Epidemic Obesity: An Evolutionary Perspective on the Modern Obesity Crisis to a Rationale for a Treatment

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1 Obesity and Other Chronic Non-communicable Diseases

The modern world including most industrialized countries and an increasing number of low and middle-income countries is experiencing an unprecedented epidemic of overnutrition. As a result, life expectancy has been predicted to decline for the first time in recent history. Children born today may die at a younger age than their parents (Olshansky et al., 2005). Non communicable disease (NCD), including cardiovascular disease (CVD), type 2 diabetes (T2D), chronic lung disease, allergy, some forms of cancer, cognitive decline, osteoporosis, sarcopenia are the world’s biggest killers. They account for 35 million deaths per year, which is 60% of all deaths globally. The World Health Organization (WHO) (2002) statistics suggests that 80% of these deaths occur in low and middle-income countries. The WHO predicts an increase of 17% in NCD over the next decade globally (WHO, 2008).

In Brazil NCD responded for 72% of all deaths in 2004 and 66% of disability-adjusted life years (DALYS) in 1998 (Schramm et al., 2004). Obesity is rising in epidemic proportions that herald dramatic negative influences on the health of the population in the decades to come. In the last 30 years the rates of obesity have more than doubled in adults and tripled in children and youth in western populations. In Brazilian adults 48% of women and 50% of men were considered overweight in 2010 (IBGE, 2010).

Economically the costs of obesity are rising rapidly and have been estimated to be as high as 147 billion dollars per year in US (Finkelstein & Strombotne, 2010). Data from the Brazilian government (SIH-SUS/2001) estimated an overweight-derived a year cost of hospitalization as being US$ 22 million for women and US$ 14 million for men (Sichieri et al., 2007). The overall costs of obesity and related disorder was estimated as US$ 36 million a year for an adult population of 49% overweight and 14.8% obese (IBGE, 2011).

Because established obesity is notoriously resistant to treatment much attention has 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 (Kramer, 2010). Understanding why human development may influence a predisposition to NCD even under normal circumstances can be assisted by taking an evolutionary perspective.

2 Epigenetic of Obesity: Hypothesis

Western societies have experienced an epidemic of obesity during the twentieth century. The rapidity on epidemic indicates it has an environmental cause. Yet, when studies have investigated the contribution of genetic and shared environmental factors on individual susceptibility to obesity the major effect is genetic. Obesity must consequently be a result of a gene by environment interaction (Speakman, 2007). Any change in phenotype or gene expression caused by modifications independent of changes in genotype can be defined as epigenetics (Tarry-Adkins & Ozanne, 2011). It has been widely recognized that our predisposition to obesity lies in our evolutionary history and previous evolutionary scenarios. In epigenetics the developmental origins of health and disease field has found a key mechanism for the growing epidemiological literature on associations between early-life experience and later health status (Wells, 2012).

According to the current paradigm, a gene or a set of gene predisposing to obesity presumably evolved owing to a selective advantage in ancestral “feast and famine” environment and remained in polymorphic state in the population which is turning pathological in the modern urban environment selectively affecting individuals with the gene(s). This line of thinking was first stated explicitly by Neel...
It was suggested that a “thrifty” gene helped fat storage under conditions of better availability of nutrients and allowed reutilization under starvation. The thrifty gene was under positive selection pressure in ancestral life when seasonal and climatic conditions resulted into fluctuating food availability.

Later, the observation that individuals born small for gestational age had a great probability to become obese in later life led to the concept of fetal programming (Hales & Barker, 1992; Barker, 1998; Drake & Walker, 2004). This hypothesis states that if a fetus faces inadequate nutrition in intrauterine life, the body is programmed to be “thrifty” as an adaptation. There are two possible components of this adaptation. One relates to an immediate gain internus of survival during fetal and early infant life. The others are a predictive response in anticipation of starvation in later life (Gluckman et al., 2005).

As alternatives to the thrifty gene hypothesis:

a) Corbett et al. (2009) argued that today’s obese –prone genotype was the ancestral one that had better fertility in famine conditions. In the modern era of food security since 1800 AD, an insulin-sensitive that has better fertility under conditions of food abundance started spreading.

b) Moalen et al. (2005) hypothesized that high plasma glucose lowers the freezing point of blood which prevents formation of ice crystals in cell through supercooling, and this has been suggested as an adaptation to the ice age. Ethnic groups from harsh winter environments were unable to hunt, fish, or farm during the colder months and, thus, historically could have faced regular feast and famine conditions (Baig et al., 2011).

c) Wells (2007) and Wells & Stock (2007) argued that there is maternal advantage in fetal programming in the form of optimizing maternal inputs per fetus or bet hedging, which is, distribution of risk among offspring.

d) Speakman (2007) postulated genetic drift rather than selection for obesity-related genes. Then an upper limit on obesity was set in hunter-gather life which was effectively lifted when human became free of predation. Subsequently, the obesity related genes started spreading by genetic drift.

The main theories regarding genetic predisposition to obesity are competing whether or not obesity is interpreted as process of natural selection. The thrifty gene hypothesis suggests we evolved genes for efficient food collection and fat deposition to survive periods of famine and now that food is continuously available; these genes are disadvantageous because they make us obese in preparation for a famine that never comes (Speakman, 2007). Hence obesity would be consequence of an adaptive response to our thrifty genes selected naturally from adverse ancestral scenarios.

Particularly in the non-adaptive drift hypothesis the genetic predisposition to obesity is not interpreted to be an advantageous characteristic favored by the process of natural selection. Rather it suggests that early hominids would have been subjected to stabilizing selection for body fatness with obesity selected against by the risk of predation. As predation was removed its absence led to a change in the population distribution of body fatness due to random mutations and drift (Speakman, 2007).

These theories converge to the mismatch hypothesis for the obesity epidemic. Thus human in many situations are mismatched because we are challenged by environmental conditions that extend beyond our evolved capacity to adapt to new environments or challenges not met before our evolution (Hanson & Gluckman, 2011).

The logic behind this important hypothesis is that the human body was molded over millions of generations to cope with ancestral conditions. Because agriculture was invented less than 10,000 years of age, and we ceased being hunter-gatherers, humans have changed so radically and rapidly their diet and
physical environments that natural selection has had little time to react. As a result, the Paleolithic bodies
we inherited often are mismatched with modern environmental conditions (Hanson & Gluckman, 2011).

Similarly the mismatch for the non-adaptive drift hypothesis happened with the removal of the predation around two million years ago. It is believed that predation was removed as a significant factor by the development of social, behavior, weapons, and fire (Speakman, 2007).

By summing up 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, increased the real cost of being physically active at work and at home. Moreover, there 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. Thus the changing obesogenic environment is widely in response to consumer’s demand for labor saving technology and convenient, affordable food (Finkelstein & Strombotne, 2010).

2.1 The Thrifty Hypothesis

The thrifty hypothesis for obesity includes both thrifty gene and thrifty phenotype hypothesis with the later being considered as the mother (pregnant) thrifty phenotype and the fetus phenotype. In general language thrifty implies some degree of prosperity deriving from earlier frugality and careful management of resources (Wells, 2009). 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 Homo lineage.

Nearly 50y ago Neel (1962) defined thrifty genes as those characteristic of individuals exceptionally efficient in the intake and/or utilization of food and such genes would have been favored by human populations that had been exposed to regular oscillations of feast and famine. The arguments were that those periods of gorging alternated with periods of greatly reduced food intake and then the supposed advantages of thrifty genes for accommodating periods of famine in our distant past (Neel, 1962).

Bouchard et al. (2007) suggested 5 broad types of thrifty genes categorized by variability a) metabolic rate or thermogenesis; b) predisposition for physical activity; c) efficacy of fat oxidation; d) appetite and e) adipocyte lipid storage capacity. In the absence of any definitive definition of metabolic thrift it has been proposed that thrift refers generically to the efficiency with which energy is used (Prentice et al., 2005). Then, an animal may be considered thrifty according to its ability either a) to reduce energy expenditure through physiological or behavioral alteration or b) to store energy rather than expend it (Speakman, 2007). Aside from frugality in energy turnover many mammal species also display metabolic thrift by acquiring stores of energy to offset fluctuation in supply and demand. These stores most commonly take the form of adipose tissue (Pond, 1998). Then adiposity is one form of thrift that emerged during human evolution. It is considered a consequence whether the storage of energy in adipose tissue arises from frugality in energy expenditure or up regulation of appetite (Wells, 2009). Thrifty is primary a pan-human trait, evident in our high adiposity for a tropical mammal especially in neonates, infants and reproducing females.

The generic human profile of adiposity-encapsulated in pan-human thrifty genes and observable in all populations-consolidated during the evolution of Homo erectus may be summarized: relatively high body fatness at birth increases during normal infant growth relative declines during early childhood and then the emergence of profound sexual dimorphism in fatness during adolescence before breeding. During old age, this sexual dimorphism decreases and body shape and adiposity converge the sexes (Kuzawa, 1998, Wells et al., 2007).
Contemporary variability in adiposity reflects not only genetic variability but also life history variability and behavioral variability. Genetic variability relevant to adiposity characterizes diverse components of metabolism (Bouchard, 2007) and behavior (Prentice, 2005), indicating that metabolic strategies rather than physical energy stores were the primary targets of selection (Wells, 2009).

Nearly 50y ago, it was suggested that differences in the prevalence of metabolic disease across populations might be due to the presence of “thrift genes” that would confer advantages in adverse nutritional environments but that might become detrimental in populations that were exposed to conditions in which food would be abundant (Neel, 1962). This hypothesis has served to explain the high prevalence of obesity and DM-2 in the Pima Indians as a sample of populations that evolved from hunter-gatherers that were exposed to feast or famine conditions (Duran et al., 2006).

### 2.2 The Low-Birth Weight Model

Small baby is a thrifty phenotype that represents a short-term adaptive response (preserving vital organs at the expense of less essential) to poor energy availability from the pregnancy (Hales & Barker, 1992).

The genetic thrift of neonate is attributable to our expensive brain and diverse stochastic ecosystem it allows to occupy. The brain imposes particular energy stress during early life (Foley & Lee, 1991), directly on the infant who must therefore acquire substantial energy stores to buffer perturbations in energy supply (Kuzawa 1998). Therefore the thrifty phenotype hypothesis (Hales & Barker 2001), which postulates that under conditions of suboptimal in uterus nutrition, the fetus must adapt to its environment to ensure survival of the organism through a “sparing” of vital organs such as the brain at the expense of others: pancreas, heart, kidney, and skeletal muscle. Under these conditions poor fetal growth is associated with shifts in the balance between competing organs and this widespread distribution strongly implies an adaptive component tissues may be considered as hierarchically ranked in relation to short-term survival. Hence, muscle and liver mass are sacrificed to preserve the brain with other organs more closely associated with brain metabolic requirements (Hales & Barker, 1992).

In their conceptual article Hales & Barker (1992) proposed in the thrifty phenotype hypothesis that small human neonate represents a survival phenotype with a number of characteristics that increase its likelihood of immediate survival after poor nutritional experience in uterus. The notion that the thrifty phenotype is a survival adaptation in early life appears uncontested. Some of these adaptive characteristic are known as part of the metabolic programming that occurs to promote nutrient storage to provide a survival advantage in conditions of poor post-natal nutrition. In addition to that the competing maternal capital hypothesis proposes that offspring adaptations are target at maternal phenotype, allowing on the one hand developmental trajectory to be guided by maternal capacity to provision the offspring, and on the other hand thereby allowing adaptation to the local ecology under this maternal influence (Wells, 2011). Therefore, nutritional resources are subject to maternal-offspring competition. The maternal availability of resources to the fetus is signaled by her secreted hormones. These signals guide differential investment in competing tissues and organs (brain priority) and the fetus adapts to the composite niche of maternal metabolism and phenotype (Wells, 2011). Hormones such as insulin, insulin-like growth factor, thyroid hormones, neuropeptide Y, leptin, cortisol and cathecolamines collectively signal maternal availability of resources to the fetus and guide differential investment in competing tissues and organs (Fowden & Forhead, 2009). This hypothesis assumes offspring developmental responses to stresses (Wells, 2011). The nutritional ecology occurs under the influence of maternal capital indices including size, physiology, reproductive history and social status (Wells, 2011).
In the present days fetal developmental constraint is greater in primigravida pregnancies, with higher maternal age, multiple births, and teenage pregnancy, and in women who diet before or during pregnancy. All of these circumstances are becoming more common globally, with pressure to reduce family size, changes in reproductive behavior, and lifestyles.

Besides competing “maternal capital” hypothesis that leads to a short-term adaptive responses, the long-term function of thrift includes the “predictive adaptive response” that considers thrift to involve metabolic adaptations that emerge in anticipation of a poor quality adult breeding environment (Wells, 2011). The term predictive adaptive response (PARS) has been coined by Hales and Barker (2001) to recognize responses that do not confer an immediate benefit but rather prepare the fetus for the later environment that is anticipated based on its developmental experience (Gluckman et al, 2005). The notion that the offspring alters its investment strategy according to its early experience is not the same proposition that the offspring actively anticipates specific ecological conditions in adult life (Wells, 2011). Hence the predictive adaptive response hypothesis assumes that metabolic phenotype develops in early life in anticipation of the adult environment in which breeding will occur (Godfrey et al, 2010). It is widely used to interpret associations between early nutritional experience and degenerative disease risks (Wells, 2011).

Many of the components of metabolism considered adaptive for adult life in the predictive adaptive response hypothesis seem to emerge under the “magnifying glass” effect of the modern obesogenic niche, and may simply represent “protective normalization” to preserve homeostasis. For example, blood pressure (BP) increases in relation to adult weight in order to maintain renal homeostasis; the lower the nephron number, the higher the BP increases required to normalize the load of a given body weight (BW). Likewise insulin resistance may initially follow the hyperinsulinemia that accompanies increased levels of weight gain. The lower the skeletal muscle in mass the lower the tolerance of muscle tissue to a given glucose load (Wells, 2011). However, these adaptations can lead the postnatal development of NCD in conditions of adequate nutrition or overnutrition (Tarry-Adkins & Ozanne, 2011) as robustly supported by many adult-epidemiologic studies worldwide (Hales & Barker, 2001).

Thus, it suggests that poor nutrition development could induce changes that would provide short-term advantage but become detrimental under conditions on energy excess and lack of exercise such as those observed in current industrialized countries (Uauy et al., 2011). As the balance between energy intake and expenditure becomes more obesogenic children are more likely to be mismatched even of their prenatal development was not greatly constrained (Gluckman & Hanson, 2004).

Namely the classic thrifty phenotype hypothesis and maternal adaptation hypothesis involve fetal programming. It is suggested that more than one type of metabolic programming may be involve in obesity and they may be induced in various stages of life (Baig et al., 2011). Behavioral programming is also likely to affect metabolism since associations are known between then (Belsare et al., 2010).

2.3 Criticism of Thriftiness

One of the key questions is when in human history could selection for thriftiness, if any, have operated. Hominids were hunter-gather for the most part of human evolutionary history and paleoarcheological data suggests that chronic starvation was uncommon during hunter-gatherer stage (Sahlins, 1974). Signs of chronic starvation on teeth, such as linear enamel hypoplasia, are more common in early agricultural than in hunter-gather societies (Speakman, 2007; Speakman, 2008; Lukacs & Walimbe, 1998). On the other hand intensive agricultural and industrial societies are modern phenomena. Hence it is difficult to argue that thrifty genes evolved from all the three possible nutrition scenarios to explain the polymor-
phism observed for obesity (Baig et al., 2011). Additionally both the concepts of thrifty gene and thrifty phenotype by fetal programming have faced serious criticism on several grounds (Speakman, 2006; Speakman, 2007, Speakman, 2008, Benyshek & Watson, 2006; Waxe & Yajnik, 2007; Wells, 2007) with the main objection as follows:

a) As originally suggested by Neel, in individuals prone to obesity and T2D a “quick insulin trigger” ensures rapid glucose uptake which is then converted into fat. That made sense at that time (1960s) but after insulin resistance was discovered it became clear that “quick insulin trigger” is unlike to work on more conversion of cellular glucose on fat. Actually today it is known that insulin resistance arrests lipogenesis (Klöting & Blüher, 2005);

b) If thriftiness is due to lower metabolic rate conserving more energy which gets stored in fat tissue a lower metabolic rate should be observed in people having a predisposition to obesity. No consistent correlations were found between birth weight and metabolic rate (Eriksson et al., 2002; Kensara et al., 2006) and studies using doubly labeled water have not consistently found lower metabolic rated in people with sedentary lifestyle in the modern urban societies (Westerterp & Speakman, 2008; Black et al., 1996);

c) Impaired fat oxidation appears to be the main contribution to obesity of developmentally stunted individuals (Zurlo et al., 1990; Hoffman et al., 2000), then under the inability to reutilize stored fat it is unlikely that excess of tissue fat would help under “famine” condition (Baig et al., 2011). The doubly labeled water studies also suggest that obesity is more a product of hyperphagia than metabolic thriftiness (Westerterp & Speakman, 2008; Black et al., 1996);

d) Evidence that obese people have a significantly better chance of surviving famines is debatable (Speakman, 2008) as well is doubtful whether obesity actually offered sufficient advantage during famines to get selected in spite of the fact that obesity is associated with reduced fecundity (Norman et al., 1998);

e) The thriftiness hypothesis focus on energy homeostasis alone and as it is known obesity and insulin resistance is associated with number of changes in the different body systems and their functions as diverse as ovulation, spermatogenesis, innate immunity, wound healing, memory and cognitive brain function (Waxe & Yajnik, 2007);

f) The cost of thriftiness is justifiable based on the reproductive effects of obesity. It is assumed that thrifty individuals are fast to become obese in feast conditions, and these are multiple mechanisms by which obesity causes reduction in fecundity and the effects of obesity on male (Uauy et al., 2011) and female (Fowden & Forhead, 2009) fertility become additive if a couple is obese (Gluckman & Hanson, 2004).

3 The Early Growth-Later Disease Model

The adaptation in early growth is a necessity for all human offspring, who rely on signals from maternal metabolism to guide early developmental trajectory. Epidemiological evidence suggests that both fetal and post-natal periods are important in the induction of disease risk (Wells, 2011).

The associations between early nutritional experience and degenerative disease risks are widely used in the thrifty phenotype hypothesis and in early growth and later disease model (metabolic risk).
The disease is attributed to a high metabolic load relative to a limited metabolic capacity (Wells, 2011). Metabolic risk is resulted from either metabolic capacity decreasing and/or metabolic load increasing. Metabolic capacity and load are properties of all humans and disease risks increases whenever the balance between load and capacity is high (Wells, 2011).

The conceptual model of two fundamental components of phenotype (Wells, 2011; Wells, 2009) involves: (1) metabolic capacity which refers to a variety of aspects of organs structure and function that emerge during fetal life and infancy when the growth process is dominated by hyperplasia; (2) metabolic load which refers to the burden imposed by the tissue masses and their physiological condition on this homeostatic metabolic capacity (Wells, 2011; Wells, 2009). The guiding of early offspring growth by maternal phenotype generates a continuous range of variability in offspring metabolic capacity. Metabolic capacity is resulted from physiological traits contingents on fetal/infant development such as pancreatic B-cell mass and the capacity to secrete insulin, lung airway function, nephron number and broadly, continuous association with birth weight (Wells, 2011). The metabolic capacity accrued by the offspring in thus a function of that resources the mother could supply during early window of plasticity and the consequences of this investment then track into adulthood regardless of future ecological conditions.

Later in life (childhood or adulthood), metabolic load shows dose-response associations with total body mass (Weiss et al., 2004) and likewise with dietary glycemic load (McKeown et al., 2004), and inversely with physical activity level (Andersen et al., 2006, Ford et al., 2005).

In contemporary obesogenic environments the interaction of metabolic capacity variability with variable metabolic load during childhood and adulthood accounts for variability in metabolic risk (Wells, 2011). This model offers an explanation for why the effects of physical activity, rich diet, rapid childhood weight gain, and obesity are all relatively similar—each exacerbates metabolic load, though through different physiological pathways or developmental periods (Wells, 2011).

Approximately 20 years ago in a series of studies Backer et al. (1989) and Hales et al. (1991) have shown that men (at age of 64 years) with (recorded) lower birth weight and lower weight at 1y of age had the highest death rates than did those of normal birth weight. From those data they established the concept of metabolic programming during early life.

Interactive effects of birth weight and current weight may vary by disease outcome such as blood hypertension (Lurbe et al., 2009), insulin resistance (Newsome et al., 2003, Fagerberg et al., 2004) diabetes (Forsen et al., 2000, Bhargava et al., 2004) plasma cholesterol, triglycerides markers of inflammation and CVD (Wells, 2011).

### 3.1 The Role of Lean-Body Mass on Growth

Nutrition during early life is now understood to impact on later size, physique, lean mass and obesity. The competing “maternal capital” hypothesis considers thrifty to involve reductions in lean mass and organ phenotype arising through constraints on maternal phenotype reflecting both maternal developmental experience and current ecological conditions. Hence, thrifty phenotype is a continuous trait, primarily reflecting adaptation in growth of lean mass and competing organs, which tailor offspring development to the composite niche representing maternal phenotype within a broader ecological environmental (Wells, 2011).

The physiological strain on fetal development by maternal-placental constrains affects pancreatic β-cell mass, nephron number and muscle mass. Birth weight is strongly predictive of subsequent lean mass whereas associations with birth weight and later fat mass or fat distribution are inconsistent (Wells, 2011).
The variability in lean mass and its component organs are a key component of thrift and may be more fundamental than alterations in metabolism and adiposity (Wells, 2011). Studies have indicated that early infant catch up following low birth weight is more strongly associated with later lean mass than fat mass (Wells, 2011).

Low birth weight is associated with lower adult body size, muscle mass and altered fat distribution, but because the differences in adiposity only emerged after adjustment for current weight, BMI or height birth size did not directly induce a more central fat distribution. Rather, the primary effect of low birth weight was to constrain lean mass, muscle mass, and peripheral fat (Wells, 2011).

In summary, in early infancy the most notable component of thrifty is the variability in skeletal muscle mass and organ mass; limb muscle mass is depleted peripheral fat mass is likewise, whereas central adiposity is relatively unaffected. The main compensatory hormonal effect is hyperinsulinemia, which initially seems to promote catch-up in length (Wells, 2011).

From this perspective, such traits do not represent anticipatory adaptations to poor energy availability in adults life rather they emerge when a thrifty growth pattern (low lean mass and reduced metabolic capacity) is subsequently exposed to high metabolic load, and confer protection against it without such metabolic load, characteristic of the modern obesogenic niche, growth variability in early life appears to have little consequence for metabolic risk (Wells 2011).

The metabolic thrifty that often follows low birth weight in adulthood (insulin resistance, central fatness) is not strongly evident at birth or infancy, but rather emerges through the impact of the obesogenic niche or variability in metabolic capacity and thus seems protective rather than anticipatory (Wells, 2011).

Brazilian fetal and infant weight gain were associated with later height and lean mass, whereas weight gain from 1 year was associated with later fat mass (Wells, 2011). Similar findings were reported from India (Sachdev et al., 2005). If is persisted beyond the second year it was associated with adult BMI (Ezzahir et al., 2005). In populations, remaining lean and fit and consuming a traditional diet with low energy density (Prentice & Jebb, 2003), birth weight variability was not associated with adult variability in either the glucose/insulin axis or other risk factors for CVD (Moore et al., 2001). On the other hand, when migrating or exposed to the obesogenic niche this population present high risk for CVD (Wells, 2011).

4 Implications for Genetic of Obesity

An increasing number of loci and mutant associated with obesity are being indentified. However there have been certain paradoxes between data from the prior genomic era studies (based on familial twin-pair) and the actual genomic studies. The former predicted a large heritable component in obesity (Wells, 2006) whereas the genome-wide studies have identified a larger number of associations, but together they explain a very small fraction of variance in obesity parameters (Beyerlein & von Kries, 2011; Hauner et al., 1995; Petruschke et al., 1994; Lucas et al., 1980; Pico et al., 2011), leaving a large gap between the pre-and post-genomic picture. We are yet to understand the reasons for this discrepancy, but a most likely implication goes against all hypothesis that assume a gene or a set of genes for obesity (Baig et al., 2011). These hypothesis include Neel’s Thrifty gene, Speakman’s drifty gene, Corbet et al’s reverse selection, and Moalen et al’s cold adaptation. On the other hand, fetal programming has a promise for fill-
ing the gap between the familial studies and the genomic-wide association studies. The programming is likely to involve epigenetic mechanisms as well (Baig et al., 2011).

The classical thriftiness family of hypothesis would expect genes associated with metabolic rates to be the obesity genes. The behavioral origins hypothesis, on the other hand, expects genes involved in sexual function, cognitive abilities, immunity, regulation of aggression, and other behavioral traits to be associated with obesity and related disorders (Baig et al., 2011).

5 Post Natal Modulators of Metabolic Plasticity

Epigenetically hyperadiposity is resulted from the expression of genes favoring the storage of excess calories as fat that becomes maladaptive in a rapidly changing environment that minimizes the opportunities for energy expenditure and maximizes the opportunities for energy intake.

Physiological plasticity allowed the emergence of variability across the life course in response to ecological was experienced directly or by very recent ancestors. Plasticity protects the genome from selective pressures by tailoring the organism to ongoing ecological conditions (Wells, 2009). The mechanistic basis to support the developmental plasticity of predictive adaptive responses is provided by the occurrence of epigenetic changes that affect gene expression (Barker, 1998). By taking into account more subtitle periods of development during post-natal life: first, fetal life and early infant are potential for epigenetic effects with life-long impacts on DNA expression and hence on metabolic capacity (Wells, 2011). These modifications include methylation of DNA and modifications of histones, including acetylation (Tarry-Adkins & Ozanne, 2011). Epigenetic regulation of transcription factors is now emerging as common mechanism of early life programming, including PPAR-α (Lillycrop et al., 2005) with effects on both DNA methylation and histone marks.

Excess or deficits in nutrients, hormones, or metabolites may trigger changes in DNA or histone methylation, which in turn suppresses or enhances gene expression; in addition, changes in small noncoding RNA activity act by modulating gene expression. This novel, more mechanistic concept emphasizes the idea that extreme challenges during early post-natal development are not essential to elicit PARs, but later environment that renders detrimental a particular phenotype (Uauy et al., 2011).

5.1 Breast Feeding

The period of plasticity, when growth adapts to nutritional supply is brief and largely restricted to the windows of pregnancy and lactation. The metabolic capacity accrued by the offspring is thus a function of what resources the mother could supply during early window of plasticity, and the consequence of this investment then track into adulthood regardless of future ecological conditions (Wells, 2011). The brain imposes particular energy stress during early life directly on the infant and also indirectly on the mother who meets the breast fed infant’s energy supplies up until weaning (Wells, 2006).

Three meta-analyses reported significant protective (and one not) effects of breast feeding against overweight in later life (Beyerlein & von Kries, 2011). Breast milk contains bioactive factors that may modulate epidermal-growth factor and TNF, both of which are known to inhibit adipocyte differentiation in vitro (Hauner et al., 1995; Petruschke et al., 1994). On the other hand fat deposition is stimulated by the plasma insulin found significantly higher in infant who were bottle fed compared with those breastfed (Lucas et al., 1980).
Breast feeding, compared with infant-formula feeding confers later protection against obesity and leptin represents a candidate for the programming of the lean phenotype. High leptin sensitivity, which is associated with leanness and leptin resistance in obesity, may be programmed by the early life environment (Pico et al., 2011). Leptin was discovered by Zhang et al. (1994) as a signaling molecule from adipose tissue. It is a hormone that decreases food intake and increases energy expenditure while modulating metabolism in peripheral tissues, body temperature, reproduction and other functions (Flier & Maratos-Flier, 1998; Myers 2004). Milk-borne leptin and leptin synthesized in adipose tissue and the stomach may contribute to leptinemia in newborns. A negative correlation between leptin concentrations in breast milk and body weight of infants until 2y of age was found in humans (Pico et al., 2011). It was shown that human milk intake was associated with lower plasma leptin concentrations in adolescent suggesting a higher leptin sensitivity (Singhal et al., 2002).

In adult organism’s defects in leptin signaling result in hyperphagia, lower metabolic rate, hypothermia, and severe obesity. Leptin acts through its receptors, and the long isoform is highly expressed in the hypothalamus and the short isoform has been observed in peripheral tissues (Myers, 2004).

The stimulation of muscle AMPK occurs rapidly through a direct interaction of leptin with its receptor in the muscle and more slowly depending on the central activation of the sympathetic nervous system and α-adrenergic receptors in the muscle by leptin (Suzuki et al., 2007). AMPK stimulates mitochondrial biogenesis in the muscle and plays a major role in the regulation of fatty acid oxidation, while inhibiting FA synthesis (by the phosphorylation of AcCoA-Carboxylase) and reducing malonyl-Coa levels, which results in the enhancement of the activity of carnitine palmitoyltransferase-1 and β oxidation of FA (Minokoshi et al., 2002, Cohen & Friedman, 2004). In tissues such as liver AMPK inhibits gluconeogenesis and lipogenesis while augmenting lipid catabolism (Lage et al., 2008). In adipose tissue, AMPK decreases lipolysis (Minokoshi et al., 2002). In the peripheral tissues, leptin was shown to stimulated the lipid oxidation and uptake of glucose in skeletal muscle by activating AMPK which is the sensor and master regulator of intracellular energy status (Suzuki et al., 2007; Lage et al., 2008) that interacts with another key fuel-sensing intracellular regulatory pathway, the histone/protein deacetylase sirtuin 1 (Canto et al., 2009; Ruderman et al., 2010).

Central effects of leptin, which result in 1) an increase in energy expenditure in peripheral tissues mediated by the sympathetic nervous system and 2) the depression of food intake, depend on the modulation of the activity of hypothalamic neurons in the accurate nucleus by leptin, namely the inhibition of the activity of orexigenic neurons (expressing Agounti-related protein and neuropeptide Y) and the stimulations of the activity of anorexigenic neurones (expressing propiomelanocortin) (Schwartz et al., 2000). In the hypothalamus leptin inhibits AMPK activity whose suppression leads to depression of food intake (Andersson et al., 2004; Minokoshi et al., 2004).

Defective responses of AMPK to leptin in skeletal muscle and the hypothalamus may contribute to a resistance to leptin action on energy expenditure and food intake in the obese state. The vast majority of obese people appear to be resistant to the action of leptin, showing increased concentration of leptin in circulation (Surwit et al., 2000, Martin et al., 2006).

### 5.2 Lifestyle Modulation of Obesity in a Dwelling-Community Sample

The increasing prevalence of obesity is due to complex interactions between genetic and environmental factors, like dietary intake and physical activity. The most important factors underling the obesity epidemic are the current opportunities of energy intake coupled with limited energy expenditure (Biro &
The next paragraphs outline results from our studies in Brazil linking an evolutionary perspective on the modern obesity crisis to a rationale for a treatment.

The Nutritional and Exercise Metabolism Centre (CeMENutri) of the UNESP-Medical School is a multiprofessional teaching and research centre located in Botucatu city, a middle size city (around 125,000 inhabitants), in a middle western part of Sao Paulo, a Brazilian southeast state. The city economics is based on industry and agricultural and the city hall along with federal welfare provide basics food supply and money transfer for the low-income population mainly family bearing children.

The CeMENutri Health Care programs for local community aim to attend school children and adults (over 35 years old). The Health Care intends to promote healthy lifestyle through adequate (counseled or advised) nutrition and appropriated (supervised) physical exercises which are undertaken in two steps. First in cross-sectional studies involving lifestyle diagnosis of physical activity, fitness, dietary quality and food intake along with body composition, plasma biochemistry and diagnosis of non communicable chronic diseases. The second step involves longitudinal studies with interventions either with physical exercises or diet or both.

Cross sectional studies with children and adolescents showed rates for obesity and overweight of 16.3% (boys 18%) and 15% (girls 17.2%), respectively (Rinaldi et al., 2012). The waist circumference (WC) measure was above the references values in 40.4% of the schoolchildren (Rinaldi et al., 2012) and MetS prevalence among overweight scholars ranged from 10 to 16.5% accordingly to different diagnostic criteria (Rinaldi et al., 2010). Both obesity and excessive abdominal adiposity predispose children to be unfit in abdominal strength/resistance and aerobic resistance as excess of body adiposity increased the likelihood of poor trunk flexibility (Andreasi et al., 2010). Moreover, low physical fitness is associated with higher sedentary behavior illustrated by the TV time (Angelo et al., 2012). When assessing the MetS components in this population it was found a positive correlation of body weight and WC with blood pressure and plasma triglycerides. Besides body composition, dietary intake (excessive intake of food rich in saturated fat and sugar) was also associated with MetS (Rinaldi et al., 2012).

Socioeconomic status plays an important role in the prevalence of MetS and its comorbidities in free living Brazilian adults. Cross sectional studies with adults showed that low-income doubles the chance for higher BMI (Siqueira, 2012) and it is an important determinant for the diet quality, mainly vegetable oil intake (Mclellan et al., 2010) when compared to individuals with higher income and higher education. Some dietary factors and dietary patterns are associated with obesity and overweight in our studies. Obesity is associated with low intake of vegetables whereas overweight is associated with low intake of fruits and dairy products, and high intake of total fat (Siqueira, 2012). Moreover, a healthy dietary pattern rich in non-starchy vegetables, fruits, fresh juice, whole-wheat bread, low-fat dairy products, fresh and homemade popcorn is best related to lower risk of abdominal obesity (Marsola et al., 2011). The association of obesity with physical activity and fitness was also studied. Our data showed that moderate/vigorous physical activity was seen as protective factor against overweight and obesity (Siqueira, 2012), and in this low-income community hyperadiposity is associated with physical activity, but not exclusively (Michelin et al., 2009).

Different protocols of exercises and dietary interventions were conducted in free-living adults to verify the effects of lifestyle changes (diet and physical fitness) on obesity, diabetes, hypertension, dyslipidemia, and metabolic syndrome. Some of the results show success in weight loss (3.3kg) followed by a reduction of body fatness (2.9%) after a 3-year physical-exercise (aerobic) protocol (Burini et al., 2011). When this protocol was applied to post-menopausal women for 6 months, body fatness was reduced in 3.7% in obese and in 4.1% in non-obese women without major changes in BMI and waist to hip
The comparison between aerobic and combined (aerobic + strength) protocols showed after 6 months a higher decrease in body fatness under the combined exercises protocol (Nadai et al., 2002). The additional physical exercise (aerobic) to a food-energy restriction protocol conducted during 40 weeks in adults resulted in higher body weight loss ($5.3 \times 2.3\text{Kg}$) and WC decreasing ($7.6 \times 4.8\text{ cm}$) when compared with the group exercised only (Monteiro et al., 2004).

The effects of a lifestyle modification program (LMP) including both supervised (aerobic) physical exercises and nutritional counseling conducted in adults for 2 years decreased obesity rates in 4.8% after 6 months of intervention, in 8.4% after 12 months, and in 5.7% after 24 months, similarly in men and women (Coelho et al., 2010). For similar length of protocol (20 – 24 weeks) walking (aerobic) or cross-training (walking + strength) protocols (including dietary counseling) resulted in significant body weight loss and BMI decrease differently of strength exercise protocol that maintained the baseline values. Six-months of LMP in overweight subjects reduced obesity by 5.5% in hyperglycemic and by 8.0% in normoglycemics against 3.4% in non LMP hyperglicemics. Only LMP groups presented significant reductions in WC and body fatness (Mota et al., 2011).

A 20 week-intervention protocol of exercise or exercise plus omega-3 polyunsaturated fatty acid with 61 adults ($50 \pm 13.8$ years old, 85% of women) showed an additional effect of omega-3 on decreasing body fat percentage and waist circumference when compared to the group with exercise alone (Talon, 2011). Likewise, a short-term LMP intervention with obese subjects including exercise or exercise plus a high dietary fiber intake leaded to a decreased body fat composition among those individuals with a high dietary fiber intake after a 10 week-intervention protocol (Mecca et al., 2012).

The data collected from 271 adults ($53 \pm 8.8$ yrs) participating in protocols of LMP including exercises (aerobic and/or strength) associated either with dietary counseling or intervention (with dietary fiber) lasting 2 to 12 months showed different efficacy in weight loss. For the same length of LMP aerobic exercises were more efficient than combined or strength only exercises in promoting weight loss, reaching better results after a 12 months intervention. After 6 months of aerobic exercises 3.4% of overweight subjects became eutrophic. Identical rate was achieved in only 2 months of LMP when combined exercises were associated with recommended dietary fiber intake (25 g/day). Considering the estimated extra cost of overweight/obese Brazilians as being US$0.50/subject (US$36 mi/72573.235 subjects) the economy of this LMP for the public health (3.4% eutrophy promotion) would be of US$ 1.23 mi in either 6 months of LMP with exercises and dietary counseling or in 2 months of LMP associated with dietary fiber intervention. This economy would be enough to replicate this LMP in all existing Brazilian cities, with 80 patients/each for more than 100 years to come (Castanho et al., 2011).

6 Summary

The modern world is experiencing an unprecedented epidemic of overnutrition. Economically the costs of obesity are rising rapidly as it is the dramatic negative influences on the health of the population in the decades to come. 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 generation coping with the modern dietary and physical environments. The mismatch hypothesis involves obesity either as natural selection or not. As an evolutionary selection obese human has over expression of thrifty genes evolved for efficient food collection and fat deposition to survive periods of famine. Then adiposity is our form of thrifty that emerged from frugality in energy expenditure or up
regulation of appetite. In this hypothesis there are at least three windows for metabolic plasticity: pregnancy, lactation, and later life. Because established obesity is notoriously resistant to treatment much attention has been focused on prevention and understanding why human development may influence the predisposition to obesity can be assisted by taking an evolutionary perspective. Our aim was to link an evolutionary perspective on the modern obesity crisis to a rationale for a treatment outlined in our studies in Brazil. 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. Moreover, 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. Our lifestyle modification program (LMP) has promoted body eutrophy with supervised physical exercises and dietary counseling/intervention for the last 20 years. The proposed LMP is costless and effective to be replicated worldwide.

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