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Review

Food made us human: Recent genetic variability and its relevance to the current distribution of macronutrients

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ABSTRACT

Numerous dietary strategies are currently used for the prevention of metabolic diseases and for weight loss. Some of the strategies that are used do not have an appropriate physiological-nutritional basis and do not take into account the genetic changes that have occurred recently. Thus, in certain cases, they can be harmful to human health. This review aims to explain the genetic mutations that have occurred during human evolution from the first hominids to *Homo sapiens* and to explain how they have influenced the way we feed ourselves. Some mutations favored brain development and others are related to the digestion of nutrients such as lactose and starch. The influence of the domestication of food and the practice of cooking on human nutrition is also explained. In addition, this review intends to justify the current recommendations on the caloric distribution of macronutrients based on the important influence of genetic changes and adaptations that have occurred in our species.

Introduction

There is currently social pressure regarding body image that has led to the emergence of dietary myths [1] and the appearance of new dietary trends for weight loss [2] and health improvement. These supposedly healthy nutritional strategies have caused great confusion in the general population [2]. Some of these dietary trends are the hyperprotein diet, the ketogenic diet, the Paleolithic diet, the dairy-free diet, and the low-carbohydrate diet, among others. Most of these strategies do not have a proper physiological-nutritional basis; they may even have adverse effects on human health [3–5]. In addition, they do not comply with the macronutrient distribution recommendations of the European Food Safety Authority (EFSA), which proposes that 45–60% [6] of total energy should come from carbohydrates, 15% should come from protein [7], and 20–35% should come from fat [8]. The dietary strategies mentioned above are mainly based on modifying the macronutrient composition of the diet, and despite their popularity in the general population, they have been questioned by researchers. A meta-analysis comparing the impact of various popular diets on weight loss showed that the main reason for weight reduction was a decrease in caloric intake, regardless of the dietary strategy used [9]. Furthermore, these diets may not be adjusted to individual dietary requirements to decrease caloric intake. For example, the Paleolithic diet has long been based on our ancient ancestors' being primarily carnivores, when the reality is that their diet was primarily plant-based [10]. This misconception can lead to increased protein and fat intake, with the latter leading to excessive calorie consumption.

In addition, popular diets are justified on the basis of genetic adaptations that have occurred during the past million years. The Paleolithic diet is based on anatomic and physiological changes that occurred in the *Homo* lineage approximately 2.5 million y ago, when it was believed that they began to increase their meat consumption [10–12]. However, the latest genetic approaches tell us that relatively recent mutations have occurred, and it was determined that the currently recommended macronutrient energy pattern would be the result of what has happened in the past 10,000–12,000 y [13,14].

Therefore, this review attempts to examine the most recent genetic changes that determine the current dietary pattern and to explain why certain dietary trends may not be suitable for human health.

Early hominins: Key mutations

The increase in body size of the early *Homo*, with respect to australopithecines, brought with it an increase in brain size. This, together with new and more complex behaviors, favored new survival strategies for obtaining food [15]. In other primates, brain

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metabolism represents 7–8% of the resting metabolic rate, but in our species, *Homo sapiens*, it represents 20–25% of the resting metabolic rate in adults and 60% of the resting metabolic rate in infants [16]. The increase in brain and body size was accompanied by manual dexterity. It has been proposed that the ability of early hominins for bipedal locomotion allowed them to have their hands free to use objects, which may have also contributed to brain development. Likewise, the great brain development would have allowed the improvement of manual agility [17]. However, the pace of these evolutionary adaptations, ranging from bipedalism, brain development, and increased body size to the anatomic and physiological changes linked to them, appears to be more complex [18].

The RNF213 *gene*

Humans, gorillas, and chimpanzees are descended from an unknown species of extinct hominoid [19]. In this ascendant species, a gene called RNF213 began to evolve rapidly, producing a widening of the carotid artery (Fig. 1). This widening may have stimulated the flow of blood to the brain. Increased blood flow to the brain would allow for a greater supply of energy and nutrients and would thus favor brain development [20].

In humans, RNF213 mutations cause Moyamoya disease, which is characterized by a progressive stenosis of large intracranial arteries. This disease causes a lack of cerebral irrigation, leading to the deterioration of the brain capacity [21]. The diversity of the RNF213 gene variants predisposes distinct populations to different cerebrovascular diseases such as intracranial aneurysm, Moyamoya disease, or intracranial major artery stenosis or occlusion [22].

The SLC2 A1 *and* SLC2 A4 *genes*

The energy compensation hypothesis is based on the fact that the energy allocation among body tissues changed during human origins to favor brain expansion. The SLC2 A1 and SLC2 A4 genes encode the glucose transporters GLUT-1 and GLUT-4, respectively [23]. An increase in the amount of SLC2 A1 or SLC2 A4 protein results in greater glucose uptake by a given tissue. Changes in the expression of these transporters have been found in the cerebral cortex and skeletal muscle of humans and chimpanzees [23]. In humans, the expression of SLC2 A1 in the cerebral cortex is higher than that in chimpanzees (Fig. 2). GLUT-1 is not insulin-dependent and has high affinity for glucose molecules. This ensures that the brain receives adequate glucose levels for its proper function [23]. The expression of SLC2 A4 in skeletal muscle is higher in chimpanzees than in humans (Fig. 2), so the energy in these primates is preferentially directed to muscle [23]. This may indicate that in early hominids, tissue-specific gene expression changed with a reallocation of energy [18] from skeletal muscle to the brain. This would divert glucose in that direction, and such a detour would possibly stimulate and enable brain growth [23]. "In Homo sapiens, we have selected reasoning/thinking by fleeing/walking."

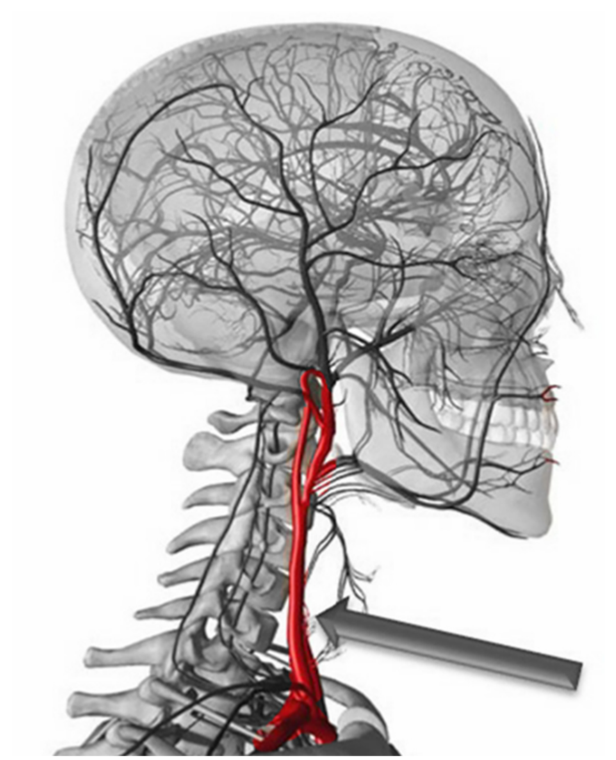

Fig. 1. Widening of the carotid artery caused by mutation of the *RNF213* gene.

Genes related to personality, memory, and creativity

A team of researchers from the University of Granada identified 267 personality-related genes that are unique to Homo sapiens. These genes are part of three networks that are related to personality, learning, and memory. The most primitive network arose in monkeys and apes 40 million y ago and is related to emotional reactivity. The second network arose 2 million y ago and regulates self-control. The third network arose 100 000 y ago and regulates creative self-awareness [24]. The genes for the emotional reactivity network are very similar in chimpanzees, neanderthals, and modern humans (H. sapiens). However, the genes for the self-control and self-awareness networks are different among the three species, with those of neanderthals being halfway between chimpanzees and modern humans [24]. Our species has more than 200 nonprotein coding genes that regulate the expression of other protein coding genes. These genes enable humans to be creative and prosocial and to live longer lives by conferring greater resistance to diseases, injuries, and aging [24]. The regions in which such genes are overexpressed are those involved in self-awareness, creativity, and well-being [24]. Greater creativity favors cooperation between individuals, technological innovation, flexibility, and adaptability of behaviors, which allowed Homo sapiens to expand more successfully [24].

Animal foods and brain development

A "good quality diet" refers to a diversified and balanced diet that provides sufficient energy and essential nutrients to meet the needs of a living being. In primates, brain size is positively correlated with diet quality, and humans are at the positive end of this relationship. That is, they have a larger brain and a better-quality diet than the other primates [16,25]. Owing to adaptations to a high-quality diet, humans have a relatively smaller gut [26]. In addition, humans are poorly muscled and have a higher body fat percentage than other primates [27]. This helps humans compensate for the high energy demands of the brain [16,25,28]. There is evidence that indicates that the great brain increase occurred with Homo ergaster/erectus and was associated with important changes in diet and body size [16,25]. The paradigm of the large amount of meat consumption presupposed for these hominins is still debated today [29]. The size of the teeth decreased, and the proportions of the limbs were similar to those in humans. Their subsistence behaviors were also changing in the face of new ecosystems and available resources [16,25]. In addition, this species improved its

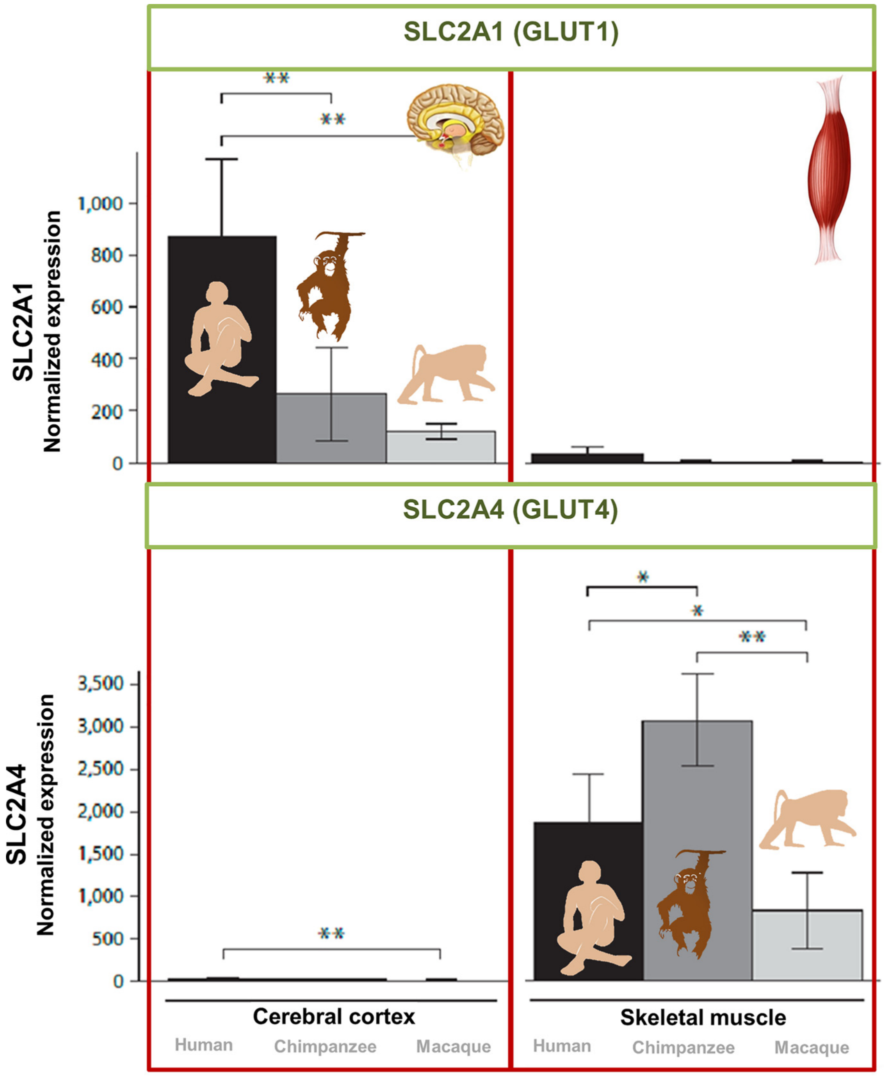

Fig. 2. Expression of *SLC2 A1* and *SLC2 A4* in humans, chimpanzees and macaques. Image modified from Fedrigo et al., 2011 [23].

manufacture of stone tools. These tools allowed access to animal carcasses, especially bone marrow, which is rich in fat. These tools also made access to some plant resources more efficient [11]. The consumption of animal foods was favored by climate change. The climate became drier approximately 2.8 million y ago [30]. Tropical forests, where fruits are abundant throughout the year, reduced their extension in favor of savannas. In savannas, plant foods that are edible for hominins are scarce, but animal foods are more abundant and accessible [25]. This made animal foods increasingly attractive and abundant in the diet of hominids [25].

The brain is a metabolically demanding tissue. Therefore, a larger brain size requires more energy, a high-quality diet, and a supply of fatty acids that allows proper neuronal functioning [16,31]. Animal protein is easier to digest than vegetable protein [32,33]. The latter comes from unrefined cereals and legumes, which contain high levels of insoluble fiber and antinutritional factors [33]. Meat protein also presents a valuable source of essential amino acids, essential fatty acids, fat-soluble vitamins, and minerals [25,32]. These nutrients satisfy the demands of the brain. Thus, the consumption of animal foods helped to provide more energy and nutrients to the brain, thus favoring its rapid evolution [16,34].

Food domestication

Food has not always had the same density of macronutrients, micronutrients, and nonnutrients as it does today. In the past, vegetables were poorly digested and had a reduced amount of carbohydrates and sugars. However, human intervention has reshaped the genomes of crops, and these have acquired traits. These traits demonstrate a tendency toward a cycle that allows a greater number of harvests and the generation of larger fruits with great variability in shapes and colors [35].

The current corn ear comes from the teosinte, which is a grass of Mexican origin. The current ear is four times larger than the teosinte ear, which over time and through artificial selection has given rise to more than 60 varieties of corn. Another domesticated crop of American origin is the tomato [35]. The variety of colors, flavors, and textures of today's tomatoes comes from a yellowish berry with a bitter taste that is a hundred times smaller than today's tomato. The carrot, however, comes from the Middle East and was first cultivated for its leaves and not for its root. This root was yellowish in color with a tendency toward purple. A gene has been identified that acts on carotenoids and is involved in the accumulation of the pigments responsible for the current orange color [35].

Duan et al. [36] compared the genomes of 117 diverse wild and cultivated apple varieties to explain apple speciation, differentiation, and evolution. The study showed a consistent selection for larger, sweeter, and firmer fruits in the history of apple domestication. In addition, disease-resistance genes and genes involved in various abiotic stresses were discovered [36]. These genes contained highly divergent non-synonymous single nucleotide polymorphisms between domestic and wild apples [36]. The results suggested that adaptations to different growing environments occurred [36]. The larger size of domestic apples is probably because domestication was initiated from M. sieversii, which has larger fruits than other wild apples. A firmer texture gives the fruits a longer shelf life and better disease resistance, which probably aided selection [36]. The sugar content and acidity of the fruit have also been altered during domestication. The resulting balance between sugars and acids produced sweeter and less acidic fruits [36].

Non-domesticated ancestral food was highly loaded with xenobiotics, which would likely play an important role in modulating the methylation pattern [37]. The type of xenobiotic determines which alterations will occur to favor or inhibit specific bacterial species. For example, arsenic significantly decreases the bacteria of the phylum Firmicutes but alters the metabolic profile at the functional level of the gut microbiome [37]. Moreover, xenobiotics induce the gut microbiome to express genes related to xenobiotic metabolism. Polycyclic aromatic hydrocarbons (PAHs) are substances formed during waste burning and in grilled meats [37]. When metabolized by intestinal bacteria, PAHs are transformed into potentially toxic metabolites. Some of these metabolites have mutagenic effects, so altering the metabolism of PAHs may enhance or reduce these mutagenic effects [37]. The same is true for heavy metals and arsenic. In addition, gut microbial biotransformation can reduce the toxicity of certain environmental chemicals such as deoxynivalenol, which is a mycotoxin present in cereals [37].

Determining techniques in the development of human nutrition

The practice of cooking and other food-processing techniques is an essential feature of human adaptation, but its origin is still under dispute. Some researchers have proposed that the sporadic use of fire began approximately 2 million y ago [38–41]. However, archaeological evidence places the control of fire as early as 1 million y ago and its regular use for cooking and processing food as early as 250 000 y BC [42]. Culinary preparations became more sophisticated with the incorporation of new techniques for the soaking, grinding, pressing, seasoning, salting, maceration, and fermentation of cereals and fruits [43].

Fire

The use of fire became a daily occurrence with the neanderthals, who, in addition to using it for heating and cooking, may also have used it for preservation techniques such as smoking [44]. However, there is no archaeological evidence that unequivocally confirms this [43]. The use of fire in culinary preparations favored the digestibility and caloric intake of food [45]. The cooking of tubers and other vegetables served to soften them, which increased the bioavailability of energy and nutrients. Cooking these vegetables could also avoid the toxicity of some foods and combat pathogens [46]. Furthermore, some starchy plant foods should be cooked to make them edible, supporting the importance of the beginning of cooking in the human lineage [47]. However, generating heat for cooking requires fuel, and access to it could pose a problem. It appears that the caloric benefit gained from cooking meat was quickly lost with the increased cost of cooking, whereas starchy plant foods were worth cooking [47].

A study carried out on the neanderthal settlements located in eastern Spain suggested that neanderthals were able to discern between the combustion properties of wood in different states. They selected partially rotten wood to obtain a greater amount of smoke during combustion. In addition, this wood was easily accessible and did not require great effort to obtain [48].

The use of fire leads to the formation of dioxins that are generated during combustion. There are data showing the potential effect of dioxins in inducing epigenetic alterations and toxic effects over multiple generations [49]. The transgenerational impacts of dioxins arise with cellular epigenetic modifications, including altered methylation patterns [49]. It is believed that some of the epigenetic alterations could have provided benefits in nutrient use.

Food preservation

Homo sapiens began to apply food preservation techniques to guarantee food availability in times of scarcity. The most commonly used techniques were drying and dehydration, freezing, smoking, meat and blood mixtures, fat mixtures [50], and fermentation [51]. In addition, as many hunter-gatherers do, they could have established stores along migration routes to ensure food availability [43].

Fermentation

Owing to the domestication of edible species, new products such as bread, wine, beer, and cheese were discovered. The discovery was probably accidental and owed to the spontaneous fermentation of surplus grains, fruits, and milk [43]. In Israel, brewing beer from wheat and barley began 13 000 y ago. There is archaeological evidence of alcohol production in China between 7000 and 8000 y ago from different fermentation techniques using starch granules, phytoliths, and fungi [52]. In beer brewing, alcoholic fermentation was carried out using cereals, and the phytoliths varied according to the region [52]. In some regions of China, three changes occurred that innovated the elaboration of alcoholic beverages. These changes were the expansion of millet and rice domestication, the appearance of more suitable types of pottery for fermentation, and the development of two fermentation methods. One method used malts and the other used moldy grains as starters [52].

Recent mutations or gene variants

Changes in the human genome that are associated with dietary adaptations, subsistence mode, and environmental variables have been identified. A recent variant that has been associated with diet is the increase in the number of copies of the amylase gene, which allows starch digestion. Additionally, the variants of the lactase gene, which allows adults to digest fresh milk, have been associated with diet [53].

Amylase and starch incorporation

Starchy tubers were proposed as a key resource in the early phases of human evolution [54,55]. Salivary amylase is an enzyme that plays a key role in the digestion of starch and is responsible for its hydrolysis. The number of copies of the amylase gene (AMY1) is variable, and the concentrations of the enzyme are proportional to the number of copies of the gene [56]. There is evidence that the copy number of the amylase gene is higher in populations with starch-rich diets. Numerous studies on chimpanzees show that the increase in gene copy number has occurred recently in the human lineage (perhaps within the past 200 000 y) [57]. Japanese, European, and American populations with high-starch diets show signs that selective pressure began with the domestication of grains 10 000 y ago [56]. The exploitation of carbohydrates in the genus Homo is confirmed by the presence of starch-adapted oral bacteria. These bacteria are characteristic of the human oral microbiota and distinct from those of chimpanzees and gorillas [58]. Starch consumption is a prominent feature of agricultural societies and hunter-gatherers in arid environments. In contrast, hunter-gatherers in tropical rainforests and circum-Arctic and some pastoralist populations consumed less starch. This variation raises the possibility of a selective pressure of starch consumption on amylase expression [56].

Lactase persistence

Humans developed mechanisms for lactase persistence 7500 y ago, and as a result, most humans can digest lactose after infancy. The single nucleotide polymorphism that is responsible for lactose tolerance is rs4988235. People with the sequence “CC” in this gene are genetically lactose intolerant, whereas people with “CT” or “TT” are genetically tolerant [59].

In Kenya and Malawi, lactase persistence is still prevalent; however, in Peru and China, lactase persistence is low. Two complementary hypotheses have been proposed to explain the differences in intestinal lactase persistence [59]. On one hand, continued milk intake when the lactation process ends could stimulate lactase biosynthesis by acting on the enzyme coding genes [59]. On the other hand, if the environment favors the inclusion of milk in the diet, individuals carrying the mutation responsible for lactase persistence would have been favored by natural selection. This is because milk consumption would increase the availability of calories and nutrients such as calcium [59]. These individuals would have higher survival rates and a greater chance of transmitting this mutation to their offspring. In addition, European individuals carrying the lactase persistence allele produce up to 19% more fertile offspring than noncarriers do [59]. Some researchers have indicated that if natural selection has acted in this way, then the allele responsible for persistence will have reached high frequencies in those populations that have practiced livestock farming continuously since the Neolithic period [59].

To explain the high frequencies of lactase persistence in northern Europe, a hypothesis related to calcium absorption was proposed. This hypothesis proposes that rickets and osteomalacia would have been an important selective pressure under conditions of low solar radiation at extreme latitudes [60]. The appearance of lactase persistence provides great genetic advantages. The consumption of milk has allowed advancements in human nutrition, because it is a food that provides nutrients of high biological and nutritional quality [61].

Domestication of wheat, milk, and honey

It is known that the domestication of livestock began at least 10 000 y ago [17]. The emergence of livestock during the evolutionary development of human beings made meat and milk more readily available. This availability helped them meet their energy needs and improve their growth, development, and immune system [61]. The pattern of consumption in the Iberian Peninsula has been described. During the Neolithic period (in Europe 7270–5320 cal BP), individuals in the Iberian Peninsula mainly consumed ruminant meat (cows, goats, and sheep). However, during the Chalcolithic period (in Europe 5030–4190 cal BP) and the Bronze Age (in Europe 3878–3702 cal BP), pig and horse consumption predominated over ruminant animals [62]. A study carried out with ceramic samples from the Sierra de Atapuerca (Burgos, Spain) shows that in the Neolithic period, the presence of dairy products was limited. This can be related to the fact that this Neolithic population was still lactose intolerant, as shown by studies of their DNA [62]. It is believed that in the Neolithic period, dairy products began to be incorporated in the face of food shortages. However, it was later, during the Chalcolithic period and Bronze Age, when the consumption of milk and its derivatives, such as yogurt, cheese, and butter, increased [62]. Parallel to the domestication of animals, the cultivation of vegetables developed (Fig. 3). This was probably owed to the difficulties in obtaining sufficient meat and the

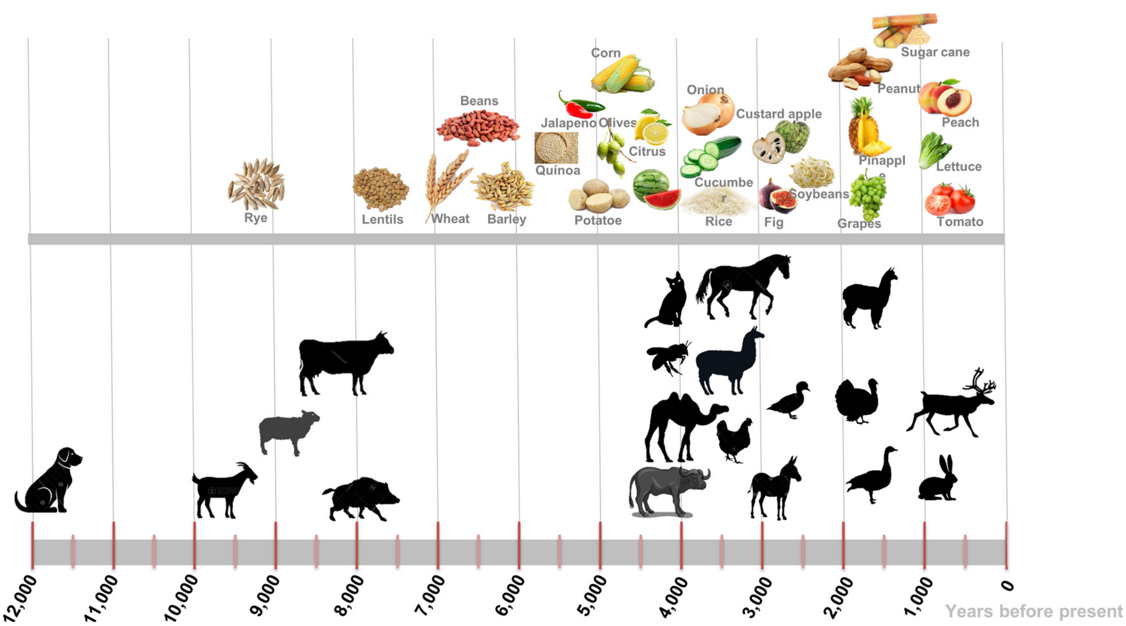

Fig. 3. Chronology of plant and animal domestication.

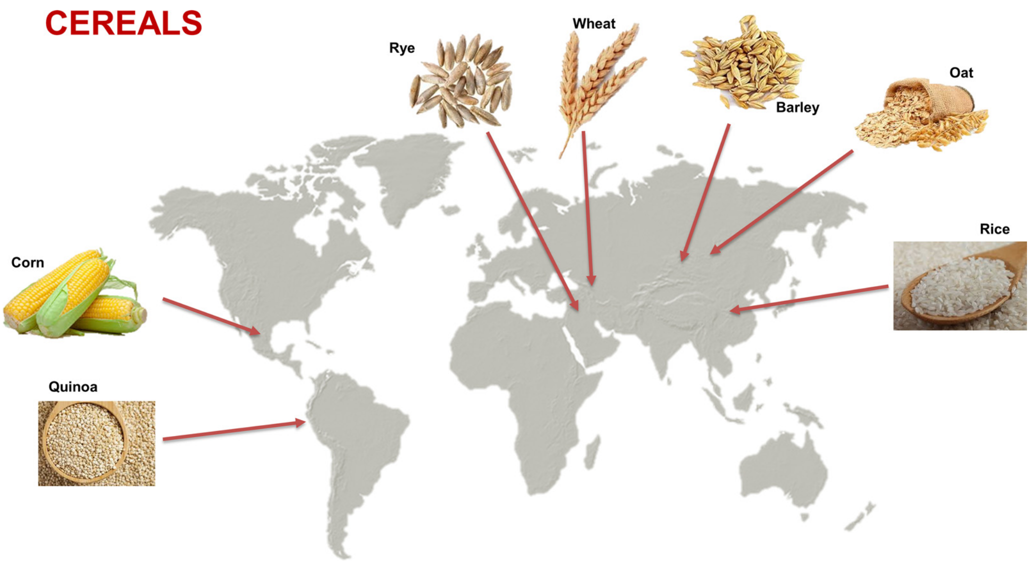

Fig. 4. Origin of the harvesting of different cereals.

dangers of exclusive dependence on vegetable crops [17]. In the Middle East, wheat and barley began to be domesticated. In China, domestication began with rice and soybeans, and in Mesoamerica, it began with corn and beans (Fig. 4) [35]. Later, in Africa, sorghum and coffee began to be domesticated, and in New Guinea, sugar cane and banana were domesticated. Plant species were chosen on the basis of different qualities such as edible fruits with a pleasant taste or ease of growth and storage [35] (Figs. 3 and 4).

There is also evidence for the habitual consumption of honey [63,64] throughout human evolution. A team of researchers demonstrated that beeswax was collected in regions of Anatolia, Europe, and North Africa 9000 y ago [65]. The presence of wax also implies the exploitation of honey by Neolithic farming populations since the beginning of agriculture. It has been shown that honey has been continuously and extensively exploited since then. In addition, the search for honey can also be interpreted from rock art [65].

Some authors note that early Homo followed a flexible subsistence strategy that allowed them to adapt to the irregular and seasonally variable distribution of food resources. They developed more efficient ways of extracting resources from the environment and opportunistically adapted to a more diverse and varied diet (Fig. 3) [25]. Moreover, the dietary variety of hominins is biologically programmed. The greater the variety of foods, the greater the possibility of obtaining a balanced diet that includes all the necessary micronutrients and the greater the possibility of limiting the potential amount of toxins ingested [16].

Current dietary trends

Palaeolithic diet

The Paleolithic diet or Paleo diet is a modern interpretation of what humans ate during the Paleolithic era, which starting 2.5 million y ago [10]. A review conducted in 2019 found 14 different definitions of a Paleolithic diet [66]. Most definitions of the Paleo diet include fruits, nuts, vegetables, fish, eggs, and lean meats and exclude dairy, cereals, grains, legumes, added salt, sugar, and refined fats [66]. There are contradictions about the inclusion of potatoes [66]. It is a popular misconception that our Paleolithic ancestors ate mainly meat, when the reality is that their diet was mostly plant-based [10,54]. In addition, Australopithecus and early Homo consumed animal fat, especially bone marrow. They were scavengers and accessed animal carcasses that had already been consumed by other large predators. The Paleolithic diet mainly included tubers, seeds, nuts, barley, and legumes [67,68,69]. In the Lower Paleolithic, they consumed large prey, which was acquired by either hunting or scavenging [67,70,71]. The consumption of small game became important from the Middle-Upper Paleolithic onward, including Neanderthals and modern humans [67]. Regular consumption of marine resources dates back to the Upper Paleolithic (in Europe 40 000 cal BP), although there is evidence of sporadic consumption of aquatic resources in Africa 1.94 million y ago [72]. In any case, evidence of aquatic resource consumption before 160 000 Kyr is very scarce [73]. Insects and bee honey were also consumed, but milk was not consumed. This was because it was years later that the domestication of animals began [10]. Therefore, the Paleolithic Homo consumed quality foods that were rich in nutrients and fiber. Compared with modern diets that include many ultra-processed foods that are high in added sugars and salt, the diet that was consumed in ancient times was healthier. However, this should not translate into replicating the exact diet of our ancestors but rather taking some key Paleolithic foods and adapting them to today's lifestyle. This is because although the diet of our ancestors benefited their digestive tract, it is unknown how the Paleolithic diet may affect human health in the long term [10].

Low-carbohydrate diet

Low carbohydrate diets are considered to be those that provide less than 45% of energy in the form of carbohydrates [74,75]. Some authors define a low-carbohydrate diet as containing between 50 and 150 grams of carbohydrates per day [74]. Some studies show that these diets have beneficial effects when accompanied by caloric restriction; however, without caloric restriction, these benefits are lost. In addition, many studies do not take into account whether the carbohydrates come from vegetables, fruits, and whole grains or from processed foods, and it is known that different metabolic effects are obtained depending on the source of carbohydrates [75]. Some reviews have concluded positive short-term effects of low-carbohydrate diets, with benefits on weight loss, blood glucose, and insulin. However, data supporting their efficacy, safety, and long-term health benefits are lacking. In addition, owing to reduced fiber intake, adverse effects on stool quality and the production of short-chain fatty acids by the large intestinal flora have been demonstrated. If these effects are prolonged over time, they may result in intestinal disease [74].

Intermittent fasting

Intermittent fasting consists of taking periodic breaks in eating [76]. There are numerous types of intermittent fasting. The most common are prolonged periodic fasting, time-restricted feeding, and alternate-day fasting [76]. Prolonged periodic fasting consists of fasting for 24 h once or twice a week and, on the other days, maintaining ad libitum food intake [76]. Time-restricted feeding consists of eating for 8 h a day and fasting the remaining 16 h [76]. Alternate-day fasting consists of alternating days of ad libitum food intake with fasting days in which 25% of energy needs are restricted [76]. The health benefits of intermittent fasting have been demonstrated in animal studies. It appears to have positive effects on obesity, diabetes, cardiovascular disease, cancer, and neurodegenerative diseases; however, these results cannot be extrapolated to humans [76,77]. The clinical studies that have been conducted in humans have been short-term. Thus, it has not been determined whether people would be able to maintain intermittent fasting for years and accrue the potential benefits observed in animals [77]. In some human studies, the dropout rate has been as high as 40%, which translates into a lack of adherence to this strategy. Therefore, the clinical relevance and feasibility of maintaining intermittent fasting over time is currently questionable [76].

On the other hand, although some studies have found psychosocial benefits in people who implement intermittent fasting, possible associations between intermittent fasting and eating disorders should be evaluated in the long term [76]. Other studies have shown variations in sex hormones and gonadotropins during periods of fasting. A study conducted during the month of Ramadan with healthy men showed a decrease in testosterone and an increase in follicle-stimulating hormone, especially in the last days of Ramadan [78].

A randomized controlled trial that was conducted with healthy and lean adults indicated that intermittent fasting was equally effective in reducing body mass as an equivalent energy restriction. However, energy restriction resulted in greater fat mass loss than fasting [79]. Changes in fat-free mass were not different between the groups, so it appears that fasting does not favor preservation of lean mass during weight loss. The triacylglycerol concentration was lower in the energy restriction group; however, none of the strategies affected the fasting or postprandial plasma concentrations of glucose, insulin, nonesterified fatty acids, glycerol, or cholesterol. The metabolic rate was also unaffected; however, a reduction in physical activity was observed in the fasting group. Furthermore, the plasma leptin concentration was decreased in the energy restriction group; this was probably because this hormone is secreted in proportion to fat mass [79].

In conclusion, solidly based clinical research studies on fasting are scarce in the scientific literature [80]. Furthermore, it is still unknown which individuals would benefit from intermittent fasting and which form of fasting would be most effective. In addition, there appear to be contraindications to the practice of intermittent fasting for certain health conditions, psychosocial barriers, and eating disorders. Therefore, the research is not strong enough to recommend intermittent fasting as a standard practice [76].

Gluten-free diet

A gluten-free diet consists of completely eliminating gluten from the diet. Gluten is a protein present in wheat, rye, and barley [81]; thus, foods containing these grains should be eliminated in a gluten-free diet. In addition, many products such as sausages, soups, ice cream, and soy sauce may contain hidden gluten [82]. Other products, even those labeled as “gluten-free,” may contain traces of gluten, mainly owing to cross-contamination [82]. Despite the numerous studies conducted to develop alternative therapies for celiac disease, there is evidence that the gluten-free diet is the only effective strategy to date to avoid symptoms [82]. Thus, individuals with celiac disease should follow a lifelong gluten-free diet. In addition, patients with celiac disease should avoid cross-contamination, because small amounts of gluten may cause health problems [81]. However, many healthy individuals follow this dietary strategy, pursuing different aesthetic or health goals. Energy and macronutrient intake are often inadequate in gluten-free diets. This is because the focus is usually placed on avoiding gluten, and nutritional quality is often downplayed [83]. Gluten-free products tend to be higher in carbohydrates and lipids than their gluten-containing counterparts. In addition, these products tend to have a high glycemic index and lower protein content and are often richer in saturated fat. Such diets increase the risk of obesity [83].

A gluten-free diet is characterized by a lower amount of dietary fiber than a gluten-containing diet. This lack of fiber could be related to the poor quality of gluten-free processed products, which are made with starches and refined flours lacking fiber. It may also be a consequence of avoiding cereals, which are very fiber-rich foods. There is sufficient evidence that adequate intake of dietary fiber has beneficial health effects, such as the prevention of obesity, colon cancer, diabetes, and cardiovascular diseases [83].

A gluten-free diet is also associated with vitamin and mineral deficiencies. The most deficient vitamins in this type of diet are usually folate, vitamin B12, and vitamin D [83]. Magnesium, zinc, and iron deficiencies have also been found. Magnesium is essential for various enzymatic functions such as DNA transcription and replication, mRNA translation, and the correct functioning of ionic pumps and calcium channels. It also plays a key role in protein, nucleic acid, glucose, and fat metabolism [83]. Zinc deficiency can affect protein synthesis and can hinder growth [83].

There is no evidence to date that the gluten-free diet has beneficial effects in healthy individuals. Moreover, caution should be exercised with this type of diet owing to the macronutrient mismatch and micronutrient deficiencies it can cause. For individuals who have gluten-related disorders and must follow a gluten-free diet, it is essential to provide dietary education and counseling to avoid any nutritional deficiencies [84].

Dairy-free diet

A dairy-free diet completely excludes milk in all its forms, including products containing milk and milk products such as butter, cheese, and yogurt [85]. Dairy has been a very important part of the human diet for 8000 y and is part of the official nutritional recommendations of many countries [86]. Dairy products provide key nutrients that are difficult to obtain from low-dairy or dairy-free diets [86]. Milk is an important source of proteins, fats, minerals, vitamins, nucleotides, and polyamines, but above all, calcium and vitamin D stand out. These are present in large quantities and have high bioavailability in dairy products [61]. Both nutrients are related to bone growth and maintenance, blood coagulation, energy and neuromuscular metabolism, the function of different enzymes, and cell differentiation [61]. It is true that there are other sources of calcium, such as mineral water, cabbage, dark vegetables, and legumes, but it is difficult to meet daily calcium requirements with these foods because their bioavailability is reduced

[86]. In addition, dairy provides more magnesium, potassium, zinc, and phosphorus per kilocalorie than any other food [86].

The consumption of dairy products has decreased because they have been labeled as unhealthy. However, there has been no scientific evidence to support this. In addition, the increase in food intolerances and allergies has led many people to avoid consuming lactose and milk proteins because they have mistakenly been considered responsible for these conditions [61]. The products that are replacing dairy do not provide the same nutrients, especially protein, calcium, and vitamin D. Thus, the intake of these nutrients is below the recommended daily intakes. This can result in nutritional deficiencies and health problems [61]. Vitamin D regulates calcium homeostasis and bone mineralization and is involved in cell differentiation processes, in immune and neuroprotective processes, and in the regulation of blood pressure [61]. Thus, it is essential to achieve an adequate intake of vitamin D.

Dairy products are currently a vehicle for good-quality nutrients at a more affordable price than other animal products [61]. The consumption of three servings of dairy per day, which is the established national nutritional recommendation, is completely safe and beneficial for health as long as these foods do not displace the consumption of other foods that are also necessary.

Conclusion

Major evolutionary changes in human anatomy and physiology have been accompanied by dietary changes, resulting in an adaptative framework that affects the modern diet [16,87,88]. Despite the stability of the human genome, adaptations to the environment and new ways of feeding have allowed the species to thrive and adapt to different conditions [59]. Recent genetic changes have determined the current dietary pattern and explain why the current recommendations on the caloric distribution of macronutrients are different from the dietary patterns of predecessor species. Thus, the EFSA energy distribution recommendations, which propose that most energy should come from carbohydrate intake, would be justified.

Numerous dietary strategies are currently being introduced that are labeled as the solution to good health [10] or to achieve certain aesthetic goals. However, one should not fall into these new trends because it is still unknown what effects they may have on human health in the long term. Universities and educational institutions should try to transmit healthy dietary guidelines and appropiate energy-distribution recommendations, whose beneficial effects on health, both in the short and long term, are supported by scientific evidence. These guidelines translate into a higher consumption of vegetables, fruits, legumes, nuts, seeds, whole grains, fish, and lean meats and a lower consumption of processed foods rich in added sugars, salt, and poor-quality fats.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.nut.2022.111702.

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