Vol 10, Issue 4, July – August 2022 DOI: https://doi.org/10.31426/ijrpb.2022.10.4.10401

Indian Journal of Research in Pharmacy and Biotechnology (IJRPB)
www.ijrpb.com ISSN: 2321-5674 (Print), 2320-3471 (Online)

Cross Ref DOI: https://doi.org/10.31426/ijrpb **Indexed in CAS and CABI, Impact Factor: 0.64**

FOOD SCIENCE AND TECHNOLOGY DEVELOPMENT, NUTRITION AND HUMAN HEALTH AND AGEING: THE SEARCH FOR AN IDEAL NUTRITION

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Keywords:

Ideal Nutrition,
Food Science and Nutrition,
Human diets,
Human Health
.

ABSTRACT

The objectives of this perspective review article are to describe the possible ways to motivate nutritional researchers to direct their efforts and thinking towards an ideal nutrition. In this context I tried to cover some aspects relative to important topics, such as: an historical introduction of important findings in food science and nutrition during the last century; following mechanisms of cellular damages and susceptibility to diseases; human adaptation to environment, including human diets and dietetic profiles and human health. The importance of genetics and nutrigenomics was emphasized in developing nearly ideal individual diets. However, nearly ideal large population diets could only be achieved, at present, by following the health principles of some well-known health diets, such as: Mediterranean diet, the DASH diet and the MIND diet. At present, the concept of a human ideal diet remains as a utopian thinking.

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Introduction

1. **Historical Marcs (Events)**

Until the beginning of last century foods were considered as simple source of some nutrients such as proteins, carbohydrates, fats, and a few minerals, without any detailed knowledge of their chemical structures, essentiality and their specific functions in the human organism. In the first half of the past century (1900-1945) was already described the essentiality (qualitative and quantitative) for different classes of nutrients such as proteins (amino acids), fats (fatty acids), minerals and vitamins. The concepts of daily quantities of energy and dietetic fibers were still topics of studies and controversies.

Advances in human nutrition are intimately linked and dependent from food preparing technology, as well as advancement in medicine and pharmacology. Along the last century (20º century) important technical and conceptual advances were registered in the above cited areas (1).

As Discipline Nutrition constitute part of Biology and is based on disciplines as anatomy, physiology, Biochemistry and Genetics. In this context its purpose is to understand and explain the mechanisms by which the organism process ingested foods to utilize then through the various systems to produce energy and use the nutritive components and regulators in the metabolism necessary for the formation, growth and harmonic functioning of the whole human body. The nutrition practice become even more complex since it depends on several factors equally important such as, availability of foods, food composition, food conservation and food security, involving areas as agricultural, governmental as well as socioeconomical, cultural and environmental aspects related to the aimed population. In parallel to the chemical studies experimental methods were developed with laboratory animals which permitted to study the nutritional metabolic and physiological importance of the substances which we presently know as essential for the development and maintenance of human health. With these knowledge food composition tables could be constructed and the nutritional requirements, for different ages, gender and physiological states for the human species established. At this point it was known the chemical basis, the biochemical and physiological knowledge of what we can call today of classical nutrition or the general principles of human nutrition (2).

The two world war, particularly the second one, affected humanity with hunger, misery and economics drops in both industrialized an non-industrialized countries. In the 1960-1970 decades, researchers from various countries, such as England (3), United State of America (4), México (5), Chile (6) demonstrated that under nutrition during pregnancy and in the new born (until 3 years of age) cause damage not only on child physical development (body weight and height but) also retardation in learning that may affect physical and mental development throughout adult life.

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From 1980-1990 decades a deep transformation occurred in the concept of human diet and nutrition. The concept of Healthy Functional Diet originated in Japan (7,8,9). The use of food as medicine was always a tradition in Asian countries however in empirical form. Scientific study aiming at understanding the beneficial effects and their mechanisms only started in the second half of the last century in Japan with the objective of lowering the health maintenance cost of the aged population in that country. A multidisciplinary program was established linking together governmental agencies food industries and universities to develop special foods (Foshu) to attend special needs of old people of different ages and genders, so that these foods could be used to replace medicine, therefore lowering the medical and social assistance to these sub-sections of the Japanese population.

Between the years 1980 to 2000 there was an extraordinary progress in healthy and functional foods and bio-active compounds (not considered nutrients) many of them with allegation of species benefits to health, approved by the Regulatory Agency in their respective country.

According to Arai (8) in 2001 the Japanese industry already commercialized over 200 functional foods (Foshu). These researches and development in Japan stimulated research in practically all countries in the world including Brazil.

Some examples of food products and or ingredients with allegation of nutritional functionality are commercialized in Brazil as presented in Table 1 (1).

2. Update comprehension of human ageing

Human ageing is a result of a progressive accumulation of cells defects which start to appear very early, probably in the maternal uterus during pregnancy. Along human life these defects increase and become more damaging, eventually resulting in dysfunctions of cells and tissues. They can extend to organs and systems and can cause a progressive reduction of the ability of adaptation to physiological changes which occur with ageing (10).

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Table 1. Examples of food products or ingredients with functional properties allegations (approved or not) in Brazilian Market

Product/Ingredient	Commercial name	Producer	Allegation
• Fluid milk			
1. Addition of soluble fiber (Inulin 1,5%)	Fibresse	Parmalat	Fiber source
2. Reduction of lactose (90%)	Zymil	Parmalat	Milk of easy digestion
• Powdered milk:			
1. Addition of soluble fiber (Resistent Dextrin)	Molico Actifibras	Nestlé	Prebiotic action
2. Addition of FOS+Insulin	Ninho (Prebio^1)	Nestlé	Prebiotic action
3. Addition of FOS+Insulin	Ninho (Prebio^3)	Nestlé	Prebiotic action
• Fermented milk Lactobacillus casei shirota)	Yakult and Yakult 40	Yakult	Prebiotic, contributed to intestinal flora equilibrium
Fermented milk: Added of Lactobacillus paracasei+ zinc	Chamyto	Nestlé	Prebiotic action immune-stimulant
Yogurt	Activia	Danone	Prebiotic function intestinal microbiota equilibrium
Yogurt (Lactobacillus acidophyllus + Bifidobacterium lactis+ soluble fibrer	Biofibras	Batavo	Contribute to microflora equilibrium
Yogurt (Bifidobacterium animalis) + soluble fiber	Nesvita	Nestlé	Help intestinal function
Margerine: + Soluble fiber	Qualy	Sadia	Contain soluble fiber, help intestinal function

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Table 2. Examples of food products or ingredients with functional properties allegations (approved or not) in Brazilian Market (continued)

Product/Ingredient	Commercial name	Producer	Allegation
• Margerine			
1. With soluble fiber + AGstω3+ω6	Becel	Unilever	
2. Margerine + fitosterol	Becel	Unilever	Contain fatty acids W6 and W3 + soluble fiber + fitosterol (reduce seric cholesterol)
• Soybean			
Protein	Concentrate; isolate	Several	Control of seric cholesterol; may contain isofavones
Flower/Flaks	Farinha Granola	Several	Cholesterol control; may contain isoflavones
Hydro-Soluble	Ades	Unilever	Contain fruit juices (varios types); vitamins (B complex) + Iron and zinc
Coagulated Extract	Tofu	Aarutaka Ind. Com. Pilões Agr. Ind.	Seric cholesterol control; may contain isoflavones
Fermented extract	Yogurt	Several	Cholesterol control, prebiotic bioactive peptides
• Collagen Purifyed/hydrolysed	Gelatin, hydrolysed gelatin	Gelita Group	Ingredients for many formulations; stimulate collagen synthesis; protect joint and muscle
• Collagen hydrolysed	Gelamin	Advanced Nutrition	Low energetic value, stimulate collagen synthesis, protect joint; contain vitamins (A,C,D,E, biotin) + Cu, Se, Zn, Mn
• Gelatin	Gelatina Dr. Oetker	Oetker	Fruit taste (several); contain vitamins A,D,B1,B6, Fe, Zn

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3. Mechanisms of cells damage

As shown in Sgarbieri, et al. (11), aging involve multiple mechanisms bio-physiologic which impact human organisms at different levels.

Many evidences suggest that an important agent connecting different types of cell's damages are the reactive oxygen species (ROs). Also known as free radicals which are produced as secondary products in the cellular energy generation products in the human body (12). Of special significance are the damages produced by ROs on cellular DNA through: 1) DNA damage to the cells nuclei chromosomes resulting in disturbances to genes functioning; 2) damage to telomeres structures of DNA protection located at the end of chromosomes; 3) damage to DNA existing in the cells organel interior generation of energy, as mitochondria, resulting in a blockage of energy production. In addition it has become apparent that with ageing there are progressive alterations of the genome epigenetic function mainly alterations in DNA methylation, which may result in deep effects in gene expression and cellular functioning.

3.1. DNA damage and repair

Although DNA repair may assume several forms, it is estimated that the oxidative damage is among the most important adding a great number of oxidative attacks per cell and per day. The main agent in the immediate induced damage of DNA by free radicals oxygen species (ROs) is the polymerase-1 enzyme (PARP-1), that recognize lesion in the DNA and attack then for the repair. Grube and Bürkle (13) discovered a strong positive correlation of PARP-1 with long life species; cells extracted from long life species having more elevated PARP activity than cells extracted from short life species. In the same line it was found that in centenarian humans, in general, they had maintained good general health, and presented more elevated polymerase-1 (PARP-1) than the general population.

3.2. Telomers

In many humans somatic tissues the decline of cellular division capacity with age seems to be linked to the fact that the telomers, which protect the chromosomes terminal becomes progressively shorter with cells division. This is due to the absence of the telomerase enzyme which is expressed only in stem-cells (ovaries and testis) and in certain stem-cells. Telomerase erosion below certain critical values seems to promote a specific cellular cycle resulting in an incapacity of cells to continue dividing. The telomers shortening is too accelerated in cells under increased stress. The clinical relevance of understanding telomers maintenance and their interaction with stress is important.

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An increasing number of evidences suggest that the telomers length is linked with ageing and mortality (14). The telomers not only become shorter with normal ageing in various tissues (ex: lymphocytes, vascular endothelial cells, kidney, liver), but their reduction is also more accentuated in certain pathological states. For example, it has been determined an incidence 100 times higher of vascular incidence in individuals with a premature shortening of telomers (15). The vision that oxidative stress accelerate telomers loss suggest an intriguing possibility that premature telomers shortening "in vivo" may be an indicator that of previous stress exposition and may therefore function as prognostic indicator for disease conditions in which stress condition could been the cause.

A cross-sectional study in women showed that the telomers length decreased in a constant manner from 27 pairs of bases (pb) for each year of age. However, the telomers showed 240pb shorter in obese women compared to non-obese; in terms of telomers length obese women were 9 years older than the non-obese womens. In addition there was a significant close-dependent reduction in telomers length with obesity and cigarette smoking (16).

3.3. Mitochondria

An important connection between oxidative stress and ageing was found by mitochondrial DNA deletion and pontual mutations with ageing (17). Mitochondria are intracellular organells, each one carrying their genomic DNA which is responsible for cellular energy generation. As by-product of cellular energy generation, the mitochondria are also a major source of ROs within the cells, therefore are responsible for production of cellular energy and major site of oxidative stress. Any increase in mitochondrial DNA mutation (mtDNA) related to ageing will probably contribute for a progressive decline in cells and tissues, capacity to produce energy. An increase related to ageing in frequency cells deficient in the enzyme citochrome C oxidase has been reported in human masculine tissue (18) and in the cerebrum (19). Evidences for accumulation of mtDNA mutations were obtained mainly for central nervous and muscular systems were cellular divisions are rare (20). However, more recent work have revealed a strong relation of dependence with age in accumulation of mtDNA mutations in human intestinal epithelium which slow a higher cell division velocity than any other body tissue (21). It seems that the accumulation of mutations of mtDNA may be a generalized phenomenon.

3.4. Epigenetic alterations

Epigenetic describes modifications in the genome that are copied from a cell generation to the next but that are not involved in changes in the primary sequence of the DNA (22).Such modifications involves DNA methylation and "tails" pos-translational of histones which are part of the nucleosomes globular proteins (structural part of the chromatine which involves the DNA). It is

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possible that these two types of modifications take place at the same time perhaps acting in a cooperative way, but, in the ageing context the major part of the available data are related to DNA methylation.

The ageing is associated with a simultaneous reduction in the total content of nuclear genome methyl group and in hyper-methylation (abnormal increase in methylation) of a subgroup of rich regions in cytosine known as CpG islands in the promotors (regulatory regions of DNA) of certain genes. Similar alterations, although probably in different genes and in other DNA domains where tumorigenesis occur. Holiday (23) suggested that this epigenetic alteration may be responsible for abnormal gene expression during an oncogenesis (tumour formation) and also for ageing. Since then it has been clearly demonstrated that a hyper-methylation of the CpG island result in gene silencing of the associated gene. For example, Issa, et al., (24) observed that ageing was followed by CpG island hyper-methylation in the gene promoting region that express the estrogenic receptor (ESR1) with a blockage of this protein.

Hyper methylation promoters of various genes with increase in age has been reported for various tissues including colorectal epithelium (24), cells from the immune system (25), and gastric mucosa (26). These losses of epigenetic control can result in adverse effects in ability of the cells to maintain homeostasis.

The epigenetic that include mechanisms of gene expression and regulation independent of DNA changes in its sequence, regulate the expression of genes by chromatine structure modulation or by transcriptional ligation to DNA. Several studies showed that the defects of epigenetic mechanisms promote alterations of gene expression resulting in several diseases related to ageing. Alterations in these mechanisms are also linked to genes that occur during ageing processes that occur in different tissues. In a recent revision the authors Pagiatakis, et al., (27) propose: as part of their conclusions the authors state that much progress will still be necessary to understand the epigenetic changes in the aged cardiomyocyte (both physiologic as pathologic), the reactions that are critical for the maintenance of the cardiomyocyte, which are key factors that influence in the architecture and govern the alterations in gene expression that promote diseases. As to cancer, in spite of decades on carcinogenesis, the mechanisms (genetic and epigenetic) which govern aberrant genes expression changes, cellular identity and responsiveness to the cellular signals leading to cancer, still remain unknown. The studies have revealed that the understanding of the epigenetic mechanisms would exert a deep and generalized progress in the elimination of the tumorigenesis. Similarly to other pathologies, many questions still remain as to how correlate carcinogenesis and ageing mechanisms.

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4. Diet, Metabolic Processes And Susceptibility To Diseases.

Research on traditional nutrition has based in the supposition that all individuals have the same nutritional necessity in spite of health profetional recognizing existence of differences in relation to gender, phases of life and health condition. Dietetic recommendations to population as RDIs (Recommend Dietary Intakes) which were developed so that the majority of the individuals receive beyond their daily nutritional needs, and also some benefits in terms of disease prevention. In spite of the RDAs (Recommend Dietary Allowances) being periodically revised to adequate themselves to new knowledges that have been generated in the fields of nutrition and Dietetics the chronic diseases related to nutrition still continue to increase in the last years, Fenech, et al., (28). The present movement toward a more personalized nutrition is guided by an increased body of evidences, demonstrating individual needs in regards to products of medicamental use both for prevention as for treatment of diseases. In the complex relation between food, diseases and functioning, of the organism, food can be considered the cause as well the cure of many diseases, Ghosh (20). It is recognized the great number of individuals that die annually for different medications, Ng, et al., (30). For nutrition such premises are not different and one can see daily examples in the clinical practice. In Sgarbieri, et al., (11) it was emphasized a strong inter-relation existent between genetics factors (traces inherited from our parents and/or ancesters) and the environment, and lifestyle), among which diet figures as the most important.

A classical example of interaction among genes and nutrients is the coelic diseases in which one uses routinely a personalized nutrition. This debilitating diseases results of the organism incapacity to deal with gluten which occur in a few foods in the diet, resulting in serious inflammatory processes causing intestinal villi alterations and nutrients bad absorption. The treatment is based on diet therapy, includes food-containing gluten exclusion (wheat, oat, rye, barley) in addition to prepared foods which contain such components in their preparations (31).

The specific protein unity that cause the problem are gliadins (protein component soluble in alcohol present in the wheat gluten) in addition to phytogenetically related protein components like secalins of rye and the hordeins in barley. Differently of the majority of allergic food reaction, in which immunoglobulin E (IgE) is involved, in coeliac disease an immunoglobulin G (IgG) also participate and involve an autoimmune component, having a strong genetic association with the human leucocytary antigen (HLA), belonging to class II antigen, Mine and Yanga (32).

With the purpose to solve practical problem, many gluten-free foods have been developed and are commercialized. The hereditary component of the coeliac disease is well known. Twins children have approximately 75% similarity in this disease development, Greco, et al., (33). However, carrying the genes for the coeliac disease do not necessarily cause the disease development, but it

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reveal a genetic predisposition against such dietetic factors. Presently it is known that genetic multiple variations are involved in the coeliac disease development. Among them it seems that the most consistent seems to be a variation to the gene HLADQ (DQ2 and/or DQ8), according to Romanos (34). In spite of genetic tracing not being used in the clinical practice for diagnostic purpose, measurements of these genetic variations is important, because they help to identify individuals at high risk of developing the disease. In this way one could have a follow-up and the precocious dietetic management avoiding adverse events related to their pathology.

A great diversity exists in the genetic inheritance among individuals and ethnic groups that directly affect nutrient bioavailability and metabolism. Differences also exist in the nutrient availability and in food choice among individuals due to series of cultural and economics and individual preferences for a determined taste. In addition malnutrition, both for under as over nutrition can affect gene expression and genomic stability. These conduct to mutations at chromosomic level and in the genes sequence and an promote abnormal genic expression causing appearance of adverse phenotypes during life stages (28).

Similarly of what occur in coeliac disease, interaction exists between genes and nutrients routinely, however only at a little over one decade the evidences of these interaction have received the due attention. It is hoped that in a new future we can utilize such a knowledge produced by the nutrigenomic study for the development of nutritional routs every time more personalized and more efficacious, not only for treatment but mainly for a prevention of diseases in the population.

The Nutrigenomic or Nutritional Genomics, is the Science that aims at understand the molecular mechanism of how diet and foods, as well as nutrients and bioactive compounds reach the metabolism and health of individual separately or in a group, by influencing the expression of genes and proteins, consequently affecting their phenotype. That is, as physical and physiological manifestations of such expression influences directly the process of health and disease (35). In other words, a nutrigenomic aims to understand the effect that food/nutrients/bioactive compounds exert on functioning of the organism and the manner they can promote health benefits through diet, as well as to contribute for the treatment of pathologies by the selection of certain types of foods.

The terms nutrigenomic and nutrigenetic, are generally confounded however each one of then expresses different objective and meaning. The Nutrigenetic is a Science that aims to understand in what manner the genes of certain individuals interact with a diet the foods/nutrients/active compounds consumed by these individuals can promote different effects on the phenotypic manifestations of these people (28). On the other hand Nutrigenomic focus on effects of diet/food/bioactive compounds on the genic expression process, metabolism and the physiology of the organism, the nutrigenetic focus on how certain genetic profile answer to these compounds originated from the diet, promoting different metabolic and physiological effects.

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In such way, the major objective of the genomic study is to establish a personalized diet for each individual, according to their genetic profile and metabolism aiming at optimizing this individual organism functioning for the maintenance of their health and possible disease prevention: The Nutrigenomic also uses this knowledge for helping to control possible pathological processes of being treated by diet improving the prognostic of these processes and contributing for a larger lifespan of the patient. In addition the acquired knowledge by applying genomic information to nutritional research also will improve the quality of evidences used for elaboration of nutritional recommendations at populational levels.

According to Patras and Tudose (36) the genomic is a discipline in the frontier of Ecogenomic that study individuals route of genetic polymorphism and the influence of diet as risk factor for the occurrence of chronic diseases. The genetic interaction with dietetic factors conduced to this field of research, that relates the genetic role with nutritional requirements and susceptibility to chronic diseases related to nutrition. Patras and Tudose (36) describe in an excellent review article some of the well know interactions between, dietetic factors and genetic traces that result in metabolic disturbs and diseases whith normally can be controlled by dietetic managements. In addition we have phenylketonuria; genes interacting with lipids metabolism; food allergies; deficiency of the enzyme glicose-6-phosphate dehydrogenase (G6PD), among others.

The phenylketonuria is a genetic defect in the metabolism of the amino acid phenylalanine caused by the genetic failure in the production of the enzyme phenylanine hydroxidase (FAH). A deficiency in the FAH activity results in over 300 genetic mutations which conduct in an hyper-phenylalaninemia and phenylketonuria. The classic phenylketunuria that conduct to a progressive mental retardation can be prevented by dietary restriction of the amino acid phenylalanine and supplementation with tyrosine which is the product the FAH enzyme reaction.

Another important genetic polymorphism interaction occur with exogenous factors influencing the transport of lipids metabolism increasing the risk of cardiovascular diseases (37). More than 250 single nucleotide popymorfisms (SNPs) have been identified in about 15 genes that express key proteins in lipoproteins and lipids metabolism.

The food allergies also result from interactions of genes with diet, involving sensitization of immune answer via immunoglobulin E specific production (IgE). The antibody is distributed associated systematically with cells of individual, a subsequent contact with the allergen induce a reaction. Many food allergies are associated to a limited number allergenic sources including: bovine milk, eggs, peanuts, wheat, fish, shellfish and soybean. The symptoms common to allergenic foods include, nausea, vomit, abdominal pains, distention, flatulence and diarrheal.

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Another metabolic disturb of genetic nature is favism. Involve the enzyme glicose-6-phosphate dehydrogenase (G6PD), the first enzyme of the pentose-phosphate metabolic cycle which determine the reactions velocity of the oxidative part of referred cycle. In the blood red cells its function is to protect the cells from free radicals. In general, deficiency of the G6PD is not extreme; however, clinical manifestations occur when this low reductive capacity is coupled with exogenous oxidative stress, as exposition to one oxidative agent such as diabetic cetose, or a viral infection (38). A source of dietetic is the Faba bean (Vicia Faba), a human food common in the Mediterranean regions of European Midle Orient. The glycosides vicin and convicin, present in Faba bean are hydrolysed in the intestinal tract releasing the aglicone pirimidines, divicine an isouramil, which will cause allergic reactions.

Peña-Romero, et al., (39) in an excellent review article describe the most important genes associated with human obesity and cardiovascular diseases. The obesity is a medical condition resulting from a disbalance between ingested energy (EI) and the total energy consumption (TEC), associated with alterations in various metabolic cycles (40). The obesity assumes special importance once it can contribute with origin and development of other disease. It is considered the main risk factor for type-2 diabetes since it was estimated that over 60% of obese people will develop type-2 diabetes along their lives (41). Several genes and single nucleotide polymorphysms (SNPs) have been associated with obese phenotypes, in animals as well as in humans; some of then discovered by using a modern association (GWAs-Genome-wide association technology), according to (42,43). As presented and discussed by Peña Romero, et al., (39) four genes (FTO, INSIGZ, MC4R and APO-A) have been demonstrated by various investigators, an important participation of these genes through various polymorphysms, in the development of human obesity. The same authors also reported the participation of five other genes (MTHFR, PPAR, APO-A, APO-E, LIPIC) wich were investigated through different polymorphism between 2001-2016. How genes explain the nutrigenomic and nutrigenetic involved in the development and manifestations of pathologies observed in human cardiovascular diseases.

The phenotypic and genetic variations of certain populations may influence their answer to medicamental and dietetic treatments, as well the surgement of diseases. One example is the number of copies of the enzyme amylase that participate in the starch degradation and show variations among different populations based on adaptation of them to the abundance of carbohydrate present in the environment. Such individuals probably have a better starch digestion and could probably differentiate them in intestinal pathological processes (43). In other example, it is known that the body mass index (IMC) the risk for appearing type-2 diabetes is of 25 Kg/m2 or for individual with European ancestrality but between 21-23 Kg/m2 for those with Asian ancestrality (44). Inclusive the so called “halthy” metabolic sate also present their genetic and phenotypic variations.

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When we are evaluating the obesity, condition in which occur an excessive increased of adipose tissue, one normally think that these conditions will expose the individuals to a greater risk of developing degenerative chronic diseases (DCNT), non-transmittable and metabolic syndrome. However, obesity by itself is not necessarily a disease when evaluated from the nutrigenomic point of view. There are people which are classified as obese according to their IMC, however they may not present associated health problems. Sumô fighters, a sport practice respected in Japan, for example. These fighters have a great quantity of adipose tissue, but, if they keep on active they rarely develop disease associated to obesity (44). This means that obesity is not hereditary but the capacity of energy storage in the form of fat is hereditary. For this genetic profile to express environmental factors such as inadequate diet and sedentarism contribute many genetic mutations have been identified as being able to predispose individuals to develop obesity as illustrated in Table 2 (43).

Table 2 – Main genes associated with obesity phenotype

Gene	Phenotype	Gene	Phenotype
• ADRB3	• Obesity, IMC, visceral abdominal fat	• LPL	• IMC, in women
• APO1	• IMC, type-2 diabetic	• MC3R	• IMC, % fat, respiratory quotient
• APOB	• IMC, abdominal fat	• MC4R	• IMC, % fat, fat weight
• FABP2	• IMC, abdominal fat	• NPY	• OMC
• IL-6	• IMC (in men)	• NPY5R	• Obesity
• IL-6R	• Obesity (women)	• NR3C1	• Obesity, visceral abdominal fat
• INS	• Obesity, IMC, Waist/hip ratio (women)	• PPAR PPRα	• IMC (type-2 diabetes, % corporal fat
• IRS2	• IMC	• PPARG PPARγ	• Obesity, IMC, fat abdominal visceral
• LDLR	• IMC, obesity	• PPARGC1	• IMC, fat weight, adipocyte size
• LEP	• Body weight/IMC,	• TNRC11	• Obesity
• LEPR	• Body weight/IMC abdominal adiposity	• UCP1 (uncoupled protein)	• Body weight, IMC, metabolic rate at rest
• LIPE	• Obesity, IMC, fat		

Adapted from: Dubois Moreira (43)

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More recently, the Academy of Nutrition and Dietetic published its position about the use of nutritional genomics, stating their utility to clarify about the interaction between diet and the individual genotype and haw these interactions may affect the phenotype (45). The authors, however, make a reservation on the practical application of nutrigenomic for complex diseases, such as chronic degenerative diseases, since Nutrigenomic is still considered an emergent science and its knowledge is not ready yet for routine applications by nutritionists and professionals in the area of health care (45).

5. Human evolution and adaptation to the environment

According to what we have described in previous papers (1), (46), (47) the human species has developed and continues being adapted under pressure of a serious of factors, such as: genetic inheritance, and environmental factors (diet, environment, lifestyle).

As an introduction to this topic my attention was turned to an interview given by Sergio Pena from University of Minas Gerais (UFMG) dealing with genetic ancestrality of the Brazilian population (48).

According to the above mentioned researcher the Brazilian population has an inheritance derived from Europeans, black Africans and native Amerindians. According to Pena, specialist in medical genetics, there is no other country in the world with such a human types miscegenation as in Brazil. Working on DNA Pena and his collaborators demonstrated the existence of an ancestral similarity in the different regions of Brazil. This homogeneity derived from the fact that from 1970 up until now entered in Brazil almost 6 millions European immigrant. As a consequence of this European immigration miscegenation among Europeans, African Negros and Amerindians the Brazilian genetic constitution resulted in almost 70% European inheritance, independent of skin color and country's region. The predominance of pards in the north and northeast depends on a geographic phenomenon: the individuals are more exposed to solar radiation in these regions. It can be found in Porto Alegre (South) people with white skin, with the same levels of African ancestrality of people of pard skin from the North. What makes the skin white or pard is the environmental factors the insolation. These facts indicate that the unique acceptable criteira for the Brazilian skin colour is an autodeclaration.

A miscigenation permits that in Brazil one can find white persons with anemia falciforme, an endemic disease typical of African countries. In the same way we can find black people or pards with cystic fibrose, a disease more frequently found among Europeans. There is only 20 or 30 genes involved in skin colour determination, among the more than 20,000 genes that constitute human genome.

Indian Journal of Research in Pharmacy and Biotechnology (IJRPB)
www.ijrpb.com ISSN: 2321-5674 (Print), 2320-3471 (Online)

Cross Ref DOI: https://doi.org/10.31426/ijrpb Indexed in CAS and CABI, Impact Factor: 0.64

Unfortunately science has not yet succeeded to put into practice the fact that the above mentioned discovery should be adopted in human social relations. The genetic showed that races do not exist. That racism is a cultural construction, therefore, as we invented it, we could with some effort eliminate it. We can and we could construct a society without races (48).

5.1. Importance of diet in human evolution

It seems not to have doubt that along the history of evolution the human species have selected their foods by tentative and errors following the instinct of their taste, olfaction and brilliant colours. These themes have been discussed in recent years by scientists in the area of populational genetics with the objective to evaluate environmental factors that more strongly influences the evolution and adaptation of ethnic groups and came to the surprising conclusion that diet may be a factor much more determinant than this aspect.

Hancock and collaborators (51) stated that a diet had an influence much greater on genetic alterations than the geographic region. The authors used genotypic data of 612 humans populations. For each one of these populations they obtained environmental data of four ecoregions variables an seven variables of substance, which comprehended four subsistence strategies and three principal components of dietetic variables.

The researchers imagined that being roots and tubers sources rich in carbohydrates, the more significant set of genes for populations that depends on this source of foods, would be involved in sugar and starch metabolic cycles. Sure enough they found associated correlation with polars ecoregions, were they found a diet rich in roots and tubers. Not by chance, many of the more strong correlations found were similar to the reported in studies of ample genomic associations that implicated in phenotypes susceptible to type-2 diabetes as function of excess circulating sugars.

5.2. Dietetic diversification and the arising of carnivors

An important phase in human species adaptation occurred when the gastrointestinal system (GIS) of the vegetarian ancestrals was reduced by introduction of meat in the diet. This fact induced some researchers to propose that, with passing time, changes in the diet could have increased the velocity of human evolution. Psouni, et al., (50), for example, proposed that due to adoption of carnivory diets it was possible to human species to shorten the lactation period, decrease the size of their digestive system and develop a more voluminous cerebrum.

The authors above cited studied not only human populations, but a sample which include 67 genders originated from 12 mammal’s order. These authors encountered a high degree of similarity between relative scales of time in development and life history of the species evidencing that the impact of

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carnivory diet on duration of maternal milking in humans is quantifiable, being a critical factor for the human evolution. The precocious weaning cause a smaller intervals of the birth and a greater reproductive velocity, with profound effects in population dynamic. These finding emphasizes the carnivory habit as a fundamental happening and a human evolution determinant.

5.3. Potential for human adaptation

When selection act on polygenetic traces, that is, traces under command of more than one gene, localized in different chromosomes, instantaneous alterations in the alleles frequency (% of alleles occurrence in population) may occur in many locus (point of chromosome), in that each allele act promoting a small contribution to the population phenotype. Therefore, a phenotypic characteristic that is controlled by a set of genes, instead of a single gene, is subjected to a rich series of variations, which is probably the result of environmental pressures indicating that the personality trace suffered adaptation with time and that it is subject to modulation by the environment. As a consequence, the phenotypic flexibility appears first in time and represents genetic advantage for the species although not necessarily for all the individuals, since not all individuals of a specie posess the same expression potential. As the genotype is installed it should be maintained with a potential for adaptation and surviving of the species. However, this inherited benefit would not be completely utilized, if would it be by the existence of an abundant. DNA species in the chromosomes once named inutille DNA ("junkDNA").

The gene expression could be increased or decreased ("up regulated or down-regulated") by the action of these DNA fragments named accessories ("single nucleotide polymorphisms") or "SNPs". Therefore, Hancock et al., (51, 52) interpreted that, as roots and tubers are also poor in folic acid, a vitamin with important function in the surviving of neonates and for health, a strong signal for genes involved in the folic acid metabolic cycle should be present in populations accustomed with amylaceous foods. The above mentioned authors verified that this was the case and, interestingly, the authors also verified additional signals with those individuals usually consuming cereal diets, with SNPs implicated in type-2 diabetes and in hydrolysis of vegetal lipids.

In conclusion a series of studies conducted by Hancock and collaborators, end up with a publication in 2010 showing, in perspective, the strong influence that diet can have in evolution of humans and this impact has stronger effects than those caused by other environmental factors in the direction determination that the evolution should have. It was also suggested that, fortunately, many individuals seems to be endowed with unknown capacity to adapt themselves to the environmental pression, prove that can be encountered in non genic DNA diversity which can modulate allele expression permiting viables phenotypic variations. However, one remanescent question is the following: why each specie member do not have the same abundance of DNA resoures which could capacitate each one, to survive to the heavy weight of the environmental pression? If this were the

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www.ijrpb.com ISSN: 2321-5674 (Print), 2320-3471 (Online)

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case, the nature would be contradicting their own diversity principles increasing the risk of species extinction.

In obesity specific case, we should consider that an alteration may conduct to diverses interaction among various other metabolic cycles. For example, the fact that the polymorphism conducting to a major corporal fat deposition was activated by a dietetic factor could mean that other genes have also being regulated to express more or less of a product, altering, the insulin receptors functionality sugars stransport, and intracellular kinases. When different polymorphisms and more metabolic cycles are involved, it should not be expected to occur in the same manner for the same factor, in this way attenuation or compensator answers could be expressed in some, but not in all individuals, Hancock, et al., (52).

5.4. Velocity with which the adaptations occur

Depending on nature and intensity of environmental change, alterations in animal and human organisms can occur in a short space of time. For example, quick bone loss and reabsorption in experimental animals and humans was documented under gravity near zero, in missions and permanence in international space station, Tavella, et al., (53). Other dramatic example is the diaphragm muscular atrophy in patients under intensive care a few hour in respirators.

Genetic alterations, meaning an emergency to new genes, do not occur rapidly in superior organisms, but alterations in non-gene DNA can occur in any specie in relatively short space of time, as result of environmental pressions. As billions of organisms may die at each hour under strong pressure of an antibiotic, the genetic diversity may offer to the species the possibility that some individuals survive because of subtle differences in their non-gene DNA. But, as this DNA is not what codifies the specie characteristics, the surviving population continue being of the same specie, then we can be in the presence of resistant lineage in about a few hours.

5.5. Fat Deposition And Obesity – A Central Health Problem

Is the body fat deposition the key factor of the world obesity epidemic?

Body fat tends to be associated with obesity on account of unbalanced diet, sedentariness and a lifestyle inadequate to health. The obesity normally initiates with tissues inflammatory process which can result in non-transmittable chronic diseases. However, adipose tissue in adequate proportion, is essential for reproduction and immune function, producing and receiving diverse molecules signalization which regulates energy production necessaries to muscles and cerebrum inanition. The great number of individuals alleles associated to adipose tissue suggests the involvement and integration of the adipose tissue with a diversity of metabolic cycles in the entire organism.

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In a published revision on the epidemic character of obesity Chaput, et al., (54) concluded that, from physiological point of view, the excess of body weight gain observed in certain individuals must be understood as a normal consequence of environmental changes rather than a pathologic process. Consistent with these statements is the fact that when an obese individuals suffers a substantial body fat reduction, signals of decreased energetic consumption appears superior to the expected, in addition to an increase of hypoglycaemia and related depressive symptons, appetite uncontroll, in addition to increase in the plama and tissues, due to organic poluents liberation which promotes hormonal disturbances and metabolic complications. In contrast body fat increase generally promotes apposite adaptations emphasizing that the obesity can realistically be understood as a "a priori" biological adaptation for the majority of individuals.

After consideration about the two apparent divergent functions of body fats, we can agree with Wells (55) when he suggests that human adipose tissue, accumulated as body excess and obesity establish as result of interactions with other environmental pressions of the modern world and in this way propose that "the pathologic component of obesity could be, not necessarily in the adiposity but, in the interference of our habitat and modern lifestyle".

5.6. Dietetic profile and health

Based on previous description in this short review, one can conclude that the past century (century XX) was of great conquests in human dieting and health as a function of advances in medicine in relation to the contagious and transmissible diseases by side of great advances in nutrition and Food Science and Technology, offering foods of better quality more available to the population. Mesures were taken to eliminate in good part, diseases caused by lack or excess of determined nutrients in the diet. In addition there was a significant increase in the expectation of life length of the Brazilians, that practically doubled along the last century. These changes occurred as function of diet improvement and of the conditions and lifestyle of part of the population. As part of increase in longevity and a decrease in natality, it has been a predominant increase of the aged population and also an incidence of higher chronic and/or degenerative diseases of multiple causality and treatments, much more complex of cardiovasculars and cerebrovasculars diseases, plus diabetes, obstructive pulmonary disease, general inflammatories diseases, osteoporosis, among others, Sgarbieri (1). For these diseases, the medicine and nutrition have not yet found satisfactory solutions.

If we accept the premiss that the human specie is still under evolution, a goal to reach an ideal diet, seem unachievable; we would always be trying to reach a frontier which moves itself under evolutive pressures and environmental changes. With the genetic advancements, also in human metabolism, we could for the best apply today the nutrigenomic concepts (Genomic, proteomic, metabolomics, epigenomic) which permit to develop special diets for individuals and specific groups aiming, at best, to solve dietetic problems for short and medium times, for restrict groups but never for large populations.

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According to Kremer, et al. (56), there is a growing understanding that heath is not simply an absence of disease, but it involves also a continued adaptation to the environmental changes. A new concept of health emphasizes the organisms habilities to adapt themselves to constant challenges of physical, social and emotional domains, Huber, et al, (57). In the physiological domain a healthy organism is able to maintain physiological homeostase through changes called allostasis (58). In the metabolic health context the metabolic health has been called "phenotypic flexibility", Van Ommen, et al., (59). Chronic stresses can induce adaptation processes that go beyond normal phenotypic flexibility limits conducting to a progressive inflexibility, which otherwise can contribute for disease establishment. Micro-nutrients and bioactive substances play key-functions in maintaining phenotypic flexibility, as energy excess, high glucose ingestion, sucrose and fructose or certain trans fatty acids, causes a phenotypic flexibility decline. The micronutrients are involved in metabolic processes with exclusive and interactive functions in the organism, which have been studied mainly in isolated form.

The human health is based on a complete net of interactions among metabolic cycles, mechanisms, processes and organs. Many of these processes have to function in a continuing environmental change (diet, infections, stress, temperature, exercise, etc.), therefore, in constant fight maintaining internal homeostasis, to adapt themselves to these Changes (60).

Still according to Kremer, et al. (56), for advances in health related to nutrition, there is a clear necessity to characterize a complexity that exists in the interaction between nutrients and the metabolic net of routes, mechanisms, processes and organs, which conduct the human health. In addition, it is evident that physical health do not constitute the only aspect of human health related to nutrition, since mental health and social life interact with physical health. The authors above cited suggest that, to advance with an agenda in global nutrition, would be necessary to use integrated nutritional research, using a health marker system to cover relevant aspects of physical, mental and social health domains.

The food industries, particularly big corporations grew very rapid to attend the demand and diversity of national and international populations offering an enormous variety of processed foods to satisfy consumer requirements in respect to taste, acceptation, presentation and convenience, in addition to an aggressive promotion with the main objective to promote maximum selling and lucrativity. These new situation in constant change would require confidence of the consumers in the information furnished by dealing with foods, what frequently do not correspond to reality in favour of consumers. In this environment of uncertainties, one must also add the fact that a large number of consumers, do not have the necessary knowledge on foods composition and properties to be able to choose adequate foods to promote and maintain their health an avoid various problems including diseases, Sgarbieri (1).

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Some of most frequent problems detected in the Brazilian food habits and in processed foods available in food markets are as follows: 1) excessive ingestion of refined foods, in detriment of more complex carbohydrates, such as natural polysaccharides and dietary fibers; 2) excessive ingestion of salt (mainly NaCl), which may lead to hypertension; 3) fat containing trans fatty acids, and low ingestion of polyunsaturated fatty acids (PUFAs), particularly n-3 PUFAs, contrary to n-6 PUFAs that if ingested in excess, result in inadequate relation ω-6/ω-3 in the order of 10-15/1, instead of the ideal ratio of 1-3/1; 4) excessive ingestion of sugar as sugar added fruit juices; 5) generalized deficiencies of essential micronutrients such as: minerals (calcium, magnesium, iron, zinc, iodine, selenium) and vitamins (B1, B2, B6, B9, B12, and folic acid) in addition to the vitamins A, D, and K. Such deficiencies in nutrients equilibrium results in metabolic disturbances which can lead to obesity, metabolic syndrome and early development of chronic and degenerative diseases quite frequent in the last decades of ageing (60).

Non-transmissible diseases and, in general degeneratives, such as cardiovascular diseases, cancer, chronic respiratory diseases, diabetes, obesity and cognitive dysturbancies are the main causes of death and incapacitation in the whole world, affecting populations of developing and even developed countries, World Health Organization (61).

We have already discussed this topic with some details in recent publication (62).

According to Cena and Calder (63), a definition of what could call a health diet is continuing changing to reflect the evolution in understanding the role of different foods, essential nutrients and other food, components in health and diseases. The authors cited above describe in their revision more than 100 published works the main health characteristics of some international dietetic standards, such as: 1) Mediterranean diet (DM) – The primary basis of the daily meals which compose a Mediterranean Diet include cereals like bread of integral grains, masses, cuscus and other integral grains rich in fibers and a variety of fruits and vegetables with diverse colours and textures, which are rich in micronutrients, dietetic fibers and phytochemicals (64). Dairy products preferable yogurt poor in fat, cheese and other fermented dairy products are recommended as source of calcium needed for bone health and for heart. Olive oil as main source lipids which is provided by olive fruits, nuts and various other types of seeds. Water 1.5-2,0L/day as the main source of hydration, in addition of red wine and other types of fermented beverages with moderation always consumed with meals. Fish, white meat, and eggs as the main sources of proteins, red and processed meat are consumed with a fewer frequency and in smaller portions. Leguminous plants constitute preferred sources of vegetable proteins. On the other side, foods considered not very healthy for the cerebrum, such as red meat, butter, margerine, sweets “fast food” have limited consumption (64); 2) Diet to prevent hypertension, DASH “Dietary Approaches to stop hypertension”); study to evaluate the influence of dietetic pattern in the blood pressure (66). Patients who consumed diet rich in fruits and green vegetables and poor in fat coming from dairy products, and reduced quantity of total fat and

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total cholesterol presented major reduction in blood pressure than the patients that consumed a control diet, of similar composition, to the American typical diet. With DASH diet, the risk of cardiovascular disease dropped in 20%, cardiac attack in 19% and cardiac deficiency in 29%. The total risk of diabetes was reduced in 18%; such as diets included high ingestion of fruits, green vegetables, nuts, leguminous plants and seeds, reduced dairy fat and high integral grains. The dietetic pattern derived from the DASH study emphasizes the consumption of a series of vegetables including coloured vegetables, leguminous plants and starchy vegetables, fruits, dairy products without fat or low fat content, integral grains and proteins of various vegetable sources, Campbell (67). 3) Standard – DASH for intervention in neurodegenerative retardation (MIND). The diet MIND combines elements from Mediterranean Diet (DM) and the DASH diet with objective of sustain cognitive health as time goes by (68). The DM as well as the DASH diets have been linked individually to positive cognitive events including prevention of the cognitive decline and to a better cognitive performance (69).

Two high quality studies of coorte reported associations between the adherence to the MIND diet and a 53% lower risk of developing Alzheimer's disease, p=0,002 for a linear tendency, Morris (69) and slower decline in the global cognitive function or in specific domain, such as; episonic, semantic working the memory velocity of perception and organization. The MIND diet focuses on the increase in the ingestion of fresh fruits and vegetables and emphasizes healthy food for the cerebrum, such as: green leaves vegetables, nuts, savages fruits "berries" beans, integral grains, fish, chicken, olive oil and wine with moderation.

Healthy diets, developed either by tradition or experimentally, share many common aspects and generally align themselves with the OMS Global Plan of Action for the prevention and control of non-transmissible diseases. In comparison with the Occidental patterns of diets these healthier alternatives contain more foods of vegetable origins including fruits and fresh vegetables, integral grains, leguminous plants and seeds, nuts and lower contents of foods of animal origin particularly processed meats and fats. Evidences from epidemiologic studies and clinical assays indicates that these dietetic patters reduce the risks of non-transmissible and chronic diseases varying from cardiovascular diseases to cancers. More efforts will be necessary to integrate these healthier dietetic patters with choices of lifestyle in communities and turn back these healthier habits of eating accessible and sustainable.

In a book on functional foods, edited by Robinson and Emerson (70), the authors discuss source, biotechnological applications and chalanges of functional foods for health human. The topics include the leguminous plant potential for health and their bioactive compounds; phytonutrients promotors of health and lactic bacterias in olives; benefits to health of Mediterranean Diet and European consumers acceptance for healthier products, among other topics of interest.

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The chapter on leguminous plants, by Vergara-Castañeda, et al; 2013, describe, in details how the leguminous plants contribute to human health, mainly in the prevention of chronic diseases, hypertension, cancer, diabetes and obesity. The responsible mechanisms by its protective role involves gene-nutrients complex interactions and/or bioactive compounds (non-nutrients) whose details and complexity are beyond the escope of this text.

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Indian Journal of Research in Pharmacy and Biotechnology (IJRPB)
www.ijrpb.com ISSN: 2321-5674 (Print), 2320-3471 (Online)

Cross Ref DOI: https://doi.org/10.31426/ijrpb Indexed in CAS and CABI, Impact Factor: 0.64

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