNA (gene silencing)
Peppers	Methionine	Methylates DNA (gene silencing)
Spinach and Other Leafy Vegetables	Methionine and Folic Acid	Methylates DNA (gene silencing)
Broccoli	Sulphoraphane	Acetylates Histones (activating genes)
Other Vegetables	Vitamin B6	Methylates DNA (gene silencing)
Garlic	Diallylsulphide (DADS)	Acetylates Histones (activating genes)
Soy or Soy Products	Choline, Genistein	Methylates DNA (gene silencing)
Milk	Vitamin B12	Methylates DNA (gene silencing)
Bakers Yeast	Folic Acid	Methylates DNA (gene silencing)
Whole Grain Products	Vitamin B6	Methylates DNA (gene silencing)
Fish	Methionine	Methylates DNA (gene silencing)
Shellfish	Vitamin B12	Methylates DNA (gene silencing)
Beef	Vitamin B12	Methylates DNA (gene silencing)
Veal	Choline	Methylates DNA (gene silencing)
Chicken	Choline	Methylates DNA (gene silencing)
Liver	Folic Acid	Methylates DNA (gene silencing)
Egg Yolk	Choline	Methylates DNA (gene silencing

Source: [70]

VI. Conclusion

Different nutrients and bioactive food components or total diet can alter DNA methylation and consequently alter gene expression. These epigenetic changes may affect physiologic and pathologic processes in the body of humans.

Reference

[1]. McKay, J. A. and Mathers, J. C. Diet induced epigenetic changes and their implications for health A. doi: 10.1111/j.1748-1716.2011.02278.x: Acta Physiologica 2011.
[2]. Bird, A. Nature, USA: 2007: 447, 396-98
[3]. Razin, A. EMBO, USA: EMBO J, 1998.

[4]. Payne, G., Laporte, A., Deber, R and Coyte, P. C. Counting backward to health care's future: using time-to-death modeling to identify changes in end-of-life morbidity and the impact of aging on health care expenditures. The Milbank Quarterly: 2007; vol. 85, no. 2, pp. 213–257

[5]. Yazdanyar, A and Newman, A. B. The burden of cardiovascular disease in the elderly: morbidity, mortality, and costs. Clinics in Geriatric Medicine, 2009; vol. 25, no. 4, pp. 563–577

[6]. Mesterton, J., Wimo, A., Langworth, S., Winblad, B and Jonsson, L. Cross sectional observational study on the societal costs of Alzheimer's disease. Current Alzheimer Research, 2010; vol. 7, no. 4, pp. 358–367.

[7]. Barker, D. J. P and Osmond, C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. The Lancet: 1986; vol. 1, no. 8489, pp. 1077–1081

[8]. Kensara, O. A., Wootton, S. A., Patel, A. A, Patel, M., Jackson, A. A. and Elia, M. Fetal programming of body composition: relation between birth weight and body composition measured with dual-energy X-ray absorptiometry and anthropometric methods in older Englishmen. The American J of Clin. Nutr; 2005.

[9]. Osmond,C., Barker, D. J. P., Winter, P D, Fall, C. H. D. and Simmonds, J. S. Early growth and death from cardiovascular disease in women. British Med. J: 1993; vol. 307, no. 6918,

[10]. Hales, C. N and Barker, D. J. P.Type 2 (non-insulin dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia, 1992; vol. 35, no. 7, pp. 595–601.

[11]. Cooper, C., Fall, C., Egger, P., Hobbs, R., Eastell, R and Barker, D. Growth in infancy and bone mass in later life. Annals of the Rheumatic Diseases: 1997; vol. 56, no. 1, pp. 17–21

[12]. Ozanne, S. E. and Hales, C. N. Lifespan: catch-up growth and obesity in male mice. Nature 2004, vol. 427, no. 6973, pp. 411-412.

[13]. Vehaskari, V. Prenatal programming of kidney disease. Current Opinion in Pediatrics, 2010; vol. 22, no. 2, pp. 176–182

[14]. Bergmann, A. and Lane, M.E. Trends Biochem Sci: 2003; 28(9):461–3

[15]. Vo, N., Klein, M.E, Varlamova, O., Keller, D.M and Yamamoto, T. Proc Natl Acad Sci, USA: 2005: 102(45):16426–31

[16]. Henikoff, S., McKittrick, E. and Ahmad, K. Cold Spring Harb Symp Quant Biol: 2004; 69:235–43

[17]. Meaney, M.J. and Szyf, M. Trends Neurosci, 2005, 28(9):456–63.

[18]. Szyf, M.Trends Pharmacol Sci : 2001.;22(7):350–4

[19]. McCay, C. M., Crowell, M. F and Maynard, L. A. The effect of retarded growth upon the Length of life span and upon the ultimate body size, The J of Nutr 1935, vol. 10, no.1, pp. 63–79,

[20]. Anderson, R. and Weindruch, R. Metabolic reprogramming in dietary restriction. Interdisc. Topics in Geront. 2007; vol. 35, pp. 18–38

[21]. Kennedy, B. K., Steffen, K. K. and Kaeberlein, M. Ruminations on dietary restriction and aging. Cellular and Molecular Life Sciences: 2007; vol. 64, no. 11, pp. 1323–1328

[22]. Piper, M. D. W. and Bartke, A. Diet and aging. Cell Metabolism, 2008; vol. 8, no. 2, pp. 99–104

[23]. Colman, R. J., Anderson, R. M. and Johnson, S. C. Caloric restriction delays disease onset and mortality in rhesus monkeys. Science, 2009. vol. 325, no. 5937, pp. 201–204.

[24]. Roth, G. S., Ingram, D. K. and Lane, .M. A. Caloric restriction in primates and relevance to humans. USA: Annals of the New York Academy of Sci: 2001; vol. 928, pp. 305–315

[25]. Walford, R. L., Mock, D., Verdery, R. and MacCallum, T. Calorie restriction in biosphere 2: alterations in physiologic, hematologic, hormonal, and biochemical parameters in humans restricted for a 2-year period. The J. of Geront. A, 2002; vol. 57, no. 6, pp. B211–B224

[26]. Fontana, L., Meyer, T.E., Klein, S and Hollo, J. O. Long term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans. Proceedings of the National Academy of Sciences of the United States of America, 2004; vol. 101, no. 17, pp. 6659–6663

[27]. Fontana, L., Villareal, D. T. and Weiss, E. P. Calorie restriction or exercise: effects on coronary heart disease risk factors. A randomized, controlled trial. American J of Physio: 2007; vol. 293, no. 1, pp. E197–E202

[28]. Hofer, T., Fontana, L. and Anton, S. D. Long-term effects of caloric restriction or exercise on DNA and RNA oxidation levels in white blood cells and urine in humans. Rejuvenation Research, 2008; vol. 11, no. 4, pp. 793–799,

[29]. Heilbronn, L. K., De Jonge, L and Frisard, M. I. Effect of 6-month calorie restriction on biomarkers of longevity metabolic adaptation, and oxidative stress in overweight individuals: a randomized controlled trial. J of the American Med. Assoc., 2006; vol. 295, no. 13, pp. 1539–1548

[30]. Racette, S. B., Weiss, E. P., Villareal, D. T. One year of caloric restriction in humans: feasibility and effects on body composition and abdominal adipose tissue. The J of Geront. A, 2006; vol. 61, no. 9, pp. 943–950,

[31]. Redman, L. M., Rood, J., Anton, S. D., Champagne, C., Smith, S. R. and Ravussin, E. Calorie restriction and bone health in young, overweight individuals. Archives of Internal Medicine, 2008; vol. 168, no. 17, pp. 1859–1866

[32]. Martin, C. K., Das, S.K. and Lindblad, L. et al. Effect of calorie restriction on the free-living physical activity levels ofnonobese humans: results of three randomized trials. J of Applied Physio, 2011; vol. 110, no. 4, pp. 956–963

[33]. De Magalhaes, J. P., Curado,J. and Church, G. M. Meta-analysis of age-related gene expression profiles identifies common signatures of aging. Bioinformatics, 2009; vol. 25, no. 7,pp. 875–881

[34]. Park, S. K. and Prolla, T. A. Lessons learned from gene expression profile studies of aging and caloric restriction. Ageing Research Reviews, 2005; vol. 4, no. 1, pp. 55–65

[35]. Tsagareli, V., Noakes, M. and Norman, R. J. Effect of a verylow-calorie diet on in vitro fertilization outcomes. Fertility and Sterility, 2006; vol. 86, no. 1, pp. 227–229

[36]. Meyer, T. E., Kov´acs, S. J., Ehsani, A. A., Klein, S and Fontana, L. Long-term caloric restriction ameliorates the decline in diastolic function in humans. J of the American College of Cardiol., 2006; vol. 47, no. 2, pp. 398–402

[37]. Fontana, L., Klein, S., Holloszy, J. O and Premachandra, B. N. Effect of long-term calorie restriction with adequate protein and micronutrients on thyroid hormones. The J of Clinical Endocrin &Metabolism, 2006; vol. 91, no. 8, pp. 3232–3235

[38]. Fontana, L. and Klein, S. Aging, adiposity, and calorie restriction. J of the American Medical Assoc, 2007; vol. 297, no. 9, pp. 986–994

[39]. Holloszy, J. O. and Fontana, L. Caloric restriction in humans. Experimental Geront, 2007; vol. 42, no. 8, pp. 709-712

[40]. Willcox, B. J., Willcox, D. C. and Todoriki, H. Caloric restriction,the traditional okinawan diet, and healthy aging: the diet of the world's longest-lived people and its potential impact on morbidity and life span. Annals of the New York Academy of Sci, 2007; vol. 1114, pp. 434–455,.

[41]. Cruzen, C and Colman,R. J. Effects of caloric restriction on cardiovascular aging in non-human primates and humans. Clinics in Geriatric Medicine, 2009; vol. 25, no. 4, pp. 733–743

[42]. Cangemi, R., Friedmann, A. J., Holloszy, J. O. and Fontana, L. Long-term effects of calorie restriction on serum sex hormone concentrations in men. Aging Cell, 2010; vol. 9, no. 2,pp. 236–242

[43]. Trepanowski, J. F. and Bloomer, R. J. The impact of religious fasting on human health. Nutr J: 2010; vol. 9, no. 1 article 57
[44]. Soare, A., Cangemi, R., Omodei, D., Holloszy, J. O. and Fontana, L. Long-term calorie restriction, but not endurance exercise, lowers core body temperature in humans. Aging, 2011; vol. 3, no. 4, pp. 374–379
[45]. Rochon, J., Bales, C. W. and Ravussin, E. Design and conduct of the CALERIE study: comprehensive assessment of the long-term effects of reducing intake of energy. The J of Geront. A, 2011; vol. 66, no. 1, pp. 97–108
[46]. Trepanowski, J. F., Canale, R. E., Marshall, K.E. and Kabir, M. M. Impact of caloric and dietary restriction regimens on markers of health and longevity in humans and animals: a summary of available findings, Nutr. J 2011, 10:107.
[47]. Marti, A., Martinez-Gonzalez, M. A. and Martinez, J. A. Interaction between genes and lifestyle factors on obesity. Proc Nutr Soc, 2008. 67: 1–8.
[48]. Vickers, M. H. Developmental programming and adult obesity: the role of leptin. Curr Opin Endocrinol Diabetes Obes; 2007; 1417–22
[49]. Sinclair, K. D., Allegrucci, C., Singh, R., Gardner, D. S., Sebastian, S., Bispham, J., Thurston, A., Huntley, J. F., Rees, W. D., Maloney, C. A., Lea, R. G., Craigon, J., McEvoy, T. G. and Young, L. E. DNA methylation, insulin resistance, and blood pressure in offspring determined by maternal peri-conceptional B vitamin and methionine status. USA: Proc Natl Acad Sci; 2007; 104: 19351–19356
[50]. Kotsopoulos, J., Sohn, K. J. and Kim, Y. I. Postweaning dietary folate deficiency provided through childhood to puberty permanently increases genomic DNA methylation in adult rat liver, J Nutr 2008: 138: 703–709.
[51]. Waterland, R. A. and Jirtle, R. L. Transposable elements: targets for early nutritional effects on epigenetic gene regulation. Mol Cell Biol; 2003. 23: 5293–5300.
[52]. Lillycrop, K. A., Phillips, E.S. , Jackson, A. A. , Hanson, M. A. and Burdge, G. C. Dietary protein restriction of pregnant rats induces and folic acid supplementation prevents epigenetic modification of hepatic gene expression in the offspring, J Nutr ; 2005; 135: 1382–1386
[53]. da Costa, K. A., Kozyreva, O.G. , Song, J., Galanko, J. A., Fischer, L. M. and Zeisel, S. H. Common genetic polymorphisms affect the human requirement for the nutrient choline., Faseb J; 2006. 20: 1336–1344.
[54]. WHO/FAO. Vitamin and mineral requirements World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland: Publishing and Multimedia Service, Information Division, 2004.
[55]. Nepomuceno, J. C. Antioxidants in Cancer Treatment, Current Cancer Treatment, 2011. [Online]. Available: http://www.intechopen.com/books/current-cancer-treatment-novel-beyond-.
[56]. Pajares, M.A, Durán C, Corrales F, Pliego, M.M, and Matto, J. M. Modulation of rat liver S-adenosylmethionine synthetase activity by glutathione, J. Biol. Chem. 1992, 267(25):17598-17605.
[57]. Lillycrop, K, A., Phillips, E.S., Torrens, C., Hanson. M.A., Jackson, A. A. and Burdge, J. C. Feeding pregnant rats a protein-restricted diet persistently alters the methylation of specific cytosines in thehepatic PPAR-alpha promoter of the offspring, Br J Nutr; 2008; 100: 278–282
[58]. Gabory, A., Attig, L. and Junien, C. Epigenetic mechanisms involved in developmental nutritional programming. World J Diabetes; 2011; 15; 2(10): 64-175
[59]. Fujii, T.M.M., Medeiros, R. and Yamada, R. Nutrigenomics and nutrigenetics: important concepts for the nutrition science. J Brazilian Soc Food Nutr; 2010; 35(1): 149-166
[60]. Milner, J. A and Romagnolo, D.F. Nutrition and Health: Bioactive Compounds and Cancer.Edited by: J.A. Milner, D.F. Romagnolo, DOI 10.1007/978-1-60761-627-6_2, Humana Press 2010: 824p., 2010.
[61]. FAO/WHO/UNU.Protein and Energy Requirements. WHO Technical Report Series, no. 724. Geneva: WHO, 1985.
[62]. Phillips, T. The role of methylation in gene expression. Nature Education 2008. http://www.nature.com/scitable/topicpage/the-role-of-methylation-in-gene-ex
[63]. Choi, Sang-Woon and Friso S. Epigenetics: A New Bridge between Nutrition and Health. Adv Nutr: 2010: 1: 8–16,
[64]. Ames, B.N and Wakimoto, P. Are micronutrient deficiencies a major cancer risk, Nature Reviews Cancer 2002; 2:694–704.
[65]. Berrino, F., Krogh, V and Riboli, E. Epidemiology studies on diet and cancer. Tumori: 2003: 89: 581-585.,
[66]. Davis, C., D. Nutritional Interactions: Credentialing of Molecular Targets for Cancer Prevention of Diseases, Crit Rev Food Sci Nutr: 2005; 45(4): 287-306,
[67]. Willett, W. Diet and Cancer an Evolving Picture. JAMA: 2005; 293(2): 233-234
[68]. Ames, B. N. DNA damage from micronutrient deficiencies is likely to be a major cause of cancer., Mutation Res ;475: 7-20., 2001.
[69]. Dashwood, R. Frontiers in Polyphenols and Cancer Prevention. J Nutr: 2007; 133 (2)267S–269S
[70]. University of Utah. Epigenetics,Your Environment, Your Epigenome. http://learn.genetics.utah.edu/permissions/ 2009. Accessed 23/01/16.