Research Article ISSN 2639-9326

Diabetes & its Complications

"Human Obesity from Evolutionary-Medicine Understanding to a Behavioral-Medicine care" A Compilatory Data-View

Roberto Carlos Burini*

UNESP - Sao Paulo State University, School of Medicine, Botucatu, Brazil.

***Correspondence:**
Roberto Carlos Burini, UNESP - Sao Paulo State University, School of Medicine, Botucatu, Brazil.

Received: 08 Aug 2025; **Accepted:** 15 Sep 2025; **Published:** 24 Sep 2025

Citation: Roberto Carlos Burini. "Human Obesity from Evolutionary-Medicine Understanding to a Behavioral-Medicine care" A Compilatory Data-View. Diabetes Complications. 2025; 9(2): 1-14.

ABSTRACT

The epigenetic recognizes our predisposition to obesity as the key assumption of the mismatch between the human genome molded over millions of generations (thrifty genotype) evolved for efficient food collection and fat deposition to survive periods of famine, now frugally coping with the modern dietary and physical environments of energy dense foods and/or sedentary lifestyle. Having fat as major energy-yielding substrate, the thriftiness to effectively detect, metabolize, and store fats likely provided tremendous selective advantages "(meat-adaptive genes)" to our ancestors. Among adipocytes, white-fat cells are specialized for the storage of chemical energy as triglycerides, a neutral non-toxic fat. Under excess of energy, adipocytes become enlarged and their secreted growth factors led neo-adipocyte to differentiate resulting hyperplasia. Leaked or broken open (hypertrophied) adipocytes are phagocytosed by resident and embed macrophages. Then, obesity-derived inflammatory stress is a systemic orchestrated metabolic network triggered by the chronic accumulation of lipids into adipose tissue. The resident macrophages amplify the inflammatory signal which is enhanced by the cross talk among endothelial cells (adhesion molecules), adipocytes (leptin), and resident macrophages, which together contribute to the production of pro-inflammatory cytokines resulting in the elevated circulating levels of insulin, leptin that accompany obesity. Differently from treating low-level targets by drugs (homeostatic model), the allostasis model has a more rational goal of intervention, the basis of Behavioral Medicine. As a model of Behavioral Medicine, our community-based ongoing epidemiological study, "Moving for Health Program" (1991 to 2019) with lifestyle re-education with supervised physical exercises and diet-counseling program, had promoted proactively, alternatively to homeostatic model, eutrophy and significant reductions of overweight-related NCDs with considerable economic impact on Health Care.

Keywords

Body-fat thriftiness, Obesity, Environmental risks, Lifestyle-change.

Abbreviations

ACSM: American College of Sports Medicine, AMP: Adenosine Monophosphate, AMPK: AMP-activated Protein Kinase, BMI: Body Mass Index, BW: Body Weight, CHD: Coronary Heart Disease, CHO: Carbohydrate, CoA: Coenzyme A, CRP: C-Reactive Protein, FFA: Free Fatty Acids, HDL: High-Density Lipoprotein, HEI: Healthy Eating Index, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, hs-CRP: high-sensitivity C-Reactive Protein, IL-6: Interleukin-6, IPAQ: International Physical Activity Questionnaire, IRS: Insulin Receptor Substrate, JNK: c-Jun N-terminal Kinase, LiSM: Lifestyle-changing, MCP-1: Monocyte Chemoattractant Protein-1, MDA: Malondialdehyde, MS: Minimum waive, NAFLD: Non-Alcoholic Fatty Liver Disease, NCD: Non-Communicable Disease, NF-κB: Nuclear Factor kappa B, PAI: Plasma atherogenic index, PPAR: Peroxisome Proliferator-Activated Receptor, PUFA: Polyunsaturated Fatty Acids, T2D: Type 2 Diabetes, TG: Triglycerides, TNF-α: Tumor Necrosis Factor-alpha, VO_2max: Maximum Oxygen Consumption,

W-3: Omega-3 fatty acids, WC: Waist Circumference, WHO: World Health Organization.

Introduction

As a major NCD, obesity is rising in epidemic proportions that herald dramatic negative influences on the health of the population in the decades to come [1]. In Brazilian adults, 48% of women and 50% of men were considered overweight in the first decade of this century [2]. The overall costs of obesity and related disorders were estimated as US$36 million a year for an adult population of 49% overweight and 14.8% obese [3].

From the emerged biological or behavioral plausible causes of obesity [3] body fatness is considered a positive concordance of thrifty genes in a famine condition, resulting in thriftiness of energy economy [4]. Though, as an evolutionary selection, obese human has overexpression of thrifty genes evolved for efficient food collection and fat deposition to survive periods of famine. From the evolutionary theory, the body is not a product of design but of natural selection and the genetic traits may be positively or negatively selected relative to their concordance or discordance with environmental selective pressures. Therefore, bodies are bundles of compromises shaped by natural selection in small increments to maximize reproduction, not health. Consequently, bodies are vulnerable to disease, and remarkably resilient, precisely because they are not machines built from a plan" [5].

Then, an evolutionary view suggests that many genetic variants interact negatively with environments and other genes during development to influence disease phenotypes [6]. The genetic homology of obesity is uniformly high, affecting 40%-60% of the population worldwide. Still, weakening the sole genetic cause, the fact that the rates of obesity have risen in epidemic proportions over the last 60 years, with more than doubling in adults and tripling in children and youth in Western populations, 2 indicates that obesity must be a result of an ancestral genome molded by environmental interaction.

In its ignorance to the evolutionary principles, current medicine remains largely pre-evolutionary, excelling in description and mechanistic explanations, but only beginning to explain the variability in disease susceptibility in individuals and populations. Supporting different view, Evolutionary Medicine rests on the assumption that functional biological characteristics are the result of evolutionary adaptive processes. Thus, Evolutionary Medicine [6] aims to explain diseases based both on recent physiological causes (most commonly addressed by medicine) and on more distant evolutionary causes. Far from suggesting quick new cures, the general messages of Evolutionary Medicine help to explain why disease is so prevalent and difficult to prevent. By ignoring human evolution, actual medicine [6] focuses upon proximate mechanical causes, seeking explanations for diseases, or their symptoms, signs, and cause in single, materialistic changes within the body [7]. Consequently, drug therapy is used worldwide as a measure in halting and reversing the NCDs epidemic. Underlying why drug therapy has been largely unsuccessful in halting and reversing the NCDs epidemic would be the ineffectiveness of the treatment approach by the homeostasis model [8]. Additionally, understanding why human development may influence the predisposition to obesity can be assisted by taking an evolutionary perspective [3]. Because established obesity is notoriously resistant to treatment [8] much attention has been focused on prevention, especially during infancy and childhood when life-long habits of dietary intake and physical activity may be established and metabolic pathways may be set [8]. Differently from treating low-level targets by drugs (homeostatic model) and generating iatrogenesis, the allostasis model has a more rational goal of intervention with lifestyle modification of environmental factors [8]. This is the basis of Behavioral Medicine. Among its principles, dietary adequacy and physical activity as pillars of treatment, which can be a natural remedy for recovering part of the imbalance caused by modern lifestyles, costless and without the side effects of many pharmacological treatments [9,10].

As a model of Behavioral Medicine, cost-effective lifestyle modification programs have, alternatively to the homeostatic model, promoted, proactively, eutrophy and reduced blood hypertension, T2D, and Metabolic Syndrome in community-based adults [11]. This community-based ongoing epidemiological project, "Moving for Health Program", was conducted from 1991 to 2019, in a very much tune with the ACSM's "Exercise is Medicine" and WHO proposals [11]. The effectiveness in reducing overweight [12], T2D [13-15], hypertension [16], and Metabolic Syndrome [17,18] resulted in considerable economic impact on the National Health care [19].

Human Evolutionary Thriftiness of Survival

Body Energy Thrifty for Encephalization

Evolution by natural selection is a central organizing concept in biology, once it shapes organisms in functioning within a particular set of environmental conditions [20]. Humans share a common ancestor with the chimpanzee and bonobo that probably lived in East Africa some 6 million years ago. At the genetic level, humans are very similar to chimpanzees but we clearly differ from other primates in many aspects of anthropometrics and behavior [21]. The evolution of *H. erectus* in Africa is widely viewed as a "major adaptive shift" in human evolution. Hominids have since then experienced a tremendous body weight and brain growth, and assumed an upright position [22]. Humans grew in body and brain sizes but the most important of the evolutionary features is our high levels of encephalization (large brain: body mass). It is often taken for granted that the benefit of a larger brain is an increase in "intelligence" that makes us stand out amongst other mammals, including our nearest relatives, the primates [23].

The first task for the greater brain would be the energy yield for the extra mass [24]. The central nervous system accounts for only 2% of the whole-body mass but expends 23% of our daily energy. Over the last three million years, hominid brain sizes tripled. The high energetic costs of the human brain highlight the importance

of strong selective benefits to having a larger brain and enhanced cognitive abilities [25]. Large brains are rare and are achieved only when animals are under strong selection. The trigger for brain expansion in marine mammals was probably environmental, specifically the cooling of the southern ocean [26] and higher food supply. In the case of humans, there have been two environmental pressures associated with the two major periods of human brain expansion. The first occurred with bipedal running when the mobility, the freeing of the hands as he evolved to an erect stature, and the stereoscopic vision, most certainly contributed greatly to this task of survival by favoring those individuals who had the capacities conducive for the gathering of the available food supply [27]. The second period of human brain expansion is coincident with the domain of fire and the introduction of cooking [24,28].

Thus, environmental pressures seemed critical for mammals brain enlargement and, although dietary change was not being the sole force responsible for the evolution of large brain size, the exploitation of high-quality foods likely fueled the energetic costs of larger brains and necessitated more complex behaviors. Specific human brain expansion was associated with changes in diet, foraging, and energy metabolism [24]. Primitive humans with enlarging brains became more efficient hunter/gatherers and so gained greater access to more nutritious and easily digestible foods (e.g., fruits, nuts, and meat) and so no longer needed the large gastrointestinal tract. The "expensive-tissue hypothesis" (expensive tissue trade-off) suggests that the massive expansion of the neocortex in humans came at the expense of the gastrointestinal tract [28]. However, from the major environmental pressures, the energy cost of evolutionary encephalization can be explained by three proposed hypotheses: the direct metabolic constraints, the expensive tissue trade-off, and the energy trade-off [24,29]. However, these hypotheses do not explain it totally. Though, along with improved diet quality, others factors had contributions, such as allomaternal subsidies, cognitive buffering by earlier weaning and longer juvenile periods, reduced costs for locomotion and by cooperative behavior, and reduced allocation to production, all operated simultaneously, thereby enabling the extraordinary brain enlargement in our lineage [24]. Thus, the exploitation of high-quality foods likely fueled the energetic costs of larger brains along with other complex behaviors, that would have selected for greater brain size.

Energy Thriftiness for Immune Competence

Along with higher body mass and encephalization, our ancestors experimented with extended lifespan and therefore, for millions of years, they were often faced with survival stresses [30]. Though, since the late Paleolithic era, there was a fight for survival, not only in the face of food shortage, but also in surviving epidemics and changes in climate encountered during migrations [31]. Survival of multicellular organisms to fight infections depends on the organism's ability to stress adaptation, a high-energy-demand process [32]. Then, the metabolic and immune systems are among the most basic requirements across the animal kingdom [33,34]. An activated immune system usually requires substantial energy in a quiescent state. The energy requirement rises into an active phase of inflammation and, in infection, every oC higher means 15% higher energy expenditure [35]. Consequently, the molecular systems regulating metabolic processes and immune response have co-evolved and mutually regulate each other.

To meet the challenges of infection, an activated immune system has an urgent need for energy-rich substrates that must be allocated from internal and external energy stores (glycogen, proteins, triglycerides, or free fatty acids). Hence, it is not surprising that metabolic and immune pathways have evolved to be closely linked and interdependent and, genes controlling metabolic and pathogen-sensing systems have been highly conserved from lower-level organisms to mammals [33,36]. Under normal conditions, the integration of the metabolic and immune systems is fundamental for the maintenance of good health [37]. Energy metabolism is crucial for the maintenance of inflammation, not only in terms of energy supply, but also in the control of the immune response through metabolic signals [38]. Without inflammation, wounds will not heal, and immune competence does not act effectively [10]. It is now apparent that critical proteins act as links between nutrient metabolism and inflammatory pathway activation in immune cells. Some of these critical proteins are related to lipids and necessary for regulating energy metabolism, such as peroxisome proliferator-activated receptors (PPAR γ), Toll-like receptors, and fatty acid-binding proteins [39,40].

The Energy-Thrifty Genome

In ancient times, food supply was never consistent and it is contended that the ancient hunter-gatherer had cycles of feast and famine, punctuated with obligate periods of famine. To overcome those situations, certain genes evolved to regulate efficient intake and utilization of fuel stores. Neel [41] defined this thrifty genotype as "being exceptionally efficient in the intake and/or utilization of food". In general language, thrifty implies some degree of prosperity deriving from earlier frugality and careful management of resources. During famines, individuals with the thrifty genotype would have a survival advantage because they relied on larger, previously stored energy to maintain homeostasis [42,43]. At the broadest level, humans represent a thrifty species relative to other mammals, indicating that metabolic adaptations had a crucial role in the emergence of the Homo lineage. Therefore, metabolic adaptations had a crucial role in the emergence of the present-day Homo Sapiens lineage, in particular in buffering reproduction from ecological stochasticity [44].

The Energy-Thriftiness of Fat

During famines, individuals with the thrifty genotype would have a survival advantage because they relied on larger, previously stored energy to maintain homeostasis [42,43]. From our energy-yielding nutrients, fatty acids provide twice as many kcal/g as CHO or protein and are stored anhydrously either occupying intracellular or interorgan spaces, insulating parenchymal organs, and working as a subcutaneous cushion [22]. In a 70 kg man, nearly 135,000 calories are stored as fat, and only about 1% of this amount is

stored as CHO [45].

With the evolution of Homo erectus, to supply the body-fat stores, our ancestors began a new lifestyle oriented around a combination of meat eating and gathering [46]. Key genetic mutations were critical to promoting the enhanced lipid metabolism necessary for subsisting on diets with greater levels of animal material. Compared to large-bodied apes, humans have an enhanced capacity to digest and metabolize higher-fat diets. Our gastrointestinal tract, with its expanded small intestine and reduced colon, is quite different from those of chimpanzees and gorillas and is consistent with the consumption of a high-quality diet with large amounts of animal food. Therefore, it has been shown that the evolution of key "meat-adaptive" genes in hominid evolution was critical to promote enhanced lipid metabolism, necessary for subsisting on diets with greater levels of animal material [47]. Along with the critical selection for key "meat-adaptive" genes allowing our hominid ancestors to more effectively exploit diets with higher levels of animal fat, there is evidence highlighting the remarkable capacity of the human brain and sensory system for accurately assessing the energy content of potential food items [48]. Thus, associated with the evolution of our high-quality diet, the need for an energy-rich diet also appears to have shaped our ability to detect and metabolize high-fat foods. Consequently, we show strong preferences for lipid-rich foods and, it has been shown that these preferences are based on the smell, texture, and taste of fatty foods [49-51]. In sum, the thriftiness to effectively detect, metabolize, and store fats likely provided tremendous selective advantages to our hominid ancestors, allowing them to expand into diverse ecosystems around the world [52].

The Thriftiness of Body Fatness

Body size is one of the most important characteristics of any animal because it affects a range of behavioral, ecological, and physiological traits, including energy requirements, choice of food, reproductive strategies, predation risk, range size, and locomotor style [53]. Body composition refers to the amount and distribution of fat and fat-free tissues of the body. Hence, body mass is highly affected by variation in the size of adipose depots [54].

Body fatness had a crucial role in the emergence of the present-day Homo Sapiens lineage, in particular in buffering their reproduction rate from ecological stochasticity [44]. Normally, variable amounts of extra fat are safely stored subcutaneously, either locally hip and thigh (in adults) or spread over total body subcutaneous (in children), where it confers a metabolically protective reserve in both genders and supports pregnancy and lactation in females [55]. Particularly in women, fatty-body pattern rather than thinned-body used to be symbol of fertility, in ancient population and, before "Hollywood stars" and "miss universe", it was also a common symbol of beauty.

In general, the development of body composition is shaped early in life appearing to show important adaptations in fat metabolism to accommodate the high energy demands of the brain early in life [52]. Even in intra-utero undernourishment the Low birth-weight preserves normal brain-weight despite a severe loss of lean body mass [3].

In general, human infants are born with high body fat levels, and continue to gain fat during the first year of postnatal life [56]. At ~15%–16% body fat, human infants have the highest body fat levels of any mammalian species [57]. Consequent to large brain, human infants are born altricial (relatively underdeveloped for their age), and unlike other primates, continue rapid brain growth into early postnatal life [58].

In humans, the food-derived energy is stored mainly as fat and, in healthy adults, body weight (and fat mass) is tightly regulated despite day-to-day variations in food intake and energy expenditure. Following high-fat intake, it is induced a diet-induced thermogenesis, including the increased expression of uncoupling proteins (UCPs) which acts as a defense mechanism against weight gain. The increased heat produced by UCPs not only helps increase energy expenditure but also promotes satiety, thereby establishing energy balance. However, in the long term, positive energy balance creates the need for surplus fat storage [59]. A person gains weight if they expend less energy than they take it.

Hormonal Control of Body-Fat Stores

Physiologically, triglyceride levels of both adipose and lean tissues are substantially reduced by a direct anti-steatosis effect of endogenous hyperleptinemia. Though it presents two major effects, the hypothalamic effects of leptin in the (down)regulation of food intake and peripherally by enhancing lipid oxidation and inhibiting lipogenesis in tissues. Both effects occur via activation of AMP-activated protein kinase (AMPK). Therefore, ectopic accumulation of surplus lipids is minimal, and partitioning of body fat is well maintained [60]. Then, basically, the control of fat stores in the body, is mediated mainly by adipocyte hormones leptin [61] and adiponectin [62,63].

When caloric intake is equal to caloric expenditure, the lipo-regulatory system is at rest, and the lean tissues contain little or no un-metabolized lipids, the leptin levels are low. However, if such a person chronically consumes more calories than are needed to meet the caloric expenditure, adipocytes will expand and leptin levels will rise in proportion to the degree of lipid overload [60].

It is known that subcutaneous adipocytes provide much, if not most, of the body hyperleptinemia, by contrast, the visceral adipocytes provide less of the hyperleptinemia [64]. Deficiency of and/or unresponsiveness to leptin prevents these protective events and results in ectopic accumulation of lipids. It is known that leptin resistance plays a role in the process where appetite overrules the message of satiety.

Complementary to leptin, mechanisms of adiponectin action include increase in lipid oxidation in liver and skeletal muscle, whose action in lipid oxidation occur via activation of AMP-activated protein kinase (AMPK) and induction of peroxisome

proliferator activated receptor (PPAR) [65-67]. Additionally, adiponectin reduces lipogenesis by decreasing the activity of enzymes involved in fatty acid synthesis: acetyl-CoA carboxylase and fatty acid synthase. Thus, normally, storage surplus of fat induces an increased leptin and adiponectin secretion, hormones that enhance oxidation of surplus lipids in non-adipose tissues and reducing the activity of lipogenic enzymes.

Adipocyte-Fat Storage

Mammals have evolved mechanisms to store energy during periods of plenty, which helps to guarantee survival during periods of drought and famine. For though, dedicated fat-storing cells were necessary, because the tissues of the lean body mass lack the storage capacity to meet the fuel demands imposed by famine. Then, human organism has extensive fuel reserves in the adipose tissue, which may meet energy demands for substantial periods. Hence, the evolution of adipocytes served the purpose of extending survival during the recurrent cycles of famine [42]. Among adipocytes, white-fat cells are specialized for the storage of chemical energy as triglycerides, while brown fat cells dissipate chemical energy in the form of heat.

Excess energy is mostly stored in white-adipose tissue where adipocytes become enlarged. Both hypertrophy and hyperplasia of adipocytes occur, but hypertrophy is predominant during the initial stages of adiposity. Because the capacity to hypertrophy is limited, once adipocytes reach a critical size, neo-adipocyte differentiates and the action of growth factors secreted by the hypertrophied adipocytes is observed leading to hyperplasia [68].

The long-term storage of excessive amounts of lipid can harm health because the adipocyte is thought to be both a static storage depot for calories as triglycerides and an endocrine organ to secret many hormonal factors, including lipid mediators, stress kinases, and pro-inflammatory cytokines and chemokines. These molecules participate in regulating energy metabolism, lipid storage, and inflammatory responses [30].

Adipocyte-Macrophage Interaction and Inflammation

When expanded fat cells leak or break open, resident and embed macrophages are mobilized into the adipose tissue to clean up, by phagocytosis. Enlarging adipocytes secrete macrophage chemo-attractant protein 1 (MCP-1) and angiopoietin-like protein 2 (Angptl2) responsible for attracting macrophages and remodeling blood vessels. Additionally, once higher than normal, Angptl2 level may develop leptin resistance in fat tissues. An additional source of macrophages could be the trans-differentiation of pre-adipocytes to residual macrophages. Adipocyte hypertrophy controls both, the differentiation of neo-adipocytes (increased fat storage) and the local macrophage density for fat surplus scavenging [69]. Thus adiposity-induced inflammation is associated basically with the increased adipose tissue macrophage infiltration. However, strengthening the effects of macrophages infiltration, hypertrophic adipocytes may produce pro-inflammatory cytokines and chemokines such as TNF-alpha, IL-6, leptin, resistin, MCP-1, and PAI-1, with local effects. In orchestrated actions, endothelial cells respond through the increased expression of adhesion molecules, which along with the chemokines serve to recruit immune cells including monocyte-derived macrophages to the adipose tissue. TNF's primary role is to regulate the immune cells and induce inflammation. White blood cells then assist by releasing more cytokines [70].

Then, excess White Adipose Tissue is an overactive endocrine organ secreting an array of inflammatory adipokines, such as tumor necrosis factor (TNF-α), monocyte attractant protein 1 and interleukin 6 [71]. Additionally, once intracellular, excess nutrient intake can induce oxidative stress in the adipose tissue which exerts significant effects on adipose tissue biology and can lead to dis-regulation of adipocyte function, that manifests as inhibited adipocyte differentiation, enhanced immune cell infiltration into adipocytes and increased inflammatory cytokine secretion [72]. Thus, inflammatory cytokines may not only induce a chronic inflammatory process in adipocyte tissue, but also be released into circulatory blood spreading systemically [73]. It is possible that, as an inflammatory marker, leptin responds specifically to adipose-derived inflammatory cytokines.

A raised theory of systemic-inflammatory stress began with the accumulation of lipids in adipose tissue and the expansion of the fat mass leading to the initiation of an inflammatory process opening the possibility that, the resident macrophages serve to amplify the signal. Therefore, the inflammatory signal is enhanced by the cross talk among endothelial cells, adipocytes, and resident macrophages, which together contribute to the production of pro-inflammatory cytokines. In this way of thinking, the elevated circulating levels of insulin, leptin and IL-6 that accompany obesity may represent a common compensatory mechanism to systemic inflammation [6].

Obesity Inflammation

Obesity is characterized by the progressive infiltration of macrophages in adipose tissue. The death of adipocytes within the adipose tissue, adipose tissue hypoxia, and production of chemotactic factors have all been proposed to regulate the obesity-associated shift in the local macrophage cell profile. Macrophage-scavenger actions are part of the cell defense against fat-overstored (hypertrophied) adipocytes. The imbalance between energy intake and dissipation triggered by over-nutrition leads to a persistent, low-grade inflammatory state and an increased susceptibility to chronic diseases [74,75]. This chronic inflammation is different from the classic immune response to an infectious agent and thus has been referred to as meta- or para-inflammation [74,75]. However, the same organs at the intersection of metabolism and immune function are involved in precipitating all of these different inflammatory responses [76].

Fat Storage-Related Toxicity

By allowing surplus fuel to be stored (as neutral fat) during caloric abundance for subsequent retrieval during periods of caloric need,

we extend survival [76]. Excess fat-energy is stored as triglycerides (TG) primarily in the adipose tissue, but in some other tissues as well. TG is probably the least toxic form in which the lipid surplus can be sequestered. Therefore, the harmful lipids are quite probably not in the form of neutral fat [77], if non-adipose tissues are exposed to an excess of long-chain fatty acids, unless leptin action increases their oxidation sufficiently, unoxidized fatty acids enter non-oxidative pathways. One of more toxic pathways led to D*e novo* ceramide formation, probably the most damaging lipid [60].

Ceramides are a family of waxy lipid molecules, composed of sphingosine and a fatty acid. De novo synthesis of ceramide occurs via condensation of unoxidized fatty acyl-CoA and serine, catalyzed by the enzyme serine palmitoyl transferase [78]. As a bioactive lipid, ceramide has been implicated in a variety of physiological functions, including apoptosis, cell growth arrest, differentiation, cell senescence, cell migration and adhesion [79]. Roles for ceramide and its downstream metabolites have been suggested in pathological states, including obesity, diabetes, neural degeneration, inflammation, and cancer [80].

Ceramides induce insulin resistance by increasing c-Jun NH_2-terminal kinase (JNK) activity and, therefore, inhibiting Akt/PKB signaling. The effects of JNK are through the serine phosphorylation of the insulin receptor substrate (IRS)-1, which inhibits normal tyrosine phosphorylation of IRS-1 and downstream insulin signal transduction [81-83].

In general, reactive oxygen species, endoplasmic reticulum stress, and ceramides are increased by adiposity [84]. In mitochondria, ceramide suppresses the electron transport chain and induces production of reactive oxygen species. Reactive oxygen species, endoplasmic reticulum stress, and ceramides have been shown to activate both JNK and NF-kB [85,86]. Therefore, the inhibition of insulin signaling transduction through serine-kinase activation can be induced by the transcription factors NF-kB and JNK, both activated in pro-inflammatory and pro-oxidant states, commonly found in situations of intracellular ceramide formation [87]. Overall, the obesity-associated shift in the local macrophage cell profile is regulated by the death of adipocytes within the adipose tissue, adipose tissue hypoxia, production of chemotactic factors, and increased free fatty acid (FFA) fluxes. All have also been shown to activate both JNK and NF-kB, and consequently, promote insulin resistance [88].

Lipotoxicity in Non-Adipocyte Cells

It is important to distinguish the metabolically healthier fat storage patterns such as those safely stored subcutaneously, either locally hip and thigh in adults or spread over the total body subcutaneous in children [55], from others often associated with degenerative diseases, such as the upper body obesity, around the abdominal organs or viscera, upper body, neck, and tongue [89].

Lipotoxicity is a syndrome that results from the accumulation of lipid intermediates in non-adipose tissue, leading to cellular dysfunction and death. The lipid-induced dysfunction in the lean tissues is referred to as lipotoxicity [90], and lipid-induced programmed cell death is called lipo-apoptosis [91]. Lipotoxicity affects tissues such as liver, skeletal muscles, heart and kidneys and results, when lipid is forced into organ cells, significantly impairing function [92]. The wide consequences of insulin resistance may be one example of cell-lipotoxicity effects [93].

In non-adipocyte cell, there is usually a balance between uptake (and production) and oxidation of fatty acids. Positive cell-fatty acids balance and expansion of visceral fat mass, as well as ectopic fat accumulation in liver and skeletal muscle, results from the inability of the body to adequately store energy, a state that is driven by insulin resistance of subcutaneous adipose tissue [89]. Storage of even a modest caloric surplus in lean tissue would ultimately be manifested clinically by hepatic steatosis (fatty liver), myo-steatosis (fatty muscle), cardiomyo-lipodistrophy, renal-lipodystrophy and, consequently non-insulin dependent diabetes mellitus and lipid-renal or –cardiomyopathy [92].

Human Obesity Care

As an evolutionary selection, obese human has overexpression of thrifty genes evolved for efficient food collection and fat deposition to survive periods of famine. Though food shortage was one of our ancestral environmental pressures. Against the environmental constraints, human behavior reacted, generating the frugal genes of survival. However, because biological evolution is much slower than cultural change, Evolutionary Medicine describes that much disease arises from the mismatch of our ancestral frugal modeled-genome bodies to modern environments. Therefore, it is possible to analyze a great number of contemporary diseases in terms of adaptive vulnerabilities connected to our phylogenetic inheritance, such as human bodily inadequacies in the modern environment [6]. Thus, adiposity may be our form of thrifty that emerged from frugality in energy expenditure or upregulation of appetite. In this hypothesis, there are at least three windows for metabolic plasticity: pregnancy, lactation, and later life [3].

Today, it is clear that lifestyle factors and human health are linked through epigenetic mechanisms [24], and the modern human bodily inadequacies concerning the modern environment can be associated with either dietary inadequacy and/or physical inactivity [94].

Nutritional behavior may modulate overweight by eating high-energy-dense food, a highly refined carbohydrate (CHO) and fat diet, low-micronutrient diet [3]. In the same way, physical inactivity may modulate human physiology by reducing cardiorespiratory fitness (mitochondria biogenesis and beta oxidation) and therefore increasing body fatness through lowering the energy expenditure [9]. Obesity is rising in epidemic proportions and has more than doubled in adults and tripled in children and youth in Western populations [2]. Human obesity has a polygenic heritage attributed to nearly 2,313 genes, mostly regulating the appetite, with a

homology estimated as 40%-70% [3]. The high genetic homology and the rapidity on the epidemic indicate it has an environmental (epigenetic) cause [7]. Any change in phenotype or gene expression caused by modifications independent of changes in genotype can be defined as epigenetics [95].

The epigenetic recognizes that our predisposition to obesity lies in our previous evolutionary scenarios and has the key assumption of the mismatch between the human genome molded over millions of generations coping with the modern dietary and physical environments. As an adaptation to an individual's environment, obesity is especially prominent following prolonged periods of positive energy balance and may be most pronounced when foods are energy-dense and/or a sedentary lifestyle [6]. The rise in obesity rates internationally might be considered a result of changes in the environment that have lowered the cost of food production, lowered the time and monetary cost of food consumption, and increased the real cost of being physically active at work and home. Moreover, there have been decreased health consequences resulting from obesity by bringing a host of new drugs and devices to the market to better manage the adverse health effects that obesity promotes [4]. Thus, the changing obesogenic environment is in response to consumers demand for labor-saving technology and convenient, affordable food [4,96].

Treatment

Drug therapy is used worldwide as a measure in halting and reversing the NCDs epidemic. However, the burden of NCDs in Brazil has demonstrated the onerous expansion of pharmaceutical care and the free distribution of most NCDs' medications, as an ineffective action in controlling these diseases. Underlying why drug therapy has been largely unsuccessful in halting and reversing the NCDs epidemic would be the ineffectiveness of the treatment approach by the homeostasis model [11].

Homeostasis describes mechanisms that hold a controlled variable by sensing its deviation from a "setpoint" and feeding back to correct the error. Based on this model, physicians reason that when a parameter deviates from its setpoint value, some internal mechanism must be broken. Consequently, they design therapies to restore the "inappropriate" value to "normal" [7]. To treat obesity, it is argued that "a multi-drug regimen" that targets multiple sites within the weight-regulatory system may be necessary to achieve and sustain weight loss in many individuals. Then, a list of six neuromodulators that increase feeding and ten that decrease feeding is recommended [97]. There are three problems with targeting low-level mechanisms (homeostasis model) [7].

First, each signal evokes multiply cascaded effects, so even the most specific molecular antagonist will cause a cascade of effects. Second, the variables targeted for treatment are being driven to their particular levels by concerted signals from the brain in response to predicted needs. Consequently, if one signal is suppressed by a drug, the brain compensates by driving all the others harder. But adding more drugs to a complex system increases the frequency of iatrogenesis. This is why proposals to treat obesity by a "multi-drug regimen" at multiple brain sites or to screen 417 genes as drug targets for obesity seem implausible. Third, there is a cost to performance in clamping a variable to some target level by blocking the effectors designed to modulate it. By clamping it, renders that variable insensitive to predicted need, which opposes the whole point of physiological regulation. However, the major problem is considered to be the very high rate of discontinuance or change in medications. These high discontinuance rates are considered to reflect, among other factors, "a combination of adverse drug effects, cost of drugs, and poor efficacy" [7]. Differently from treating low level targets by drugs (homeostatic model) and generating iatrogenesis, the allostasis model has a more rational goal of intervention with lifestyle modification of environmental factors. That is because allostasis model attributes the pathogenesis of obesity to prolonged adaptation to hypervigilance and hypo satisfaction to social interactions. Under the allostasis model the hallmark of health is the therapeutics of contemporary chronic diseases through changing lifestyle which seems more clinically effective than drugs [7]. This is the basis of the Behavioral Medicine. Among its principles, dietary adequacy and physical activity as pillars of treatment which an be a natural remedy for recovering part of the imbalance caused by modern life-styles, costless and without the side effects of many pharmacological treatments [7].

As a model of Behavioral Medicine, a costless lifestyle modification programs have, alternatively to homeostatic model, promoted, proactively, eutrophy and reduced blood hypertension, T2D and Metabolic Syndrome reductions in a community-based adults. This community-based ongoing epidemiological project, "Moving for Health Program", was conducted from 1991 to 2019, in very much tune with the ACSM's "Exercise is Medicine" and WHO proposal [19,98]. The effectiveness in reducing overweight [12], abdominal obesity [19], T2D [13], hypertension [16] and Metabolic Syndrome resulted in considerable economic impact on National Health care [11].

Results and Comments

Data from a Behavioral Medicine Model

Following the WHO's definition [99,100] of overweight(25-29.9kg/m2) and obesity (>_30kg/m^2) and also the WHO categories of BMI [weight (kg)/height (m^2)] of 30 kg/m^2 or higher, for the three grades of obesity (99): grade I (BMI 30.0–34.9 kg/m^2), grade II (BMI 35.0–39.9 kg/m^2), and grade III (BMI≥40kg/m^2) the whole sample was distributed as eutrophic, overweight and obesity.

Normal percent body fat for an adult man was considered to be 12–20 % of total body weight and 20–30 % for an adult woman [100]. The pattern of body fat distribution pattern of hyperadiposity as gynoid (gynecoid) or android, was evaluated through waist circumference measures (>88 cm for men and >102 cm for women) [100,101] or a waist to hip ratio calculation (>0.90 for men and >0.80 for women) [102].

For large abdominal adiposity, the upright position can be replaced

by the horizontal position for measurement of the sagittal-abdominal diameter [103].

Children were classified as overweight and obese according to BMI being overweight with BMI from ≥ 85th percentile to <95th percentile and, obese with BMI ≥ 95th percentile [104]. Body fat percentage was estimated from skinfolds thickness measurements [105] using reference values proposed by Lohman [106] as high body fat percentage: ≥ 25% for girls and ≥ 20% for boys. The 5-stages scale of pubertal stage was used for data correction according to the method of Tanner [107].

Obesity Surveillance

School Children

In a sample of 988 schoolchildren (7-15 yrs old) representative of 3 different school-systems, 16.3% were obese (boys 18%) and 15% overweight (girls 17.2%). Higher WC was 40.4% [104].

Adult Sample Characteristics

In our sample of 1,218 adults 55.0 (35-85) years old, 51.2% over 60 years, 79%% females, 68.6% married, 3.7% were illiterate; 15.5% accomplished the elementary grade; 59.2% high schoo, and 21.6% university. Their income distribution was 30% <2 minimum waive (MS), 40.2% 2-5 MS, 32.8% 6-10 MS, and 1.4% >10 MS. Self-perception of health status gave 26.1% as in bad status. The applied International Physical Activity Questionnaire (IPAQ) showed 18.3% of the sample referring to physical activity lower than 150 min/wk [19].

Among the found 82.4% overweight, 39.0% were obese, completing the sample with 18.6% eutrophics. The altered WC was detected in 68.9% of the sample [19].

Obesity Associated Factors

Schoolchildren

Higher WC was associated with unfitness for abdominal strength/resistance and aerobic resistance /trunk flexibility. Low physical fitness was associated with higher sedentary behavior (TV time) and obesity [108,109].

Adults

The higher BMI-quartile was associated with lower income and lower schooling [3]. Actually, BMI distribution was associated with lower income as well as oil intake but, higher intake of oil was not significantly associated with BMI and WC [110]. Our data suggested that poor quality diet was an important determinant of obesity, mainly by the high intake of manufactured oil [110], complementary to a high intake of total fat and low intake of vegetables, fruits and dairy products [3]. Consequently, body fatness was found associated with differences in fat intake profile, with higher vegetable oil intake in lower income participants [110]. The connections of low income to the manufactured-oil intake and higher BMI, were checked by adjusting oil intake for age, gender, education, income, energy intake and HEI, and verified that individuals with higher income were less prone to have relative risks of having BMI>25 [110]. The adults presenting altered values of WC (82.5%) were predominantly older and showed higher body fatness, consuming low variety/poor quality diet, lower in fruit and rich in fat (manufactured oil by the lower income and saturate fat by the higher income subjects). However, only carbohydrate (positive) and fruit intake (negative) were considered independent risk factors for abdominal obesity [110]. A lower risk of abdominal obesity was associated with a "healthy dietary pattern", rich in non-starchy vegetables, fruits, fresh juice, whole-wheat bread, low-fat dairy products, and fresh and homemade popcorn [111].

Complementary to the dietary factors, body adiposity was associated with low levels of physical activity, but not exclusively [112]. Comparatively to eutrophy, the presence of obesity increased low-IPAQ (42.3%), low flexibility (49.7%0, low hand-grip strength (42.1%), and low VO2max. (23.1%) [64]. Lower aerobics and flexibility were also associated with being overweight. Specifically, with WC, it was negatively correlated with aerobic capacity (VO_{2max}), but not statistically confirmed as an independent factor [9]. Thus, from the cross-sectional results, moderate to vigorous physical activity was found to be a factor protecting against overweight and obesity [3], while a lower risk of abdominal obesity was associated with a "healthy dietary pattern", rich in non-starchy vegetables, fruits, fresh juice, whole-wheat bread, low-fat dairy products, and fresh and homemade popcorn [111].

Metabolic Abnormalities

Comparatively to eutrophy, the presence of obesity showed higher plasma-altered levels of biochemists such as triglycerides (43.7%), HDL-cholesterol (37.9%) and total-cholesterol (30.2%) as well as increased diagnosis of hypertension (40.0%), T2D (74.9%), hypertriglyceridemia waist (67.6%), NAFLD (65.1%), CHD -high risk (57%), PAI-high risk (47.4%) and metabolic syndrome (40%). These changes were followed by a 59.5% increase in MDA, 34.1% increase in HOMA-IR and 31.8% increase in hs-CRP [64].

Interventions

Schoolchildren

In a 12-week quasi-experimental study conducted with schoolchildren from a local private school, aiming to improve knowledge, attitudes and eating habits of the children along with increasing daily physical exercise. The 12-week school-based intervention with nutrition education and physical activity led to a successful reduction in body fatness and improvements in physical fitness and eating behavior. The obesity decreased 3.8% in boys and 3.0% in girls [113].

Adults

The effectiveness of our Lifestyle-changing (LiSM) protocols [19] in reducing BMI, WC and % body fatness showed the weekly frequency of >3 days/week (>240min/wk) better than <3 days/week (<240 min/wk) [114]. Specifically for BW loss, a 3-yr LiSM led to a 3.3kg body weight loss, 1kg body weight loss (1.33%) in

2 years, being mostly (0.8kg) in the first year [115]. The 3-year LiSM protocol in the 3.3kg body weight loss was followed by a 2.9% reduction in body fatness [116,117]. The obesity rate decreased 5.7% after 2-yrs LiSM, 8.4% after 12 months, and 4.8% after 6 months of LiSM intervention, similarly in men and women [3]. Overall, 3.4% of overweight subjects became eutrophic after 6 months of LiSM, but none originally obese subjects had reached eutrophy [12]. Similarly, to the overall sample, the post-menopausal women reduced their body fatness by 3.7% in obese and 4.1% in non-obese, after 6-mo. LiSM, without major changes in BMI and waist-to-hip ratio [116]. In both genders, aerobic protocol has proved to be more efficient than strength or combined aerobic-strength exercises, in promoting weight loss, in a 12-month. LiSM. However, for a shorter LiSM-protocol (20 – 24 weeks), both walking (aerobic) or cross-training (walking + strength) exercises resulted in significant body weight loss, but only the walking protocol decreased significantly in BMI while the strength exercise protocol maintained the baseline values [115]. Applying the 24-wk LiSM or not (control group) to overweight insulin-resistant women, only the LiSM group presented significant reductions in WC and body fatness. Obesity reduction was 3.4% in controls and, after LiSM, varied from 5.5% in hyperglycemic to 8.0% in normoglycemic [15].

Keeping the same length of LiSM, post-menopausal women showed a higher decrease in body fatness under the combined exercises protocol (aerobic + strength) than aerobic only [117]. By complementing the aerobic-exercise protocol (control group) with the food-energy restriction (experimental group), the 40-wk intervention in women resulted in higher body weight loss (2.30X) and a higher decrease in WC (1.58X) in the experimental group [118].

Body-Weight Loss Associated Factors

The body weigh loss (after 24-wk LiSM) was associated with lower income, low schooling, and living alone. On the other hand, WC decreasing was associated with gender (higher in females) and higher income [112].

The BMI reduction (after 24-wk LiSM) was associated with the increased intake of dairy, fruit, and vegetables. After adjustments, the increase in dairy product was the main dietary factor associated with reductions in body weight in overweight adults [119].

In obese subjects, a 10-wk LiSM intervention alone or with a dietary fiber adequacy(25g/day), leaded to a 4% and 7% decreasing in body fatness and WC, respectively. Severe obesity was reduced by 16% but, the rates of overweight and eutrophy were minimally affected [120]. A higher decrease in body fat composition among those individuals with dietary fiber adequacy. Similarly, in a 20-wk LiSM, without or with oral supplementation of omega-3 polyunsaturated fatty acid (3g/d), presented higher and faster decreasing of body fat and waist circumference in W-3 supplemented than the LiSM alone [121]. Thus, the data collected in protocols of LiSM, including exercises (aerobic and/or strength) associated either with dietary counseling or intervention (with energy restriction or supplemented with dietary fiber or W-3 (PUFA) lasting 2 to 12 months, showed different efficacy in weight loss [3]. As seen, long-lasting LiSM (longer than 12 months) has proved as more efficient than short-term protocols for body-weight loss. However, this conflicts with the rate of compliance to LiSM, 47% in 12 mo., 12.4% in 2 yrs., and 6.3% in 3 yrs. Considering LiSM a re-education program for a healthy lifestyle, we decided on a shorter period, prioritizing higher compliance of 20-24 weeks (52.3%) and 10 weeks (65%) [19]. To abbreviate the length without losing the effectiveness, there was an adaptation to the type of exercise and dietary intervention. Hence, for the same length of LiSM (6-12months), aerobic exercises were more efficient for losing body weight than strength exercises. The boosting of dietary supplementation for exercise-related body-weight loss was proven efficiently by complementary energy restriction or either fiber or W-3 PUFA supplementation. When combined exercises were associated with recommended dietary fiber intake (25 g/day), the 3.4% eutrophy obtained in 6 mo. with single LiSM, the same 3.4% was achieved shortly, after only 2 mo. of mixed protocol [3].

Effectiveness

Six-month LiSM resulted in body weight loss averaging 1kg, while 3.2% of the overweight achieved eutrophy, and 6.5% of former obese individuals were normalized. However, by the recall and assessments 3.4+-1.9yrs later, 84.2% regained the body weight lost while keeping the categorized classification for BMI and WC [122]. This means the 6 mo. lessons learned for healthy lifestyle behavior were not taken home as a message.

Considering the estimated extra cost of overweight/obese Brazilians as US$0.50/subject (US$36 mi/72573.235 subjects) the public health economy led by this LiSM leading 3.4% eutrophy, would be of US$ 1.23 mi. in either 6 months of LMP with exercises and dietary counseling or in 2 months of LiSM associated with dietary fiber intervention [12].

Conclusion

An obese human may be understood as a consequence of an evolutionary selection presenting overexpression of thrifty genes evolved for efficient food collection and fat deposition to survive periods of famine. Nowadays, this evolutionary-adapted polygenic charge is overexpressed by a deteriorated lifestyle. Our data have shown that lifestyle factors such as lower physical activity (and fitness) and lower intake of raw vegetables and fruits are strong risk factors for obesity in school children and free-living adults. Similarly, the dietary pattern of industrialized (processed) foods available in public schools and the higher intake of refined oils and carbohydrates provided by the Brazilian Government to the low-income population are strong risk factors for overweight induction. From that, our existing multi-professional program ("Moving for health") promoting lifestyle re-education through physical activity and dietary adequacy (LiSM), led to a life quality improvement through better diet, physical activity and fitness. Underlying the positive health effects, it was the reduced metabolic stress, with

LiSM acting as anti-inflammatory and anti-oxidant, impacting on reductions of obesity and co-morbidities. Besides its wellness, costless, and security, the abroad implementation of the program has faced in and out resistances, hard to overcome, presently.

Future Directions

Evolutionary Medicine points that obesity has a strong frugal-gene charge molded by environmental constraints of discontinued food supply resulting in over expression of thrifty genes evolved for efficient food collection and fat deposition to survive periods of famine. Therefore, if genetics does not contrast obesity, todays it is clear that lifestyle factors and human health are linked through epigenetics mechanism. The rising rates of obesity in epidemic proportions, in the last 60 years, indicates that obesity must consequently be a result of an ancestral molded genome by environment interaction in at least three windows for metabolic plasticity: pregnancy, lactation, and later life. Though, bodily inadequacies in relation to the modern environment can be associated with either dietary inadequacy and/or physical inactivity, as shown in our 28-yr long dynamic-cohort study with a lifestyle modification (Behavioral Medicine) program. Alternatively, to homeostatic model, the program promoted proactively, body-weight loss and reduced obesity-comorbidities in a community-based adults. However, what seemed successful in NCD's care, had failed in compliance for achievement body eutrophy. The resistance in changing the present obesogenic environment seems widely in response to consumer's demand for labor saving technology and convenient, affordable (palatable) food. This modern obesogenic environment has been maintained by the lowered cost of food production, distribution and storage; therefore, lowering the time and monetary cost of food consumption, along with increasing the real cost of being physically active at work and at home. Additionally, it has been a decreased health consequences resulting from obesity by bringing a host of new drugs and devices to the market to better manage the adverse health effects that obesity promotes. From difficulties in changing modern unhealthy lifestyle, Epidemiology projects the disappearance of actual eutrophy in the middle of the century and starting next century with predominance of obese. Considering obesity as an evolutionary adaptive stage to the present lifestyle (high-energy dense foods and sedentarism), we better start to look at overweight on its pathological abnormalities leading to morbidity and linked early mortality. The underlying metabolic stress of obesity, is captained by inflammation, with chronic inflammation being considered the contemporary "predator" of obese. Then, if our protocols of physical exercises were not so efficient in promoting BW eutrophy, it was proved quite efficient in reducing metabolic stress, mainly inflammation and insulin resistance. So, it is possible to stay "fatty and healthy" as long keeping the physical "fitness". Let's maintain fitness till 'mother nature's" would provide us with other epigenetic alternative to overcome the present illness of chronic inflammation.

Acknowledgements

Dr Camila R Correa, MS Juliana S Siqueira for the computer assistance and Luís E. Sormani for the formation.

References

1. World Health Organization. Obesity: Preventing and Managing the Global Epidemic: Report of a WHO Consultation. WHO Technical Report Series. Geneva, Switzerland: World Health Organization. 2000.
2. Instituto Brasileiro de Geografia e Estatística. Pesquisa de orçamentos familiares 2008-2009: antropometria e estado nutricional de crianças, adolescentes e adultos no Brasil. Rio de Janeiro: IBGE. 2010.
3. Burini RC, de Oliveira EP, Michelin E, et al. Epidemic obesity: an evolutionary perspective on the modern obesity crisis to a rationale for a treatment. A Brazilian community-based data. Obesity Epidemic. 2013; 1: 20-38.
4. Burini RC. Human Adiposity from evolutionary energy-thriftiness to the modern inflammatory-related illness-The role of lifestyle transition. A Narrative Review J Lipidology. 2025.
5. Nesse RM, Stearns SC. The great opportunity: Evolutionary applications to medicine and public health. Evol Appl. 2008; 1: 28-48.
6. Burini RC. Understanding contemporary diseases under Evolutionary Medicine view. Atena. 2023.
7. Speakman JR. A non-adaptive scenario explaining the genetic predisposition to obesity: the predation release hypothesis. Cell Metabolism. 2007; 6: 5-12.
8. Burini RC. Stress and Distress as Basic Principles of Homeostasis and Allostasis Models for Understanding Physiological Regulations and Rational Therapeutics of Contemporary Chronic Diseases. Cap. 2021; 18: 165-186.
9. Burini RC. Physical Exercises: From the Evolutionary Thriftiness to the Epigenetics of Contemporary Diseases and Current Therapeutics for Physical Inactivity Diseasomes. Sports Medicine. 2017. www.smgebooks.com
10. Burini RC, Anderson E, Durstine JL, et al. Inflammation, physical activity, and chronic disease: An evolutionary perspective. Sports Medicine and Health Science. 2020; 2: 1-6.
11. Burini RC. The Brazilian Dynamic-Cohort Study Moving for Health as a Proactive model of Evolutionary Behavioral Medicine to Non-Communicable Diseases in a community-based subjects. International Journal of Health Science. 2022; 2: 2-23.
12. Castanho GKF, Ravagnani CFC, Morelli MYG. Cost-effectiveness of exercise program to reduce weight in adults. Rev Bras Atividade Físicae Saúde. 2011; 16: 316-321.
13. Nakagaki MS, Kano TH, Burini RC. Brazilian Primary Care of T2D with Reactive-Homeostatic and Lifestyle Changing-Allostatic Approaches: A Cost-Effectiveness Data. American Journal of Sports Science. 2018; 6: 98-107.
14. Burini RC, Torezan GA, Portero-McLellan Kátia. Behavioral risk factors and effects of lifestyle modification on adults with diabetes. A Brazilian community-based study. Emerging Issues in Medical Diagnosis and Treatment. 2013; 4: 2309.

15. Mota JF, Moreto F, Burini FHP, et al. Effect of Physical Conditioning with Lifestyle Intervention on A Community-Based Hyperglycemic-Overweight Adults. Journal of US-China Medical Science. 2011; 8: 581-587.
16. Burini RC, Simonetti LA, Maesta N, et al. Efficiency and Cost less of a Long-term Physical Exercise Program to Non-medicated Hypertensive Males. Advanced Studies in Medical Sciences. 2013; 1: 111-123.
17. Burini RC, Michelin E, Burini FHP, et al. Behavioral risk factors and effects of lifestyle-modification on the metabolic syndrome in adults. A Brazilian community-based study. In: Christopher M, Lopez Garcia, Patricia A, Perez Gonzalez. Handbook on Metabolic Syndrome: Classification, Risk Factors and Health Impact. 1ed New York: Nova Science Publishers. 2012; 1: 1-20.
18. Nakagaki MS, Kano TH, Burini RC. Metabolic Syndrome Response to Different Physical- Exercise Protocols. American Journal of Sports Science. 2019; 7: 182-192.
19. Burini RC, Kano HT, Nakagaki MS, et al. Behavioral factors of Abdominal Obesity and effects of lifestyle changes with Fiber Adequacy. New Insights Obes Gene Beyond. 2017; 1: 14-22.
20. Neel JV, Weder AB, Julius S. Type II diabetes, essential hypertension and obesity as syndromes of impaired genetic homeostasis: the thrifty genotype hypothesis enters the 21st century. Perspect Biol Med. 1998; 42: 44-74.
21. Li WH, Saunders MA. News & Views. The chimpanzee and us. Nature. 2005; 437: 50-51.
22. Antón SC. A natural history of Homo erectus. Yrbk Phys Anthropol. 2003; 46: 126-170.
23. White TD, Asfaw B, DeGusta D, et al. Pleistocene Homo sapiens from Middle Awash Ethiopia. Nature. 2003; 423: 742-747.
24. Burini RC, Leonard WR. The evolutionary roles of nutrition selection and dietary quality in the human brain size and encephalization. Nutrire. 2018; 43: 19.
25. Kotrschal AB, Rogell A, Bundsen B, et al. The benefit of evolving a larger brain: big-brained guppies perform better in a cognitive task. Anim Behav. 2013; 86: e4-e6.
26. Fordyce RE. Whale evolution and Oligocene southern-ocean environments. Palaeogeogr Palaeoclimatol Palaeoecol. 1980; 31: 319-336.
27. Di Costanzo J. Paleolithic nutrition: a model for the future. Current Opinion in Clinical Nutrition and Metabolic Care. 2000; 3: 87-92.
28. Aiello LC, Wheeler P. The Expensive-Tissue Hypothesis: The Brain and the Digestive System in Human and Primate Evolution. Current Anthropology. 1995; 36: 199-221.
29. Tsuboi M, Husby A, Kotrschal A, et al. Enhanced muscle fat oxidation and glucose transport by ACRP30 globular domain: acetyl-CoA carboxylase inhibition and AMP-activated protein kinase activation. Proc Natl Acad Sci USA. 2002; 99: 16309-16313.
30. Johnson AR, Milner JJ, Makowski L. The inflammation highway: metabolism accelerates inflammatory traffic in obesity. Immunol Rev. 2012; 249: 218-238.
31. Bradbury J. Ancient footsteps in our genes: evolution and human disease. Gene variants selected during evolution may underlie many common diseases. Lancet. 2004; 363: 952-953.
32. Blackburn GL. Pasteur's Quadrant and malnutrition. Nature. 2001; 409: 397-401.
33. Sell H, Habich C, Eckel J. Adaptive immunity in obesity and insulin resistance. Nat Rev Endocrinol. 2012; 8: 709-716.
34. Chandra RK. Nutrition, immunity and infection: from basic knowledge of dietary manipulation of immune responses to practical application of ameliorating suffering and improving survival. Proc Natl Acad Sci USA. 1996; 93: 14304-14307.
35. Straub RH. Concepts of evolutionary medicine and energy regulation contribute to the etiology of systemic chronic inflammatory diseases. Brain Behav Immun. 2011; 25: 1-5.
36. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. J Clin Invest. 2005; 115: 1111-1119.
37. Zhou MS, Aimei Wang, Hong Yu. Link between insulin resistance and hypertension: What is the evidence from evolutionary biology. Diabetol Metab Syndr. 2014; 6: 12.
38. Spies CM, Straub RH, Buttgereit F. Energy metabolism and rheumatic diseases: from cell to organism. Arthritis Res Ther. 2012; 14: 216.
39. Cipolletta D, Feuerer M, Li A, et al. PPAR-gamma is a major driver of the accumulation and phenotype of adipose tissue Treg cells. Nature. 2012; 486: 549-553.
40. Fernandez-Real JM, Pickup JC. Innate immunity, insulin resistance and type 2 diabetes. Diabetologia. 2012; 55: 273-278.
41. Neel JV. Diabetes mellitus: a thrifty genotype rendered detrimental by progress. Am J Hum Genet. 1962; 14: 353-362.
42. Neel JV. The thrifty genotype in 1998. Nutrition Reviews. 1999; 57: S2-S9.
43. Wells JC. Ethnic variability in adiposity, thrifty phenotypes and cardiometabolic risk: addressing the full range of ethnicity, including those of mixed ethnicity. Obes Rev. 2012; 13: 14-29.
44. Wells JC. Thrift: a guide to thrifty genes, thrifty phenotypes and thrifty norms. Int J Obesity. 2009; 33: 1331-1338.
45. Cahill Jr GF. Starvation in Man. N Engl J Med. 1970; 282: 668-675.
46. Anton SC, Leonard WR, Robertson WL. An ecomorphological model of the initial hominid dispersal from Africa. J Hum Evol. 2002; 43: 773-785.
47. Finch CE, Stanford CB. Meat-adaptive genes and the evolution of slower aging in humans. Quart Rev Biol. 2004; 79: 3-50.
48. Muskiet FAJ. Pathophysiology and Evolutionary Aspects of Dietary Fats and Long-Chain Polyunsaturated Fatty Acids across the Life Cycle. In: Montmayeur JP, le Coutre J, editors. Fat Detection: Taste, Texture and Post Ingestive Effects. Boca Raton: Taylor and Francis. 2010.
49. Gaillard D, Passilly-Degrace P, Besnard P. Molecular mechanisms of fat preference and overeating. Ann N Y Acad Sci. 2008; 1141: 163-175.
50. Le Coutre J, Schmitt JAJ. Food ingredients and cognitive performance. Curr Opin Clin Nutr Metab Care. 2008; 11: 706-710.

51. Sclafani A. Psychobiology of food preferences. Int J Obes. 2001; 25: S13-S16.
52. Leonard WR, Snodgrass JJ, Robertson ML. Evolutionary Perspectives on Fat Ingestion and Metabolism in Humans. In: Montmayeur JP, le Coutre J, editors. Fat Detection: Taste, Texture, and Post Ingestive Effects. Boca Raton: Taylor and Francis. 2010.
53. Aiello LC, Key C. Energetic consequences of being a Homo erectus female. Am J Hum Biol. 2002; 14: 551-565.
54. Prado CM, Maia YL, Ormsbee M, et al. Assessment of nutritional status in cancer-the relationship be-tween body composition and pharmacokinetics. Anti Cancer Agents Med Chem. 2013; 13: 1197-1203.
55. Norgan NG. The beneficial effects of body fat and adipose tissue in humans. Int J Obes Relat Metab Disord. 1997; 21: 738-746.
56. Leonard WR, Robertson ML, Snodgrass JJ, et al. Metabolic correlates of hominid brain evolution. Comp Biochem Physiol. 2003; 136: 5-15.
57. Kuzawa CW. Adipose tissue in human infancy and childhood: An evolutionary perspective. Yrbk Phys Anthropol. 1998; 41: 177-209.
58. Rosenberg KR. The evolution of modern human childbirth. Yrbk Phys Anthropol. 1992; 35: 89-124.
59. Ruiz-Nunez B, Pruimboom L, Dijck-Brouwer DA, et al. Lifestyle and nutritional imbalances associated with Western diseases: causes and consequences of chronic systemic low-grade inflammation in an evolutionary context. J Nutr Biochem. 2013; 24: 1183-1201.
60. Unger RH. Minireview: Weapons of Lean Body Mass Destruction: The Role of Ectopic Lipids in the Metabolic Syndrome. Endocrinology. 2003; 144: 5159-5165.
61. Zhang Y, Proenca R, Maffei M, et al. Positional cloning of the mouse obese gene and its human homologue. Nature. 1994; 372: 425-432.
62. Scherer PE, Williams S, Fogliano M, et al. A novel serum protein similar to C1q, produced exclusively in adipocytes. J Biol Chem. 1995; 270: 26746-26749.
63. Maeda K, Okubo K, Shimomura I, et al. DNA cloning and expression of a novel adipose specific collagen-like factor, apM1. Biochem Biophys Res Commun. 1996; 221: 286-289.
64. Wajchenberg BL, Giannella-Neto D, Da Silva ME, et al. Depot-specific hormonal characteristics of subcutaneous and visceral adipose tissue and their relation to the metabolic syndrome. Horm Metab Res. 2002; 34: 616-621.
65. Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. Endocr Rev. 2005; 26: 439-451.
66. Tomas E, Tsao TS, Saha AK, et al. Enhanced muscle fat oxidation and glucose transport by ACRP30 globular domain: acetyl-CoA carboxylase inhibition and AMP-activated protein kinase activation. Proc Natl Acad Sci USA. 2002; 99: 16309-16313.
67. Yamauchi T, Kamon J, Minokoshi Y, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med. 2002; 8: 1288-1295.
68. Gregoire FM, Smas CM, Sul HS. Understanding adipocyte differentiation. Physiol Rev. 1998; 78: 783-809.
69. Rossner S. Obesity: the disease of the twenty-first century. Int J Obes Relat Metab Disord. 2002; 26: S2-S4.
70. Mohamed-Ali V, Goodrick S, Rawesh A, et al. Subcutaneous Adipose Tissue Releases Interleukin-6, But Not Tumor Necrosis Factor-α, *in vivo*. J Clin Endocrinol Metab. 1997; 82: 4196-4200.
71. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest. 2007; 117: 175-184.
72. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature. 2006; 444: 840-846.
73. Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic disease. J Clin Invest. 2011; 121: 2111-2117.
74. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006; 444: 860-867.
75. Hotamisligil GS, Erbay E. Nutrient sensing and inflammation in metabolic disease. Nat Rev Immunol. 2008; 8: 923-934.
76. Shoelson SE, Herrero L, Naaz A. Obesity, inflammation, and insulin resistance. gastroenterology. 2007; 132: 2169-2180.
77. Listenberger LL, Han X, Lewis SE, et al. Triglyceride accumulation protects against fatty acid-induced lipotoxicity. Proc Natl Acad Sci USA. 2003; 100: 3077-3082.
78. Weiss B, Stoffel W. Human and murine serine-palmitoyl-CoA transferase–cloning, expression and characterization of the key enzyme in sphingolipid synthesis. Eur J Biochem. 1997; 249: 239-247.
79. Hannum YA, Obeid LM. Principles of bioactive lipid signaling: lessons from sphingolipids. Nature Reviews Molecular Cell Biology. 2008; 9: 139-150.
80. Zeidan YH, Hannum YA. Translational aspects of sphingolipid metabolism. Trends Mol Med. 2007; 13: 327-336.
81. Hirosumi J, Tuncman G, Chang L, et al. A central role for JNK in obesity and insulin resistance. Nature. 2002; 420: 333-336.
82. Aguirre V, Uchida T, Yenush L, et al. The c-Jun NH(2)-terminal kinase promotes insulin resistance during association with insulin receptor substrate-1 and phosphorylation of Ser(307). J Biol Chem. 2000; 275: 9047-9054.
83. Chavez JA, Siddique MM, Wang ST, et al. Ceramides and glucosylceramides are independent antagonists of insulin signaling. Cell. 2014; 289: 723-734.
84. Kogot-Levin A, Saada A. Ceramide and the mitochondrial respiratory chain. Biochimie. 2014; 100: 88-94.
85. Furukawa S, Fujita T, Shimabukuro M, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. J Clin Invest. 2004; 114: 1752-1761.
86. Ozcan U, Cao Q, Yilmaz E, et al. Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. Science. 2004; 306: 457-461.
87. Portero-Mclellan KC, Manda RM, Sloan LA, et al. Epigenetics of glucose metabolism and the basis for T2DM interventions. Type 2 Diabetes. 2013.
88. Sun K, Kusminski MC, Scherer EP. Adipose tissue remodeling and obesity. J Clin Invest. 2011; 121: 2094-2101.

89. Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006; 444: 881-887.
90. Lee Y, Hirose H, Ohneda M, et al. Beta-Cell lipotoxicity in the pathogenesis of non-insulin-dependent diabetes mellitus of obese rats: impairment in adipocyte-Beta-cell relationships. Proc Natl Acad Sci USA. 1994; 91: 10878-10882.
91. Shimabukuro M, Higa M, Zhou YT, et al. Lipoapoptosis in Beta-cells of obese prediabetic fa/fa rats: role of serine palmitoyltransferase overexpression. J Biol Chem. 1998; 273: 32487-32490.
92. Unger RH. Reinventing Type 2 Diabetes: Pathogenesis, treatment and Prevention. JAMA. 2008; 299: 1185-1187.
93. Shulman GI. Cellular mechanisms of insulin resistance. J Clin Invest. 2000; 106: 171-176.
94. Kano HT, Burini FHP, Burini RC. Nutritional and Physical-Fitness Factors Coursing with Non-Communicable Diseases from Overweight to A Higher Risk of Vascular and Liver Outcomes in A Community-Based Adults. International Journal of Health Science. 2002; 16: 2-16.
95. Tarry-Adkins JL, Ozanne SE. Mechanisms of early life programming: current knowledge and future direc-tions. Am J Clin Nutr. 2011; 94: S1765-S1771.
96. Finkelstein EA, Strombotne KL. The economics of obesity. Am J Clin Nutr. 2010; 91: 1520S-1524S.
97. Schwartz MW, Woods SC, Porte D, et al. Central nervous system control of food intake. Nature. 2000; 404: 661-672.
98. Burini RC, Burini FHP, Durstine JL, et al. The effectiveness of Lifestyle-Change Approach to the Non-Communicable Chronic Diseases. The Role of Physical Exercise to the Brazilian Dynamic-Cohort Study Moving for Health. 2025.
99. World Health Organization. Physical status: the use and interpretation of anthropometry. Geneva: WHO Technical Report Series. 1995; 854.
100. Pi-Sunyer FX. Obesity: criteria and classification. Proc Nutr Soc. 2000; 59: 505-509.
101. Lean ME, Han TS, Morrison CE. Waist circumference as a measure for indicating need for weight management. BMJ. 1995; 311: 158-161.
102. Center for Disease Control and Prevention. National obesity trends. In: Services USDoHaH, ed Atlanta: Center for Disease Control and Prevention. 2011.
103. Pimentel GD, Moreto F, Takahashi MM, et al. Sagital abdominal diameter, but not waist circumference is strongly associated with glycemia triacilglycerols and HDLc levels in overweight adults. Nutr Hosp. 2011; 26: 1125-1129.
104. Rinaldi AEM, Gabriel GFCP, Moreto F, et al. Dietary factors associated with metabolic syndrome and its components in overweight and obese Brazilian schoolchildren: a cross-sectional study. Diabetol Metab Syndr. 2016; 8: 58.
105. Slaughter MH, Lohman TG, Boileau RA, et al. Skinfold equations for estimation of body fatness in children and youth. Hum Biol. 1988; 60: 709-723.
106. Lohman TG. The use of skinfold to estimate body fatness on children and youth. J Phys Educ Recreat Dance. 1987; 58: 98-102.
107. Tanner J. Growth at adolescence: with a general condition of the effects of hereditary and environmental factors upon growth and maturation from birth to maturity. 2nd edition. Oxford: Blackwell Scientific. 1962.
108. Andreasi V, Michelin E, Rinaldi AE. Physical Fitness and Associations with Anthropometric Measurements in 7 to 15-Year-Old School Children. Journal de Pediatria. 2010; 86: 497-502.
109. Angelo JC. Associação da Aptidão Física com Indicadores Socioeconômicos Tempo de TV e Prática de Atividades Físicas de Escolares com Excesso de Peso, Monografia de Conclusão de Curso de Aperfeiçoamento/ Especialização em Exercício Físico Nutrição e Medicina na Saúde e no Esporte, Universidade Estadual Paulista Júlio de Mesquita Filho. 2009.
110. Mclellan KCP, Pimentel GD, Corrente JE. Association of fat intake and socioeconomic status on anthropometric measure of adults. Cad Saúde Coletiva. 2010; 18: 266-274.
111. Rinaldi AEM, Marsola FC, Siqueira M, et al. Association of dietary patterns with metabolic syndrome components in low-income free-living Brazilian adults. Int J Nutr Metab. 2011; 3: 17-21.
112. Michelin E, Andreasi V, Marsola FC. Efeito de protocolo de mudança de estilo de vida sobre indicadores de atividade e aptidão física de usuários de uma Estratégia Saúde da Família. In: 32 Simpósio Internacional de Ciências do Esporte, São Paulo. 35 Anos Construindo Saúde pela Atividade Física e o Esporte. 2009; 17: 45-45.
113. McLellan KCP, Bianchessi ALV, Rinaldi AEM, et al. Improvements of Nutrition Behavior Fitness and Body Fatness with a Short-Term after School Intervention Program. Food and Nutrition Sciences. 2013; 4: 18-24.
114. Ravagnani CF, Ravagnani FCP, Michelin E, et al. Efeito do protocolo de mudança do estilo de vida sobre a aptidão física de adultos participantes de projeto de extensão universitária: influência da composição corporal. Rbras Cie Mov. 2006; 14: 45-52.
115. Coelho CF, Pereira AF, Ravagnani FCP, et al. Impacto de um programa de intervenção para mudança do estilo de vida sobre indicadores de aptidão física, obesidade e ingestão alimentar de indivíduos adultos. Rev Bras Atividade Física e Saúde. 2010; 15: 21-27.
116. Nahas EAP, Pontes AG, Nahás Neto J, et al. Influência do exercício físico aeróbio e da tibolona sobre a antropometria e o perfil lipídico na menopausa. Reprodução e Climatério. 1999; 14: 132-140.
117. Nadai A, Porto M, Araujo Júnior JA, et al. Efeito do tipo de treinamento físico (aeróbio e misto) sobre a composição corporal glicemia e colesterolemia de mulheres em menopausa com ou sem reposição hormonal. Rev Bras Atividade Físicae Saúde. 2002; 7: 13-22.
118. Monteiro RCA, Riether PTA, Burini RC. Efeito de um programa misto de intervenção nutricional e exercício físico sobre a composição corporal e os hábitos alimentares de mulheres obesas em climatério. Rev Nutr. 2004; 17: 479-489.

119. Oliveira EP, Diegoli ACM, Corrente JE, et al. The increase of dairy intake is the main dietary factor associated with reduction of body weight in overweight adults after lifestyle change program. Nutr Hosp. 2015; 32: 1042-1049.
120. Mecca MS, Moreto F, Burini FH, et al. Ten-week lifestyle changing program reduces several indicators for metabolic syndrome in overweight adults. Diabetol Metab Syndr. 2012; 4: 1.
121. Talon LC, Oliveira EP, Moreto F, et al. Omega-3 fatty acids supplementation decreases metabolic syndrome prevalence after lifestyle modification program. J Functional Foods. 2015; 19: 922-928.
122. Nakagaki MS, Michelin E, Portero-McLellan KC, et al. Gained Physical Activity and Fitness Are Sustained by Adults After Their Discontinuation in A Lifestyle Modification Program. In ACSM Annual Meeting, World Congress on Exercise is Medicine and World Congress on the Role of Inflammation in Exercise. Health and Disease. 2014; 46: 952.