Abstract

Both extremes of altered cholesterolemia are worldwide disorders associated with severe health complications. Hypercholesterolemia is influenced by genetic as well as environmental factors related to unhealthy body composition, dietary inadequacy and a low level of physical fitness. Converging data are now available to support the hypothesis that, in addition to their “thrifty genotype” inheritance, individuals with hypercholesterolemia might underwent incorrect “epigenetic programming” during fetal/postnatal development due to inadequate maternal nutrition and metabolic disturbances. The mismatch of our ancient molded genome and a postnatal nutrition-rich and sedentary environment might explain much of the epidemiology of the contemporary hypercholesterolemia. On the other side, hypocholesterolemia might be caused secondarily to medical drugs. In this chapter we added the reviewed literature to our personal data, cross-sectionally analysed, from the Botucatu Longitudinal Study (BLS) on Healthy Lifestyle Promotion as a primary care for non-communicable chronic diseases (Move for Health – Mexa-se Pró-saúde). It is described that both extremes of plasma cholesterol levels are less associated to demographic and socioeconomic aspects and more related to behavioral factors of diet and physical activity as well as with the resulted anthropometrical and metabolic conditions. The predominant environmental/behavioral risk factors linked to hypercholesterolemia included energy dense/fat-unbalanced diets and physical inactivity. Surprisingly, more than one third o top quartile of cholesterol...
referred themselves as medicated and, half of medicated were considered as uncontrolled. On the other side, the lower plasma cholesterol decile assembled subjects with healthier physical activity, anthropometrics and plasma profile. From the 16% patients classified as low cholesterol-hypotrophic, one third were taking statins and, the remainder 2/3 were probably suffering from hypocholesterolemia-associated mass-consumptive diseases. On the other hand 30.1% of hypocholesterolemics were classified as hypertrophic (overweight) subjects and, 53.6% of them were under statin treatment. Therefore, our sampling showed high prevalence of statin-induced low cholesterolemia and consequently, prone for CNS disturbances of behavior. Thus, the general conclusion that altered cholesterol might “caused by an interaction between genes and environment” distracts (including statin treatment) from its causation by our current unfavorable environment carry useful information from a public health perspective. Hence, a reversion to a traditional diet and lifestyle even temporary might result in marked improvement in metabolic risk factors for this disease.

**Keywords**

Plasma Cholesterol Variation; Epigenetics, Lifestyle; CVD; CNS Disturbances

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**Fat and Cholesterol as a Thrifty for Human Encephalization**

Humans share a common ancestor with the chimpanzee and bonobo that probably lived in East Africa. Some 6 million years ago Hominids had experienced a tremendous brain growth (encephalization) and assumed an upright position [1].

As a result, human brain sizes are some 2.5–3 times those of other primates [2] and, to accommodate larger brain there were anatomic changes as well physiological adaptations in our evolutionary body [3].

The first task was to afford the massive expenditure of energy required to support a large brain. The gastrointestinal tract has a similarly high rate of organ-specific basal metabolic energy expenditure and the “expensive-tissue hypothesis” suggests that the massive expansion of the neocortex in humans came at the expense of the gastrointestinal tract reduction [4]. Additionally, human infants have the highest body fat levels of any mammalian species and continue to gain fat during the first year of postnatal life [2]. This very high level of adiposity seen in early human growth and development coincide with the periods of greatest metabolic demand of the brain [5]. For so, humans appear to show important adaptations (“fetal metabolic programming”) in fat metabolism early in life as seen under conditions of nutritional stress when the body keeps the capacity to preserve body fat reserves for brain metabolism by reducing rates of linear growth (“lin-
ear growth stunting”) associated with reduced rates of fat oxidation and increased rates of fat storage [6].

Brain composition is occupied mostly by lipids mainly cholesterol and long-chain fatty acids. As cholesterol is an essential component of myelin, not surprisingly, the size of the sterol pool in the central nervous system (CNS) increases disproportionately as brain size increases. Accounting for only 2% of the whole body mass, the CNS contains almost one quarter of the unesterified cholesterol present in the whole individual, showing a higher mean concentration than in any other tissue [7]. Besides being the major architectural component of myelin the cholesterol molecules play an important role in determining the fluidity and permeability characteristics of the membrane as well as the function of both the transporters and signaling proteins. Generation of the action potential that transmits the information critically depends upon the permeability characteristics of the plasma membrane surrounding the axon and, the evolutionary adaptation of the cholesterol-rich plasma membrane to form compact myelin made it possible to “wire” the complex brain with numerous relatively small-diameter, low-capacitance axons that manifested very high conduction velocities [8].

**Tissue Cholesterol**

In the adult, essentially all sterol in the CNS is unesterified cholesterol that is distributed among the membranes of myelin and the sterol present in the plasma membranes of neurons and glial cells [8]. In all of the remaining organs, from the lung and kidney to the striated muscle of carcass, nearly all tissue sterol is esterified cholesterol present predominantly in the plasma membranes of parenchymal cells. The organ-specific basal metabolic rate in the intestine is very high, and the rate of cholesterol turnover in the plasma membranes of this tissue is also very high. In contrast, the basal metabolic rate of striated muscle is very low, as is the rate of sterol turnover. The adrenal gland and other endocrine tissues of most species also have high concentrations of cholesterol [7]. However, despite the fact that the organ-specific basal metabolic rate is very high in the brain, the rate of turnover of the sterol pool in the CNS of the human brain is only 23.3% of the whole-body turnover. The CNS pool of cholesterol decreases 36.6% from the newborn infant to the adult [8]. However, when challenged with exogenous, dietary cholesterol the level of tissue cholesteryl esters increases, and this increase occurs only in the liver and, to a much lesser degree, the intestine [9].

**Cell and Plasma Cholesterol Homeostasis**

In essentially all tissues, there is a continuous flow of cholesterol from the endoplasmic reticulum to the cell membrane, and from this plasma membrane to the surrounding fluid. By outflowing continuously cholesterol, every cell requires a continuous supply of new sterol to
maintain constant this critical concentration in the plasma membrane [8].

Mechanisms for acquiring cholesterol are “de novo” synthesis within the cell and uptake of unesterified or esterified cholesterol from the external environment using receptors. The low density lipoprotein receptor (LDLR) binds particles that contain either apolipoprotein (Apo) E or Apo B-100, and these include the remnants of chylomicrons and very low density lipoproteins (VLDL) as well as low density lipoprotein (LDL) [10]. In a similar manner, high density lipoprotein (HDL) particles containing Apo A-I can be bound by scavenger receptor BI (SR-BI) in cells like hepatocytes and endocrine cells [11].

Mechanisms described that bring about net excretion of cholesterol out of the cell include a movement simply driven by chemical gradients between the leaflet and lipoprotein receptors in the plasma [12]. Additionally, there are the transporters ATP-binding cassette transporters (ABCG5/8 and ABCA1) and various enzymes capable of hydroxylation cholesterol. Through its various transport mechanisms there is essentially net unidirectional movement of cholesterol from the peripheral organs to the intestinal lumen [12,13].

The continuously removal of cholesterol from peripheral cells and plasma particles to the HDL is associated with circulating ApoA-I. Within the plasma space, the HDL particle enlarges as cholesteryl ester is formed under the influence of lecithin-cholesterol acyltransferase (LCAT) [8]. During the process of cell outflow, the concentration of sterol in the plasma membranes of each organ and the size of the pool of cholesterol in the whole body remain essentially constant. However, the rate of movement of sterol through the pathways, and therefore the rate of plasma membrane cholesterol turnover, is very different according to basal metabolic rates [8]. Similarly, although the concentration of cholesterol in the plasma membranes of most organs in the body is held very constant, the concentration of sterol circulating in lipoproteins varies markedly [8].

There are wide physiological fluctuations in the total cholesterol (TC) and LDL-cholesterol (LDL-c) concentrations at different times during the suckling and adult periods. Additional variation in the circulating lipid levels can be induced by either dietary or pharmacological manipulations [14].

**Dietary Transition**

The anatomic trends of human evolution (large body sizes, bigger brains, craniofacial and intestinal changes) clearly suggest major energetic and dietary shifts. Improvements in dietary quality and, the increased consumption of dietary fat appear to have been a necessary condition for promoting encephalization in the human lineage. Relative to other large-bodied apes, modern humans derive a much larger share of their dietary energy from fat [15]. Dietary fat is our second most important energy-producing macronutrient. It also contains fatty ac-
ids and vitamins essential for growth, development, and maintenance of good health [16]. This relationship implies that the evolution of larger hominid brains would have necessitated the adoption of a sufficiently high-quality diet (including meat and energy-rich fruits) to support the increased metabolic demands of greater encephalization [6].

Primitive humans with enlarging brains developed more sophisticated tool technology (including the fire cooking) and became more efficient hunter/gatherers and so gained greater access to more nutritious and easily digestible foods (e.g., fruits, nuts, and meat). Consequently, reductions of posterior tooth size (and grinding teeth) and, also the size of the face and so, no longer needed the large gastrointestinal tract. Key genetic mutations during later hominid evolution were critical to promoting the enhanced lipid metabolism necessary for subsisting on diets with greater levels of animal material. Hence, the ultimate driving factors responsible for the rapid changes at the stage of human evolution (6 mya in East Africa) appear to have been major environmental changes that promoted shifts in diet and foraging behavior, which coincided with a change from a vegetarian to a hunting-gathering omnivore–carnivore [16].

The evolutionary “higher quality” diet means that we need to eat less volume of food to get the energy and nutrients we require [15]. Contemporary foraging societies derive between 28% and 58% of their daily energy intake from dietary fat. However, the addition of even modest amounts of meat to the diet (10%–20% of dietary energy) combined with the sharing of resources that is typical of hunter-gatherer groups would have significantly increased the quality and stability of the diet of H. erectus [16].

Dietary-Induced Frugality in Cholesterolemia

Since about 100,000 years ago humans have started to spread across the whole world to become the only Homo species currently inhabiting this planet. The “Out-of-Africa” Diaspora necessitated adaptation to new conditions of existence [17]. Beginning as early as 12 thousand years ago (kya), multiple hunter-gatherer populations began developing agriculture and animal domestication [18]. Food production quickly spread to neighboring regions but periods of famine were frequent in the first few thousand years before production became stable [19]. Surprisingly, the rise of agriculture during the Neolithic period has paradoxically been associated with worldwide population growth despite increases in disease and mortality [20,21].

Plant sources of food and famine provide lower exogenous cholesterol to the body and, cell needs cholesterol into the composition of its membrane and hormones, as well as an energy store. For though, ApoE plays a critical role in regulating the uptake of cholesterol and lipids throughout the body [22]. ApoE2 is mostly common in the Mediterranean basin where agriculture is thought to have begun. The evolution of the E3 allele was important for allowing our ancestors to exploit diets with greater animal material but, ApoE4 could represent a more lipid-
thrifty variant [23] that is more efficient in sequestering cholesterol and has been better maintained in populations with a tenuous dietary supply [24]. Moreover, the positive selection effect may be mediated through the fact that the Apo E4 variant favors steroidogenesis and hence fertility [25,26]. Therefore, ApoE4 allele allowed surviving by providing higher amount of plasma cholesterol to the cell. Similarly, the reduced cholesterol efflux from the cell would be also beneficial because it implies in greater accumulation of energy, which is fundamental in periods of food scarcity. The ABCA1 plays a key role in cholesterol efflux and transfer from peripheral cells to lipid-poor Apo A1, the first step in HDL particle formation [27,28].

Cells with the altered form of the ABCA1 gene liberate 30% less cholesterol into the bloodstream. Viruses like yellow fever and dengue fever or the parasite that causes malaria seem to need cholesterol for invading the organism and reproducing. The mutation of ABCA1 must have favored the survival of individuals against these infectious diseases. With less cholesterol at the disposal of the infectious agents, more people would survive and would transmit the altered gene to future generations [29]. The people in whom the mutation in the ABCA1 gene mutation is most common live in regions with the greatest incidence of these infections. It is estimated that the variant that favors the accumulation of cholesterol in the cells appeared 8,300 years ago, almost 10,000 years after the first human beings arrived in America. This date coincides with that of the domestication of corn and strengthens the idea that the cereal may have contributed to the positive selection of this mutation [29].

Apo E4 allele and the ABCA1 gene mutation effects are among the so-called “frugal gene hypothesis” in which a genetic characteristics that prove to be advantageous in some way would be maintained in a population through a process of positive selection [30].

Years ago this alteration in ABCA1, found in 20% of the Mexican population, was more common among obese people, who have diabetes and abnormal levels of cholesterol (dyslipidemia). Among the known alterations of ABCA1 are the one that contributes most to reducing HDL levels, the most common form of dyslipidemia in Mexico. Thus, for almost 300 generations their cells have housed a genetic alteration that in the past allowed them to survive, but over the last 40 years has been contributing to ill health. Similarly, the current global distribution of the variant ApoE4 is associated with raised cardiovascular risk [29].

**Ancient Genome and Modern Diseases**

Since the agricultural revolution (i.e., some 10,000 years ago) we have gradually changed our diet and accelerated these changes from the beginning of the industrial revolution (100–200 years ago). There are seven major dietary changes since, we have shifted our dietary macronutrient composition toward carbohydrates at the expense of protein, increased the intakes of ω6 fatty acids (notably linoleic acid from refined seed oils), saturated fatty acid
(SAFA) and industrially produced trans fatty acids, decreased our ω3 fatty acid intake (both alpha-linolenic acid and those from fish oil), shifted to a carbohydrate-rich diet that contains a high percentage refined carbohydrates with high glycemic indices (e.g., highly processed grains, sucrose, fructose), decreased the intake of certain micronutrients (e.g., folate, vitamin D, magnesium, zinc), shifted toward acid-producing foodstuffs (like meat, grains) at the expense of base-producing counterparts (fruits, vegetables), increased our sodium (salt) intake and reduced our potassium intake, and decreased the intake of fiber [31].

In other words, genetically, we are for the greater part still adapted to the East African ecosystem on which our genome evolved, with some adaptations since the Out-of-Africa Diaspora. Dietary fat quantity and quality change has, together with other man-made changes in our environment, caused a conflict with our slowly adapting genome that is implicated in “typically Western” diseases. Fortunately, the majority of Western diseases occur typically after reproductive age. Rather than reducing our life expectancy, these diseases notably diminish our number of years in health. The tremendous increase of survival to reproductive age and of life expectancy, with a concomitant explosion of the world population is largely on account of the elimination of famine, neonatal diseases and infections [32].

People’s levels of physical activity have changed dramatically as a result of the move from pheasant-agricultural to urban-industrial ways of life. To survive in the wild required large expenditure energy on a daily basis for requisite activities such as foraging and/or hunting for food and water, social interaction, confrontation with or flight from predators, making and maintaining shelters and clothing, and other. This way of life represents the prototypical physical activity regimen for which our genome remains adapted [33]. Dramatic advances in technology such as those that ushered in the agricultural revolution (350 generations ago), the industrial revolution (7 generations ago), and the digital age (2 generation ago) have resulted in large systematic reductions in the amount of physical work demanded if humans in their day-to-day routines [34].

Particularly for the past 2 or 3 generations, technological advancements have, in many cases, completely eliminated the need for physical activity in our daily regimens. Economic development has the effect of reducing levels of occupational household and transport physical activity. Recreational activity is the only area in which physical activity may increase although people may not necessarily use their leisure time for active pursuits. Other factors constrain physical activity in cities such as personal safety and town planning. The profound and progressively wider discrepancy between current day physical activity and the indigenous Homo sapiens exercise patterns predictably results in atrophy, disability and disease [33].
Dyslipidemia and Dietary-Associated Cardiovascular Diseases

During the last 40 years, as the role of lipoproteins in the development of atherosclerosis was being defined. A high LDL-c and low HDL-cholesterol (HDL-c) belong to the classical CAD risk factors. The total-cholesterol/HDL-cholesterol ratio is the coronary artery disease (CAD) risk factor most often applied in algorithms for CAD risk assessment, such as the SCORE, PROCAM, and Framingham algorithms [35].

With regard to lipids it might notably be of importance to prevent the production of small dense LDL- and HDL-particles that are associated with insulin resistance and part of the so-called “atherogenic lipid triad”, that is, elevated triglycerides, low HDL-c and small dense LDL particles [36,37].

Although fat and cholesterol consumption and high serum cholesterol have for long been blamed as the principal causes of the CAD epidemic, it is now known that this so-called “lipid–heart hypothesis” is at least incomplete and that dietary fat and cholesterol quantities hold questionable relations with CAD. There is no solid evidence that a high intake of fat “per se” is harmful in terms of CAD in adults and also the influence of dietary cholesterol has been, and is still, exaggerated. Hence, it is widely accepted that atherosclerosis is associated with the consumption of SAFA and trans fatty acids by their ability to increase serum TC and LDL-c with no effect or decrease of HDL-c [38]. It has become clear that the dietary fatty acid composition may not only adversely affect serum cholesterol, but also influences coagulation, endothelial function, inflammation, abdominal obesity, insulin sensitivity, development of type 2 diabetes mellitus, and arrhythmias [39]. Such adverse conditions are likely to have been introduced by the increasing intake of SAFA, trans fatty acids and ω6 fatty acids (notably linoleic acid) in the Western diet during the past century and the concomitant decrease of the ω3 fatty acids intake from vegetable oils and fish [40].

A diet-induced proinflammatory and prothrombotic state may be part of the chronic low-grade systemic inflammation that is associated with the insulin resistance and compensatory hyperinsulinemia of the metabolic syndrome [37]. In these aspects, the insulin sensitivity that comes with fitness and low BMI might be of crucial benefits [16].

Risk Factors for Altered Cholesterololemia in a Brazilian Community of Free-Living Adults

In a cross-sectional study using baseline data from 910 subjects (79.3% females) over 35 years old (54.7 ± 11) participants of an ongoing dynamic cohort study (“Move for Health”) during the period of 2005 to 2015 were analyzed demographic, socioeconomic, dietary, physical activity, anthropometric and plasma biochemistry data.
The found abnormal plasma lipid profile was 42.3% low HDL-c, 36.9% hypertriglyceridemia and 27.9% hypercholesterolemia (TC). Patients in the top quartile of TC (≥ 206mg/dL) were similarly distributed among demographic and socioeconomic status and, discriminated by referring self-perception of being unhealthy and, reporting inadequate diet quality and low recommended physical activity. The associated alterations in food intake were in one side the higher energy intake along with its items carbohydrates and fat (saturated), and on the other side the lower fiber intake.

Higher cholesterol quartile was associated with higher body fatness, mainly abdominal and, lower aerobic fitness. The main linked plasma changes were in direction of dyslipidemic-pro inflammatory-insulin resistance states.

Lower plasma TC (84 to103mg/dL) was less frequent than higher cholesterol patients, and similarly distributed among demographic and socioeconomic status. It was discriminated by higher physical activity and ingesting better, yet inadequate quality of diet. They were leaner than the others but still presenting high rate of abdominal fatness. Consequently, markers related in some way to liver pathophysiology were present such as gamma-glutamyl-transferase (yGT), HDL-c, HOMA-IR, uric acid and urea. Therefore, main linked plasma changes were in direction of lower triglycerides (TG) and in a less extend lower fasting glucose and systemic inflammatory marker.

Sixteen percent of P10 (84 to 103mg/dL) cholesterol were distributed in the lower quartile of muscle mass index (MMI) (≤ 7.25kg/m²) and, 32.1% were taking statins. On the other hand, 30.1% of the P10 cholesterolems were on the top quartile of MMI (≥ 9.20kg/m²) and, 53.6% for those in the top MMI quartile were using statins.

### Brain Cholesterol

The transport and biosynthetic processes that bring about cholesterol accumulation in the CNS must account for the rates of growth and the size of the sterol pools found in the brain at different ages of development. The cholesterol required for cellular proliferation and myelin synthesis might come from either the synthesis in the different types of cells within the CNS or the rapidly fluctuating levels of plasma lipoproteins. Many of the proteins involved in the movement of cholesterol throughout the body are also expressed in the CNS [7].

During perinatal development, when the plasma cholesterol level is fluctuating widely, there are very high rates of synthesis in all regions of the brain and spinal cord. In adults, the rate of synthesis exceeds the need for new structural sterol, so that net movement of cholesterol out of the CNS must take place [8].

There is a compelling body of evidence that there is no net or even bidirectional, movement of cholesterol from plasma lipoproteins across the endothelial cells of the blood-brain barrier to the cells of the CNS. Therefore, essentially all cholesterol required for myelin formation in these cells came from endogenous synthesis and not from
exogenous, lipoprotein cholesterol. Indirect evidence suggests that large amounts of cholesterol turnover among the glial cells and neurons during brain growth and neuron repair and remodeling. This internal recycling of sterol may involve ligands such as ApoE and ApoAI, and one or more membrane transport proteins such as members of the LDLR family. Therefore, changes in cholesterol balance across the whole body may, in some way, cause alterations in sterol recycling and Apo E expression within the CNS, which, in turn, may affect neuron and myelin integrity [7].

The cholesterol turnover across the brain is increased in neurodegenerative disorders such as Alzheimer’s disease and Niemann-Pick type C disease. Whether there can be a causal relationship between the concentration of plasma cholesterol and abnormalities such as depression, violent behavior, and dementia is still uncertain [8].

**Plasma Cholesterol Changes and Disorders of CNS**

Although there is currently little evidence for the net transfer of sterol from the plasma into the brain of the fetus, newborn or adult, there is possibility that blood sterol manipulation might have a detrimental effect on brain function. Certainly, children with the Smith-Lemli-Opitz syndrome who cannot convert 7-dehydrocholesterol to cholesterol in the blood or CNS have profound abnormalities in brain development and function [41]. Additiona-
dementias [46-50]. All these observations come across the possibility that there is a relationship between the plasma level of cholesterol carried in LDL, HDL, or other lipoproteins and the growth, myelination, and function of the CNS. If this is true, these lipoproteins might make important contributions to the cholesterol pools within the brain and spinal cord and possibly affect, directly or indirectly, the processing of proteins such as serotonin receptors or amyloid precursor protein [51].

**LDL-Lowering Effects of Statins and Risks of CNS Disorders**

Currently, there is no convincing evidence for the net transfer of sterol from the blood into the brain or spinal cord but, pharmaceutical agents such as 3-hydroxi-3-methyl-glutaril-CoA (HMG-CoA) reductase inhibitors used to reduce blood LDL-c levels, also decrease the incidence of Alzheimer. When given orally, all currently available statins partially inhibit cholesterol synthesis in the CNS. If, for example, this inhibition slowed cholesterol movement through the astrocyte/neuron/24(S)-hydroxycholesterol pathway, it could affect the rate of processing of amyloid precursor protein [52,53].

During the last 40 years, as the role of lipoproteins in the development of atherosclerosis was being defined and, consequently in excess of 15 million individuals in the United States are being treated with pharmaceutical agents to decrease their LDL-c levels below 100mg/dl to reduce the incidence of coronary artery disease [54].

Along with atherosclerosis, currently we can add Alzheimer treatment with statins but, recently it was raised the possibility that the low level of circulating cholesterol also affects, in some manner, the function of the CNS. It was postulated, for example, that the concentration of cholesterol circulating in the plasma of the newborn infant might affect brain development and even intelligence. In the adult, it was suggested that low levels of circulating cholesterol might be responsible for depression and violent, or even suicidal, behavior [43].

Thus, LDL-c lowering by statins has indeed proven to lower CAD risk in both primary and secondary prevention trials. These studies have shown that the lowest LDL-c confers lowest risk, and have set the stage for current treatment goals. On the other hand, statin users are at risk of low cholesterolemia and consequently, outcomes of depression and violent, or even suicidal, behaviors.

**The Healthy Lifestyle Alternative for Treating Altered Cholesterolemia**

Interestingly, the current LDL-treatment goals through statins proved similar to LDL-levels encountered in traditionally living hunter-gatherer societies [55,56]. Moreover, medical and anthropologic studies have shown that hunter-gatherer societies are largely free of the degenerative diseases of Western civilization, and this has been attributed partly to their diet [15].

When primitive cultures encounter civilization and
adopt Western diets, their health worsens. Nevertheless, a temporary reversion to a traditional diet and lifestyle has been shown to result in marked improvement in metabolic risk factors in studies that involved aborigines [57,58].

Thus, it seems that our genetically determined “survival strategy” turns against us now that we can eat whatever we want and whenever we want, and need little physical activity for food procurement. This, so-called obesogenic environment has never existed in the past, was consequently not part of selection pressure, and genetic adaptations might therefore also not be expected [59]. Therefore, elimination of the meanwhile voluntarily introduced unfavorable environmental conditions and return to the dietary balance, and lifestyle in general, on which our genome has evolved, might restore “metabolic homeostasis” increase the number of years in health (life quality) and reduce the costs in healthcare [32].

**Conclusion**

Fat is a thrifty for evolutionary human as well as the cholesterol metabolism for human encephalization and fertility. Cell cholesterol is maintained by its synthesis, inflow and outflow. To maintain cell cholesterol constant the amount of cholesterol varies among the plasma lipoprotein transporters and, higher LDL and lower HDL-c are considered strong risk factors for cardiovascular diseases (CVD). The most used LDL-lowering procedure is by blocking cholesterol synthesis, using statin. Although effective in reducing plasma levels of LDL-c, there is evidence that the drug blocks also the brain cholesterol synthesis and, what in a sense would be good for Alzheimer treatment, might be deleterious for the brain development and regular nerve regeneration and repair. Therefore, although considered effective in CVD and Alzheimer treatments, statin users are also at risk of hypocholesterolemia-induced CNS disorders. Alternatively, we have shown that higher cholesterolemia has behavioral risk factors leading to common outcomes of obesity and co-morbidities. Therefore, changing lifestyle with regular physical activity and, mainly nutrition re-education (for dietary adequacy) would be the goal for avoiding the extremes of cholesterolemia.

**Future Directions**

Focusing on statin-induced low cholesterolemia and the resulted CNS disorders as the main goal, we must take preventive care of higher cholesterol risk factors marledly the ones related to overweight disorders. For so, we have to introduce lifestyle modifications on the existing sedentary/energy dense food (obesogenic) environment. The Palaeolithic (healthy) dietary composition seems somewhat abandoned since the Out-of-Africa Diaspora, since deficiencies of many of these particular nutrients are among the most widely encountered in the current world population. These dietary changes are firmly implicated in the risk of typically Western diseases. Evolutionary medicine, and perhaps common sense, teaches us that we might have to return to the lifestyle on which our genes have evolved during the past million years of evolution.
Therefore, the ultimate goal might be to return to the fat quality of our ancient diet [16].

The results obtained from Paleolithic-like diets such as Dietary Approaches to Stop Hypertension (DASH) and Mediterranean-style diets are encouraging. However, we need rethinking of the very basics of “homeostasis” and avoidance of the vicious cycle that is initiated by taking observations from Western societies as a basis of dietary recommendations and lifestyle in general. Traditionally living societies may provide us with clues for absolute standards for human homeostasis, but unfortunately many of these have meanwhile become dependent on food programs with typically Western approaches, or adopted a (quasi) Western lifestyle in general. A combination of data from traditionally living societies, (patho) physiological insight, anthropometrics, archeology, genetics, nutrigenomics, and classical trials may lead to cleverly designed RCTs to answer the question on what diet our genes have evolved and what diet consequently promotes our health at best. The lessons from such studies might especially be relevant to early nutrition, because of its importance to development and the increasingly recognized relation between early development and the risk of disease at later life [16].

Acknowledgements

The authors acknowledge their fellowships from CNPq(RCB) and from UNESP-Medical School Graduate Program of Pathology(CNMN-CNPq and HTK-CAPES).

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