

## Review Article

# AMPK as Target for Intervention in Childhood and Adolescent Obesity

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Childhood obesity is a major worldwide health problem. Intervention programs to ameliorate the rate of obesity have been designed and implemented; yet the epidemic has no end near in sight. AMP-activated protein kinase (AMPK) has become one of the most important key elements in energy control, appetite regulation, myogenesis, adipocyte differentiation, and cellular stress management. Obesity is a multifactorial disease, which has a very strong genetic component, especially epigenetic factors. The intrauterine milieu has a determinant impact on adult life, since the measures taken for survival are kept throughout life thanks to epigenetic modification. Nutrigenomics studies the influence of certain food molecules on the metabolome profile, raising the question of an individualized obesity therapy according to metabolic (and probably) genetic features. Metformin, an insulin sensitizing agent, is known to lower insulin resistance and enhance metabolic profile, with an additional weight reduction capacity, via activation of AMPK. Exercise is coadjutant for lifestyle modifications, which also activates AMPK in several ways contributing to glucose and fat oxidation. The following review examines AMPK's role in obesity, applying its use as a tool for childhood and adolescent obesity.

## 1. Introduction

Obesity is considered a new pathology in the history of Humankind, being the new food security tendency the one to blame for such a rising wave [1]. In the last century, technological advances and cutting edge science have modified human lifestyle, changing diet regimes and physical activity and therefore creating an imbalance between caloric ingestion and an energy expenditure that is not able to compensate the caloric excess ingested. This spill-over energy is accumulated in the adipose tissue manifesting itself as obesity which is considered a step closer to the new evolved man: *Homo obesus* [1, 2].

The World Health Organization (WHO) has labeled obesity as the *new epidemic* of the 21st century. According to WHO projections for 2005, around 1,600 billion adults worldwide were overweight and at least 400 million were obese; by 2015, more than 2,3 billion adults will be overweight and 700 million will be obese [3]. The values in

the pediatrics population are even less encouraging, with at least 20 million overweight children of less than 5 years of age [3]. In the United States, the prevalence has risen in the last 30 years, with a 3,8-fold for the 6–11 years old group (from 4% to 15,3%), and 2,6-fold for the adolescent group (from 6% to 15,5%) [4]. Sekhobo et al. [5] published their results based on an analysis in overweight/obesity tendency in the low-income preschoolers who were part of the New York State Special Supplemental Nutrition Program for Women, Infants, and Children, 2002–2007. The prevalence of obesity raised in 2003 [3, 6], later declining from 2003 to 2005, finally stabilizing itself at 14,7% by 2007. Nevertheless, there was an increasing prevalence of overweightness during the whole study. There is no doubt that overweight and obesity have become a major health problem [5].

Defining obesity in the pediatric group is a real challenge due to growth (weight and height) variations in childhood and adolescence. The International Obesity Task Force

(IOTF) has established that obesity and overweight will be defined by corresponding percentiles of Body Mass Index (BMI) 25–30 at 18 years of age, and that the percentiles will be conserved throughout the age groups. Some authors use only BMI values to differentiate between overweight and obesity in adolescents; nevertheless Cole et al. [7] published the percentile tables according to age and sex. With these tools, the Center for Disease Control (CDC) has defined overweight in a group 2–18 years of age as BMI equal or above 95th percentile according to age and sex. The term *risk of overweight* is applied to circumscribe children with BMI between 85th and 95th according to age and sex, since CDC prefers not to use the term obesity for psychological/social reasons [8, 9].

The Metabolic Syndrome has evolved from its first definition back in 1998 by the WHO [10]. The first published consensus was meant to detect those high-risk patients, diabetic or not, with any degree of glucose intolerance, hypertension, dyslipidemia, and/or microalbuminuria. In 1999 the European Group for the Study of Insulin Resistance (EGIR) issued another set of variables for the diagnosis excluding microalbuminuria [11]. By 2001, the Adult Treatment Panel III (ATPIII) announced their criteria suggesting that insulin resistance was not necessary for the diagnosis [12]. The International Diabetes Federation (IDF) participated in this worldwide debate when in 2005 they published their own definition, giving particular interest to the influence of ethnicity in the proper diagnosis of the disease and the cut-offs being set for the patients, particularly since abdominal obesity was now proposed as a fundamental element for its identification [13]. In 2005, the American Heart Association together with the National Institutes of Health, Heart, Lung, Blood Institute (AHA/NIHHLBI) revised the ATPIII definition, modifying normal fasting glucose levels lowered to 100 mg/dl, in accordance with the American Diabetes Association's new cut-off [14]. Finally, the IDF with AHA/NIHHLBI issued the newest MS definition in 2009 [15], emphasizing need for proper individualization of anthropometric reference values in every ethnic population. See Table 1.

Overweight/Obesity is the most studied variable of MS in children, and there is no official statement on the cut-off points for its definition in this population; in fact there is no consensus on the existence of MS in childhood due to its limited capacity for predicting outcomes like Type 2 Diabetes Mellitus (T2DM) and Cardiovascular disease (CVD). Goodman et al. [16] demonstrated in a 3-year follow-up study that 61,1% of the children with MS lost at least one of the variables during the trial, while 25,5% of the children without MS acquired at least one risk factor, defined by the authors as “*the instability in the diagnosis of metabolic syndrome.*” Nonetheless, one of the outcomes that have been explored is the risk of adult obesity in the already obese child. Around 30% of adulthood obesity starts in infancy, with even worst consequences than compared to obese adults who were lean. Overweight adolescents have 50%–70% chance to become overweight/obese adults, while only 30% of the lean children will become obese in adulthood [6, 17]. This only ensures the importance of a proper and

TABLE 1: Metabolic Syndrome criteria according to International Diabetes Federation/American Heart Association/National Institutes of Health, Heart, Lung, Blood Institute, 2009.

IDF/AHA/NHLBI 2009 <sup>14</sup>
Three of the following:
(i) <i>Abdominal Obesity</i> : Elevated waist circumference according to a population and country-specific definition.
(ii) <i>Lipid Profile</i> : Triglycerides $\geq 150$ mg/dL or treatment for elevated triglycerides.
(iii) <i>Lipid Profile</i> : HDL-c $< 40$ mg/dL in men or $< 50$ mg/dL in women. Or treatment for reduced HDL-c.
(iv) <i>Blood Pressure</i> : $\geq 130$ mmHg on Systolic Pressure. Or $\geq 85$ mmHg on Diastolic Pressure. Or on anti-hypertensive drug treatment in a patient with a history of HTA.
(v) <i>Glycemia</i> : Fasting glucose $\geq 100$ mg/dL. Or on drug treatment for elevated glucose.

early intervention to minimize or completely prevent future metabolic complications.

In 1973, two research groups described at the same time the qualities of a protein kinase that was involved in lipid metabolism, which was able to inhibit Acetyl~CoA Carboxylase (ACC) and 3-Hydroxy-3-Methylglutaryl~CoA (HMG-CoA) Reductase [18, 19]. Later on, this kinase was labeled AMPK (*AMP activated protein kinase*) since it has been activated by increased AMP concentrations. The enzyme has been the topic of several studies, which have revealed its effect on energy balance, mitochondrial biogenesis, regulation of lipid/carbohydrate metabolism, and modulation of genetic expression [20, 21].

The role of AMPK as an energy thermostat puts it at crossroads for energy homeostasis, making it fundamental to analyze the signaling pathways involved in energy metabolism, not only for academic purposes but also for therapeutical goals in childhood obesity. The purpose of this review is to analyze the role of AMPK as an intervention target in childhood obesity.

## 2. Nutrition of the Fetus: Under versus Over

**2.1. Food Intake Control.** The regulation of food intake is a very complicated network involving peripheral signals and central processing, which renders behavioral patterns that lead to weight gain or weight loss [22]. The processing of all input signals is done between the “satiety centre” in the ventro-medial nuclei and the “hunger centre” in the lateral hypothalamic area, arcuate, and paraventricular nuclei. The adiposity signals come from the pancreas and the adipose tissue, represented by insulin and leptin; both of them are destined to stop eating behaviour and food intake once

energy stores have been filled. These signals activate the Pro-Opioid-Melanocortin/Cocaine and Amphetamine-Regulated Transcript neurons (POMC/CART) inducing satiety (see Figure 1).

On the other hand, gut signals usually modulate hunger and feeding behavioral patterns [23]. Glucagon-like peptide 1 (GLP-1) is an incretin which is released while eating, inducing insulin release from the  $\beta$ -cells and halting food consumption. Peptide YY—a member of the NPY peptide family—is a 34-amino acid peptide secreted by the intestine which hinders food intake and modifies gut motility (ileal brake), and its release depends on the amount of carbohydrate or lipids in the ingested meal. This molecule inhibits NPY neurons and activates POMC population, lowering ~30% of food intake using the Y2 Receptor. PYY is negatively correlated with the degree of adiposity with reduced values when compared with normal weight subjects [24]. Ghrelin is a peptide synthesized in the stomach, and it is associated with hunger. It exerts its effects through the Growth hormone secretagogue receptor in the hypothalamus and brain stem, with the activation of Neuropeptide Y/Agouti related Peptide (NPY/AgRP) neurons, which induces appetite while inhibiting POMC/CART secreting cells. Obestatin is a 23-amino acid byproduct of the ghrelin gene breakdown, also synthesized in the A-cells in the stomach [25] whose physiological role is still under consideration; yet certain studies have linked this molecule with antiapoptotic properties in  $\beta$ -cell, and with inhibition of food consumption via upregulation of GLP1 mRNA [26]. Other factors include pancreatic peptide (PP) and oxyntomodulin (Oxm) both of which are food intake inhibitors.

Ghrelin has been one of the most researched gut-derived molecules in childhood obesity. Disturbances of its pathway have been proposed as basic pathophysiology for several diseases like: growth hormone deficiencies, anorexia nervosa, cachexia, chronic heart failure, gastrointestinal motility disorders, osteoporosis, obesity, and Prader-Willi syndrome [27]. Ghrelin enhances AMPK activity in the hypothalamus, lowering malonyl-CoA levels, inducing carnitine palmitoyl transferase-1, elevating long chain fatty acids, releasing NPY, and activating hunger [28]. As a basic rule of thumb, ghrelin levels are inversely correlated to BMI, and there is a negative association between insulin and this hormone. James et al. [29] reported that ghrelin levels are associated with slow weight gain from birth to 3 months of age, which relates it to postnatal catch up growth. In a study using 208 preterm children, Darendeliler et al. [30] reported that at prepubertal ages those preterm newborns—either small (SGA) or adequate for gestational age (AGA)—had higher ghrelin levels compared to those at-term newborn children. This sustained elevation of ghrelin might be needed for the compensatory growth which they are subjected, but it does not correlate to the degree of catch-up growth achieved nor with the levels of insulin found. Similar results were published the following year by Darendeliler et al. [31] analyzing prepubertal children who were born large for gestational age, reporting that nonobese prepubertal youngsters had lower ghrelin levels compared to AGA born counterparts, proposing that birth weight is

in fact a fundamental determinant in ghrelin levels during childhood.

Maffei et al. [32] proposed that meal-induction of insulin secretion promotes a fall in ghrelin levels, and that in insulin resistance states this blunting is reduced. Now, even though this is true, this inhibiting effect of feeding is lost in childhood suggesting that ghrelin acts as an anabolic hormone meant to provide the necessary substrates for growth [33]. This feeding reducing effect on ghrelin depends on insulin availability, and its deficiency can explain the observed hyperphagia in Type 1 Diabetes Mellitus [34]. Bacha and Arslanian [35] conducted a trial using overweight children as subjects to evaluate insulin's power of inhibition, reporting that fasting ghrelin is determined by insulin sensitivity regardless of adiposity.

Obesity is a multifactorial disease which has no clear genetic cause. It is known that obesity is a heritable syndrome, with a heritability of 0.7 to 0.8 [36]; yet the genes at play are still pending confirmation. Lessons have been taken from monogenic syndromes like the Congenital Leptin Deficiency [37–39] which is characterized by hyperphagia and early-onset obesity. The mutations causing this disease render a functional protein that cannot mediate appetite control, and the patients develop hyperphagia very early on. Subjects with this mutation are candidates for leptin replacement since it is the defective molecule. Gibson et al. [40] reported the 4-year treatment of a subject (with the  $\Delta 133G$  mutation) with subcutaneous recombinant leptin, providing beneficial and long lasting controlling effects on hyperinsulinemia, hyperlipidemia, fat mass distribution, and TSH levels. Not all mutations are located on one gene nor do they have such a profound effect like the former Mendelian syndrome; most of the genes associated with obesity [41] interact with each other to express a phenotype that will end with abdominal obesity. Genomewide scans have revealed several gene candidates [41], including adiponectin (3q27) [42, 43], adrenergic receptor  $\alpha$ -2A (10q24-q26) [44, 45], leptin (7q31.3) [46, 47], glucocorticoid receptor (5q31) [48], PPAR $\gamma$  (3p25) [49], serotonin receptor (Xq24) [50], and melanocortin 4 receptor (18q21) [51]. The interaction of these genes with environmental factors affect any check point in the appetite network, either in the behavioral aspects or in the metabolic adaptations, as can be seen in Figure 2.

The *Thrifty Phenotype* theory proposed by Barker [52] tried to explain the relationship between intrauterine growth retardation and premature death due to cardiovascular disease or T2DM complications (see Figure 3). He postulated that according to the insult enforced on the fetus, the reprogramming of several axes would determine the fetus' survival during the pregnancy phase; yet the necessary measures imprinted for salvation are deleterious during adult life. Fetal malnutrition can be achieved by several ways, but the overall outcome is always the same: hypoglycemia and hypoxia. Small placentas, which have not acquired enough spiral arteries remodeling, have trouble oxygenating and nurturing the *conceptus*, developing a hypoxic placental milieu [53]. It has been proposed that modifications in the adipoinular axis of the fetus promote hyperinsulinism and hyperleptinemia and confer the necessary epigenetic

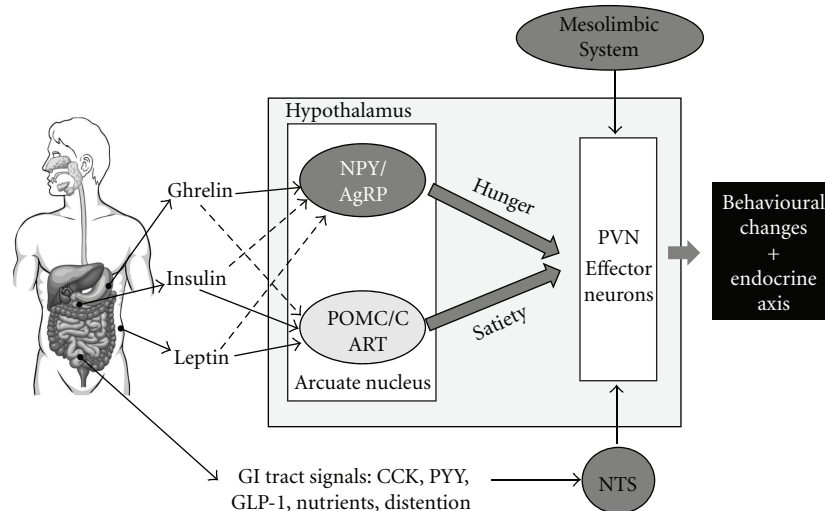


FIGURE 1: The Food Intake network is a complex system comprising several levels. See text for further information. CCK: cholecystokinin; GLP-1, Glucagon-like peptide 1, NTS, nucleus of the solitary tract, PVN, paraventricular nucleus; PYY, Peptide YY.

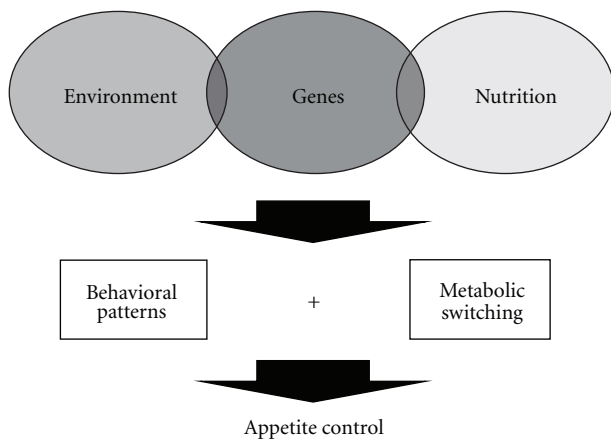


FIGURE 2: Appetite control is a very complex network, which has to intertwine genetic factors, nutritional signals, and environmental determinants. The making of metabolic switches and acquiring food-seeking related behavioral patterns is the final combination to manage food intake.

work-up to maintain this during postnatal life [54]. Fetuses small for their age are usually dysmorphic, with small bodies compared to the proportion of their head (*brain sparing*) [55], low fat mass concentrations, and blunted response to hyperglycemia apparently from small  $\beta$ -cell ontogeny and mass [56].

Leptin can be detected as early as 17-week gestation [57], modulating adipose tissue development. Leptin acts as a *lipostat* in fetal life, giving information about fat maturity and proportions. In animal models—as in humans—fetal fat has brown and white adipose tissue characteristics, and it goes along with the very fundamental fact of being born with a matured hypothalamic-pituitary axis [58]. It is noteworthy to remark that adipose tissue grows in locules (uni and multiple), and there is always a dominant unilocular tissue

which correlates with leptin concentrations. These unilocular spots have peculiar (transitional) adipocytes with abundant mitochondria, uncoupling protein 1 (UCP1), and Prolactin receptor-long type that are brown tissue characteristics; yet they are capable of secreting leptin (white adipose tissue trait). Lipid synthesis is a very expensive process, using 39 MJ/kg (compared with carbohydrates which consumes 15–25 MJ/kg), and in the fetus this pathway depends on oxygen and metabolic substrates supply [58]. In light of this, if the mother modifies the amount of food and the quality of it, the proper maturation of fetal adipose tissue can be modulated. Indeed, several animal models have shown that maternal chronic hypoxia, hypoglycemia, and hypoinsulinemia are related to low levels of mRNA for leptin [59, 60].

Vickers et al. [61] published their findings on the fetal origins of hyperphagia and obesity using Virgin Wistar rats that were mated randomly and subsequently were divided into 2 groups: those with food restriction and those with food *ad libitum*. The pups born from the malnourished group were smaller at birth and had higher food intake in the immediate postnatal period, and this behaviour was enhanced with a hypercaloric diet. They concluded that hyperinsulinism and hyperleptinemia are responsible for fetal programming and adult hyperphagia, obesity, and high blood pressure. During that same year, Ekert et al. [62] reported that maternal nutrition during pregnancy in fact reprograms leptin secretion and this pattern is maintained even in adulthood. The research group used the pig model, whose mothers were fed a restricted diet during the whole pregnancy (whole pregnancy undernourishment), and half of these were then fed 35% more food during the second quarter of the pregnancy (a migestation malnutrition and late pregnancy recuperation). Leptin's expression was measured by determining mRNA of the protein in the subcutaneous adipose tissue of the mothers, reporting a negative correlation between birth weight and leptin levels

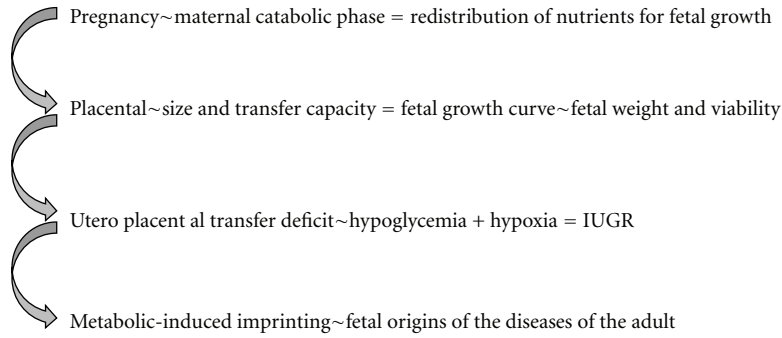


FIGURE 3: The intrauterine life is very delicate balance between fetal growth and placental transport capacity which depends on the mother’s vascular capacity. If the placenta is not fully developed (anomalous insertion, second wave invasion incomplete, or other maternal morbidity like long-term diabetes, hypertension or other related disease with vasculopathy), decreased blood flow through the umbilical cord will generate several survival responses in the fetus, all with the aim of reaching a viable weight and enough lung maturation to survive outside the womb. The mechanisms are energy-savers and try to protect the brain from damage. This metabolically induced imprinting lasts very well into adulthood, being the key feature in the development of chronic diseases like Obesity, Type 2 diabetes, Stroke, Cardiovascular disease, among others.

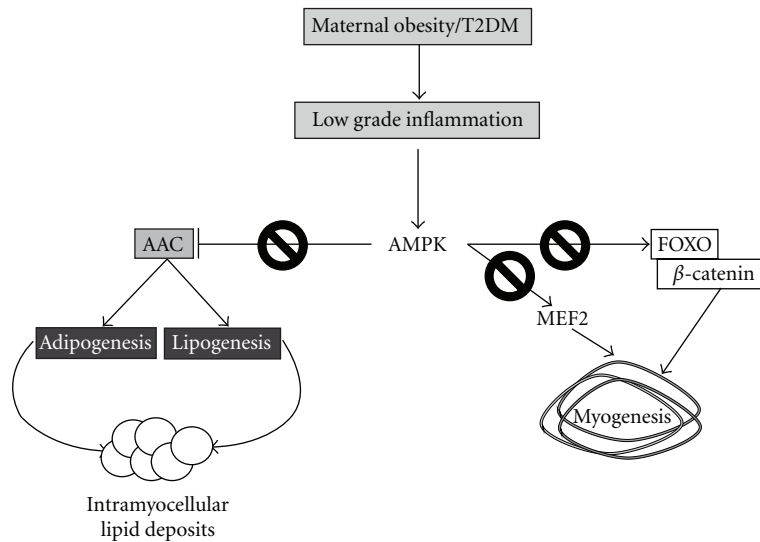


FIGURE 4: If the baby develops in a proinflammatory milieu, it is another study. The Barker hypothesis comes with an inflammatory component but it is basically aimed at the mother due to placental hypoxia (it is basically responsible for the hypertension and prothrombotic features of Preeclampsia). In the Macrosomic fetus low-grade inflammation takes its toll on AMPK activation, which due to its inhibition 2 basic pathways are modified. First, Acetyl~CoA loss of inhibition, which lets loose adipogenesis and lipogenesis with increased intramyocellular lipid deposits. Second, while preadipocyte is differentiated to mature adipocytes, myogenesis is being stalled due to loss of activation of expression of genes that regulate myocyte development. *FOXO*: nuclear transcription factor; *MEF2*: myocyte enhancer factor-2.

in subcutaneous fat; yet they were higher in the pigs born from mothers with late pregnancy recuperation suggesting that leptin is programmed in utero.

By 2001, Thomas et al. [63] used the ewe adolescent model to analyze the pattern of secretion of leptin during pregnancy. The ewes were subjected to a dietary regime from moderate to high, or high to moderate food intake. Leptin expression and protein were higher in those which were in the higher overfed group, suggesting that the produced leptin was a reflection of fat deposition in the mother due to over-feeding. Moreover, there was a negative correlation between maternal leptin levels and fetal and placental birth weight. In

the fetal sheep, leptin has been known to modulate energy-expensive processes like angiogenesis and hematopoiesis. It is expressed mostly in the brain and liver, but it can also be found in fetal skeletal muscle, kidney, and perirenal adipose depot. Mothers might have a negative correlation with fetal weight; yet neonatal leptin levels do have a positive correlation between birth weights in humans, and while maternal nutrition modification reduces serum leptin, it does not affect fetal concentrations [64]. These findings were confirmed by Mühlhäusler et al. [65], who analyzed the effect of nutrient intake on leptin levels in pregnant ewes during the second half of pregnancy. They reported that increasing

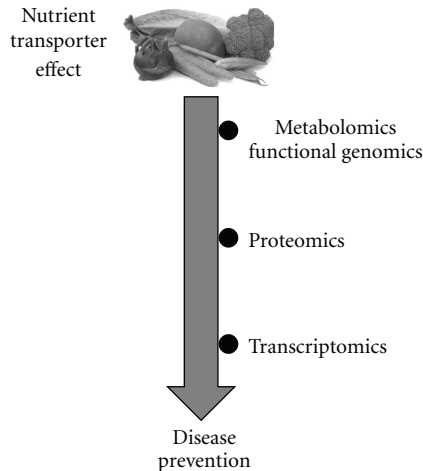


FIGURE 5: Nutrigenomics is a science that studies how food components exert their influence on metabolism pathways and manipulate genetic transcription, which can be used for disease prevention.

maternal food intake elevated glucose but not leptin levels; yet leptin was a good surrogate for fetal adiposity and poses as a moderator of endogenous energy expenditure in the fetus. Once more, in 2003 the same research team published [66] that a moderate increase in maternal and fetal supply modulates leptin and UCP1 expression, explained by the progressive capacity of the unilocular adipose mass to synthesize the proteins; these results propose that lipid storage capacity is established during the prenatal period of life.

Sheep models have been used to also evaluate the in utero programming of glucose metabolism. Gardner et al. [67] studied the effects of early and late malnutrition in sheep and evaluated its effects on glucose metabolism at 1 year of age in the offsprings of such animal subjects. The study concluded that late gestation undernutrition (50% less of requirements) influences glucose homeostasis, especially when the maximal fetal growth is being achieved. Perhaps one of the most interesting findings is that if the fetus was under malnourishment since the beginning, there was no significant alteration in insulin sensitivity or in glucose tolerance. Yet, those who starved during the second half of the pregnancy had reduced GLUT4 expression, suggesting that metabolic modifications are tissue-specific. The previous trial was conducted during late gestation showing nonsubstantial findings on early pregnancy interventions, but Ford et al. [68] published otherwise. This group reported that malnourishment from early to midgestation in sheep is related to increased body weight, fat deposition, and glucose dysregulation compared to its counterparts in adolescence. Another conclusion was the biphasic effect of undernutrition which associates with late gestation fetal and postnatal catch-up growth, all consistent with the thrifty phenotype and the accumulating data on fetal low-weightness in relation to the onset of Diabetes Mellitus, associated with a rise in

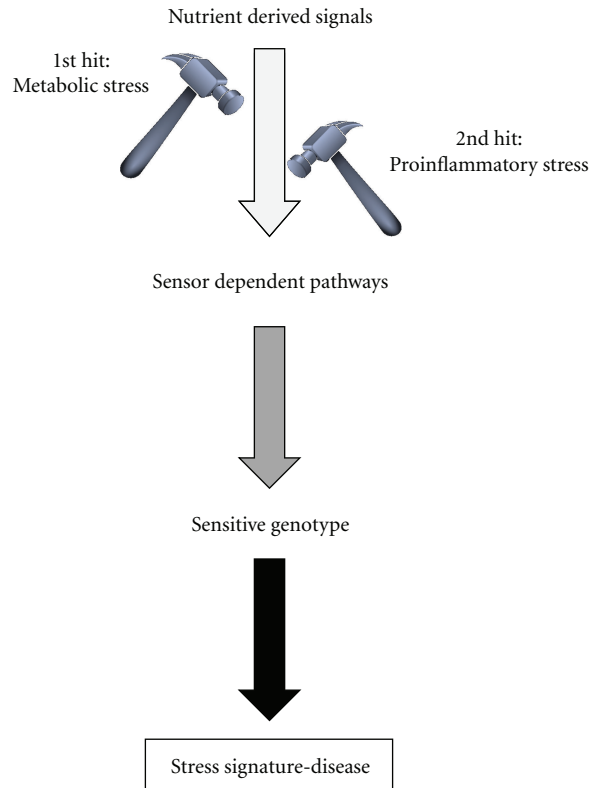


FIGURE 6: The basic idea with nutrigenomics is to determine a patient's polymorphisms and formulate a diet that ameliorates these genetic factors to minimum, regulating and maintaining weight loss.

the adipogenesis signaling cascade previous to the onset of obesity [68].

The epigenetics involved in the “Small Baby” model include methylation changes in fundamental genes which control  $\beta$ -cell ontogeny and functional differentiation [39–41, 69–72]. The Pancreatic and Duodenal Homeobox 1 (*Pdx1*) is a transcription factor which regulates the developing growth of the bud that will become the pancreas. This factor shows progressive declining of transcription in intrauterine growth retardation (IUGR), and it is associated with epigenetic regulation via histone methylation. The GTP cyclohydrolase 1 (*Gch1*) is part of the folate and biopterin biosynthesis pathways and has been positively related to endothelial dysfunction observed in diabetes. PDX1 is in charge of modulating the expression of fibroblast growth factor receptor 1 (*Fgfr1*) which is involved in glucose homeostasis. In IUGR this gene is upregulated and it is related to vessel malfunction and fibrosis of the pancreas. Finally, IUGR is associated with lengthening of  $\beta$ -cell cycle, decreasing the number of mitosis, contributing to insufficient insulin production in the postnatal life. Survival of the fittest fetus requires downregulation and shut-down of several stress and energy sensors in liver and skeletal muscle, which is advantageous during pregnancy, but has deleterious effects after birth, because nutrient sensing and insulin sensitivity are compromised [73].

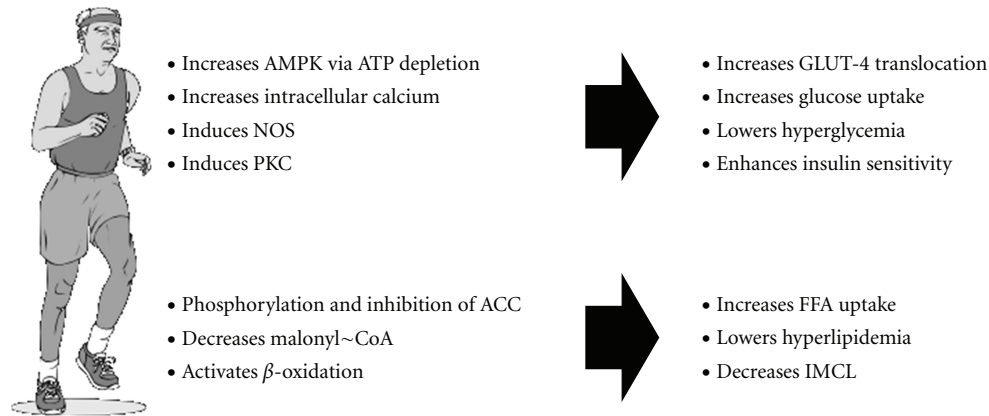


FIGURE 7: A few of the Metabolic benefits obtained through exercise.

On a final note, undernutrition in the fetus can alter the food network “wiring” providing the tools for metabolic disorders in the postnatal life. IUGR induces low levels of leptin, which is involved in the nerve fiber projecting towards the paraventricular nucleus from the POMC neuron population, which are the anorectic ones [74, 75]. On the contrary, maternal hypoxia and glucocorticoids exposure of the fetus enhances Neuropeptide Y (NPY) expression and secretion, having a role in fetal stress management and setting up the hypothalamus network to orexigenic signals [76, 77], especially since increased expression and release on NPY is maintained postnatally [78]. In simpler words, nutritional and hormonal factors may disturb the proper development of the hypothalamus and its subsequent function manifesting itself in eating habits-related disorders [79, 80].

There is another theory which was developed to explain the teratogenic ability of glucose—“*The Fuel-induced teratogenesis*”. Freinkel et al. [81] proposed that fuel in the form of hyperglycemia, is the very cause of diabetic embryopathy and fetopathy associated with fuel excess. Various clinical findings have proven this theory, especially in certain aboriginal population like the Pima Indians [82–85] and the Pacific Islanders [86–88] who have the highest prevalence of Gestational Diabetes and macrosomia. Overnutrition is known to enhance physiological and epigenetic effects of glucose, resulting in chronic hyperglycemia, hyperinsulinemia and hyperleptinemia [89]. Fuel-induced cases are associated with maternal obesity and/or diabetes rendering a specific metabolic profile: maternal hyperglycemia, hyperinsulinemia, and low-grade inflammation.

Since insulin cannot cross the placental barrier, glucose is the main secretagogue in the fetal pancreas circa the 27th weeks of gestation. Skeletal muscle development is crucial to adult life since it is responsible for the majority of glucose and fatty oxidation rates. Macrosomic newborns have visceromegaly and high amounts of adipose tissue, but scarce development of the skeletal muscle, especially type II fibers which are responsible for the energy production/aerobic capacities of the muscle. In a fuel-inducing environment there is a mismatch between myogenesis and adipogenesis, with chronic inflammation as the culprit

for this switch in differentiation [90–92] via inhibition of AMPK, downregulation of WNT pathways, and epigenetic modifications (see Figure 4).

**2.2. Reversal of Fortune.** Leptin has been considered the pivotal molecule according to animal and human analysis; yet its place was secured once it was proven that treatment with it reversed the developmental programming that occurs after maternal undernutrition during pregnancy [93]. Vickers et al. used 2.5  $\mu\text{g/g/day}$  of leptin on rat pups born from malnourished mothers, from day 3 to 13 of life, resulting in normalization of caloric intake, voluntary motor activity, body weight, glucose, insulin, and leptin levels, reversing the prenatal programming [93], which seems to be gender-specific and dependent of pre- and postnatal nutritional status [94]. Alimentary intervention trials have also proven to be effective in reducing and/or preventing the adverse outcomes of reprogramming, as it was shown by Wyrwoll et al. [95] by using  $\omega$ -3 fatty acids, and Zambrano et al. [96] by applying a dietary modification strategy prior to pregnancy.

In summary, the intrauterine environment is the key phase for acquiring the metabolic tools for surviving *inside the maternal womb*; the dilemma is what happens when the baby is born? Interestingly, these survival methods are not without risk for the unborn fetus, since each of the situations—IUGR and Macrosomia—carries a high risk for stillbirth and immediate neonatal death [97–99]; every change in the epigenetic make-up has a cost, and in the pediatrics world, it is a high one. Growth restricted babies are small for their gestational age, with small  $\beta$ -cell masses, hypoleptinemia, and showing signs of “*chronic hunger*”, while the Overfed fetuses are chubby, above the 90th weight for their age, with elevated degree of fatness and decreased muscle development. Both situations revolve around leptin levels and AMPK intracellular signaling networks.

### 3. First Arrow: Nutrigenomics

“*Nutrigenomics focuses on the effect of nutrients on the genome, proteome, and metabolome*” [100].

Diet and exercise are fundamental pillars in the treatment of overweight and obesity and related conditions such as insulin resistance, cardiovascular disease, cancer, among others. Several types of diets have been developed focusing on determining a favorable macronutrient composition in order to reach certain metabolic states that induce body weight loss; see Figure 5 [101]. Initially, diet recommendations implied low-fat, moderate-protein, and relatively high carbohydrate content diets, based on the fact that high-fat diets induce less satiety [102] and that a diminishment in diet fat consumption reduced significantly the risk of cardiovascular disease by lowering circulating lipids [103]. However, a paradoxical phenomenon was observed; subjects on this diet began to gain weight, instead of losing it, especially in Western countries.

In response to the lack of effectiveness of these nutritional recommendations, new dietary alternative schemes are being developed. Dr. Atkins is one of the pioneers of the widely popularized low-carbohydrate diets, with a low glycemic index and high-fiber content [104]. These diets induce rapid body weight loss, increased satiety [105], and an associated reduction of cardiovascular disease and diabetes risk [106]. However, there are only a few long-term and adequately randomized studies to recommend this type of diet [107, 108]. In the past decade, several studies have been carried out to analyze the effect of a high-protein content diet in weight loss, demonstrating body weight reduction along with a higher maintenance of this weight loss [109, 110]. Interest in the development of these types of diets largely derives from the theoretical effect that diet composition can have on energy consumption as well as on food consumption [111]. Studies on the physiological effects of dietary composition in human population turned out to be complicated because of lack of compliance of the diet as well as accurate reporting, which is why several animal models have been developed in order to determine the effects of diet on metabolism and are the main source of information on this topic.

Recognizing the central role of AMPK in controlling energy balance, as a sensor of cellular energy quantum [112] the following question is formulated: *What are the effects of dietary components on the activity of AMPK?*

**3.1. Lipids and AMPK.** Although the exact mechanism linked to this phenomenon remains unknown, there is substantial evidence that high-fat diet is a risk factor that promotes obesity development, glucose homeostasis alterations, and cardiovascular system disorders [113]. The main metabolic manifestations of this diet are elevated free fatty acids, decreased intracellular fatty acid oxidation, and lipid accumulation on insulin-targeted organs [114]. A high-fat diet is correlated with a decreased expression of mRNA for the AMPK- $\alpha 2$  isoform as well as AMPK phosphorylation with consequent decreased activity of this enzyme in skeletal muscle, leading to decreased glucose uptake, meanwhile in adipose tissue it promotes preadipocyte differentiation, lipolysis and the secretion of adipokines (TNF $\alpha$ ), perpetuating the process [115, 116].

AMPK has a crucial role in the hypothalamus' food intake control tower, constituting the signaling pathway of several hormones—including leptin—to regulate satiety. A high-fat diet induces hyperleptinemia which is associated with both peripheral and central leptin-resistance [117]. Reduced hypothalamic levels of leptin activity may be due, at least in part, to the constitutive alteration in the signaling pathway of AMPK. In the paraventricular nucleus of mice with diet-induced obesity, AMPK activity is constitutively diminished, and in the arcuate and medial nucleus of the hypothalamus leptin fails to suppress the activity of AMPK [118]. It has also been shown that long-chain fatty acid esters are able to inhibit AMPK kinase (AMPKK) and thus downregulate the signaling cascade of this pathway [119].

Eicosapentanoic Acid (C20:5  $\omega 3$ , EPA) and Docosahexanoic acid (C22:6  $\omega 3$ , DHA) exert prophylactic effects in cardiovascular disease, protect against insulin resistance and obesity in mice with high-fat diets, and improved insulin response in humans. The administration of polyunsaturated fatty acids has been shown to reduce the insulin resistance caused by high levels of saturated fats [120, 121]. Ingestion of diets rich in polyunsaturated fatty acids (PUFAs) has shown to suppress hepatic lipogenesis, lower TAG-rich lipoproteins synthesis in the liver, and increase fatty acid oxidation and induction of genes that regulate fatty acid oxidation (i.e., CPT1). A similar situation occurs in skeletal muscle where PUFAs increase thermogenesis, fatty acid oxidation, and glucose uptake. All these events are modulated by the action of AMPK [122, 123]. The mechanism by which PUFA may activate AMPK remains to be elucidated, but several hypotheses have been proposed such as an increase in the AMP/ATP ratio, decreased dephosphorylation of AMPK by control over the activity of protein phosphatase 2A (PP2A), or enhanced AMPK activity secondary to elevated plasma levels of adiponectin, IL-6, leptin and others [124, 125].

Conjugated linoleic acid (CLA), a group of linoleic acid isomer, has several physiological functions including anticancer properties, decreased atherosclerotic process, and modulation of the immune system [126, 127]. The CLA decreases the expression of AMPK- $\alpha 2$  and satiety and consequently decreases body weight [128].

Recent evidence suggests that short-chain fatty acids produced by fermentation of carbohydrates in the intestinal lumen could be absorbed and affect hepatic glucose metabolism [129]. The regulation of hepatic AMPK activity could play a critical role in this process; yet there is little data available on the effect of short-chain fatty acids on the activity of AMPK. In hepatocytes culture, acetate activates AMPK activity probably by increasing the rate AMP/ATP [130, 131]. Butyrate supplementation can prevent the development of insulin resistance in mice by promoting energy expenditure through the induction of mitochondrial function [132].

**3.2. Carbohydrates and AMPK.** The deleterious effect of a high-carbohydrate diet on health is well known. Using the current knowledge previously discussed here and the lack of effectiveness of low-fat diets, low-carbohydrate diets with



or without caloric restriction have been developed [133]. There is currently much interest in the potential role of foods glycemic index in the management of obesity and other metabolic disorders. It has been shown that foods with low glycemic index may be beneficial in regulating body weight in two ways: first by promoting satiety and secondly by increasing fatty acid oxidation, both explained by the action of AMPK [134]. However, a number of mechanisms that can be triggered by the glycemic index of foods consumed in the diet may explain the variability in the results of studies of weight loss using the glycemic index [135]. Glucose restriction provokes AMPK activation, resulting in the inhibition of anabolic processes which consume ATP such synthetic pathways for fatty acids, proteins, and cholesterol, and activation of catabolic processes which generate ATP to maintain cellular energy deposits like fatty acid and glucose oxidation [135].

AMPK regulates myogenesis and differentiation of skeletal muscle and preadipocyte differentiation into mature adipocytes, through SIRT1 (NAD-dependent deacetylase sirtuin-1 [*silent mating type information regulation 2 homolog 1*]) [136]. The loss of differentiation due to cellular starvation can be explained as a simple adaptation of a cell that is incapable to sustain the energy demanding activities that come with differentiation. Nevertheless, recent evidence suggests that there is a pathway activated in low-calorie cellular microambients, and it involves AMPK/Visfatin/SIRT1. Visfatin is a new adipokine which exerts insulin-like actions [137]. The pathway is characterized by AMPK-dependent—SIRT-mediated induction of Visfatin, resulting in elevation of the NAD<sup>+</sup>/NADH ratio, which induces genetic transcription shutdown [138, 139]. The beneficial effects of a low-carbohydrate diet have been observed in short-term trials, which warrant the need for long-term studies to fully evaluate and fully recommend this type of nutritional recommendation [140].

**3.3. Proteins and AMPK.** In the last 10 years, low-carbohydrate diets with high protein intake have become really popular. The evidence suggests that the main mechanism for its success is that high protein ingestion promotes weight loss by inducing thermogenesis and satiety [141]. Of course, it is not only the percentage of ingested protein but also the quality and aminoacid proportion which determines the loss-weight property [142, 143]. Proteins exert their effect in different manners, from the intestinal lumen with activation of chemoreceptors which respond to aminoacid/peptide presence releasing cholecystokinin (CCK), Glucagon-like peptide-1 (GLP-1), or peptide YY to a higher central level, modulating neurotransmitter release in middle cellular levels regulating AMPK activity [143, 144].

A high-protein diet is capable of controlling food intake due to enhanced POMC expression and repression of NPY in the hypothalamus, via activation of mTOR and low phosphorylation rates of AMPK [145, 146]. Leucine affects AMPK pathway by inhibiting it, and in doing so, it activates the mTOR signaling pathway. Intraventricular

injection of leucine in rats reduces food intake in a dose-dependent manner, and this effect is not observed with other aminoacids. Although this is true, weight reduction and food intake magnitude observe with the leucine treatment was similar to that achieved by a high-protein diet, which can explain why leucine is the most abundant aminoacid in most of the protein-rich formulated diets [146]. The exact mechanism for leucine AMPK-inhibiting activity is unknown; yet it probably relates to allosteric activation of the Glutamate Dehydrogenase (GDH) resulting in elevated substrate flux towards Krebs cycle (via glutamate conversion to  $\alpha$ -ketoglutarate), lowering AMP/ATP ratio, and reducing AMPK phosphorylation [147].

Alternative medicine has been a huge source of natural products now used in obesity and insulin resistance treatment, but the vast majority of the cases lack scientific evidence which can vouch for its efficiency and the mechanism of action is usually unknown. The bitter melon, *Momordica charantia* (Cucurbitaceae), is an Asian cultivated plant that is used as a herbal medicine and has gained fame for its hypoglycemic effects in animal models and humans [148]. Triterpenoids are the main constituent of the fruit but the active principle has not been found yet. In a recent study by Tan et al. [149], they reported that curbitanetriterpenoids (*Mormodicoside S*, and *karavilosede XI*) are capable of stimulating AMPK activity, favoring GLUT4 translocation, weight loss, and metabolic control. The Phytoalexin resveratrol (*trans*-resveratrol) is naturally produced by bacteria or some fungi species. This polyphenol is capable of enhancing AMPK, SIRT1, and Peroxisome proliferator activated-receptor gamma coactivator 1- $\alpha$  (PGC1- $\alpha$ ), reducing Insulin-like growth factor 1 levels enhancing insulin sensitivity [150, 151]. Berberine is an alkaloid found in a plant cultivated in Asia, used mainly in Korea and China for several diseases including diabetes treatment in humans [152]. Berberine acutely stimulates AMPK in myocytes and adipocytes, inducing GLUT4 translocation and lowering fat storage in adipose tissue. This substance also decreases the differentiation rate of preadipocytes by PPAR $\gamma$  by p38<sup>MAPK</sup> phosphorylation, whose activity seems to be enhanced by berberine [153, 154].

There is no doubt that nutrition is fundamental to obesity development and other major chronic diseases like CVD and T2DM, and this is especially true in the pediatric population where scientists have seen a rise in caloric ingestion based on saturated fat and cholesterol with associated low energy expenditure. Several diet regimes have been devised; yet there are not enough trials to validate them [155, 156]. It is extremely necessary to design and undertake randomized trials to evaluate the nutrigenomic properties of food and apply them to individualized diets [157]; see Figure 6.

#### 4. Second Arrow: Metformin

Even though there is growing evidence published every day concerning childhood obesity, the use of pharmacological treatment in them is still in controversy. The complexity

of this disease has delayed data gathering, most of which is extrapolated—not without difficulty—from large general population trials. It is noteworthy to add that there is no magical drug for weight loss, and most of the guidelines recommend pharmacological treatment after lifestyle modification and diet regime have failed to meet the primary goals, and that implementation of drug therapy has to be accompanied by diet and exercise [158, 159].

There are only 2 drugs FDA (Food and Drugs Administration) approved for obesity treatment in the pediatric population: Orlistat and Sibutramine [160]. Orlistat is a gastric and pancreatic lipase inhibitor, which lowers fat absorption favoring weight loss. Small pilot studies were undertaken in children and adolescents, measuring its safety and tolerability. This drug was approved by the FDA in 2003 as treatment for obesity in children beyond 12 years of ages [161, 162]. On the other hand, Sibutramine is a serotonin-norepinephrine-dopamine reuptake inhibitor, which induces weight loss via appetite suppression, which is FDA approved for adolescents above 16 years old [163, 164]. Metformin is a molecule widely used in the treatment of T2DM in children above 10 years old. The drug's mechanism of action is still partially understood; yet in 2001 there was a major breakthrough when Zhou et al. [165] observed that AMPK plays a fundamental role in this puzzle. Since neither Orlistat nor Sibutramine modulates AMPK, we will analyze the weight reduction effect of metformin applied to obese children and adolescents.

As was mentioned previously, metformin is used in T2DM due to its insulin sensitizing effects, which are efficient in the treatment of Polycystic Ovary Syndrome, T2DM, and Hepatic Steatosis. These applications have revealed that patients obtain and maintain weight reduction, making the science community take a closer look at metformin and its influence in appetite control [166, 167]. Freemark and Bursey [168] was one of the first researchers to acknowledge metformin's efficiency on weight loss in a double-blind case-controlled trial with 29 adolescents who had fasting hyperinsulinemia and T2DM family history, using 500 mgs twice a day versus placebo tablets for a period of 6 months. The study reported a 0,12 decrease SD in BMI, while there was an increase Standard Deviation (SD) of 0,23 in the placebo group. Similar findings were published by Srinivasan et al. [169] who conducted a randomized controlled trial comparing metformin (1 gram twice a day) versus placebo in 28 obese patients between 9–18 years old. The metformin group had the highest reduction in BMI ( $-1.26 \text{ Kg/m}^2$ ), in weight ( $-4.35 \text{ kg}$ ), waist circumference ( $-2.8 \text{ cms}$ ), and in fasting insulin levels ( $-2.2 \text{ mU/L}$ ). In 2008, Burgert et al. [170] published their results on the cardiometabolic benefits of metformin in 28 morbidly obese adolescents patients, who were randomized and divided into 2 groups, one receiving metformin 1,500 mgs daily ( $n = 15$ ), and the placebo group for 4 months. The placebo group had elevation of BMI ( $1.1 \text{ kg/m}^2$ ); meanwhile, the treatment group had reduction in this criteria ( $-0.9 \text{ kg/m}^2$ ). Compared with placebo, the metformin group had enhanced insulin sensitivity, subcutaneous (but not visceral) fat reduction—data which dissents from the one reported by

Srinivasan—and obtained cardiovascular function improvement.

Love-Osborne et al. [171] investigated the effects of metformin in a lifestyle modification program in insulin resistant adolescents. This was a randomized, controlled double-blind trial with 85 obese adolescents with insulin resistance who were divided into 2 groups, placebo and treatment group who received 850 mgs twice a day. The patients who finished the study and who maintained the treatment had the highest BMI reduction, with an estimated BMI reduction of 5% or more. Casteels et al. [172] studied 42 obese teenagers with motor deficit who had low physical fitness and elevated body fat. This study was conducted to analyze metformin's weight control properties compared to placebo. Six months of therapy offered weight and BMI reduction, due to lower visceral fat. Finally, earlier this year The Glaser Pediatric Research Network Obesity Study Group [173] did a 48-week Metformin Extended Release (1 gram twice a day) trial in 77 obese adolescents (13–18 years old), concluding that the drug caused significant BMI reduction, and this effect lasted after 12–24 weeks of treatment cessation.

Even though the studies are promising, they have the disadvantage of being conducted with small patient samples for short periods of time. In this matter, the REACH-Activity and Metformin Intervention in Obese Adolescents study is underway [174], applying a 2-year protocol with metformin (1,500 grams daily) and with physical activity. The recruitment is focused on obese patients between 10–16 years old alongside their parents, which will be randomly controlled and assigned drug or placebo. The preliminary results are expected in the end of 2010 with the complete results of this intervention to be published in 2012.

## 5. Third Arrow: Physical Activity/Exercise

Perhaps the grayest area in childhood obesity is how much is enough physical activity in the child and adolescent because several factors are at play here: age, gender, geography and seasoning, race, psychological factors, ecological factors, sociocultural determinants, and school activities, among others [175]. Physical activity in the pediatrics population is not only beneficial to cardiometabolic health, but it also serves as a psychological tool to improve behavioral well-being and lower the incidence of drugs, smoking, early sexual activity, and other problematic habits, shaping the lifestyle pattern the child will have as a grown adult. Overweight children and adolescents are prone to acquire risk factors associated with CVD, are likely to become obese adults, predisposed to inappropriate dieting practices like anorexia or bulimia, physical inactivity, alcohol, and tobacco use, have obesity-related health issues like asthma, sleep apnea, T2DM and nonalcoholic hepatic steatosis, and finally, are at high risk for long-term chronic disease, like stroke, cancer, and gall bladder disease [176].

Physical activity can be defined as any movement produced by the skeletal muscles which ends in energy consumption and can be measured in kilocalories [177].

Another definition is any daily activity of at least 30 minutes (occupational, leisure, home-related), which can be vigorous or moderate, planned or unplanned, and is inserted in the daily lifestyle of the subject [178]. Exercise is immersed in the concept of physical activity, and the difference between them relies in the very fact that exercise has a physical fitness purpose [177, 178]. How much or what type of exercise can be recommended for the patients is still in controversy, since it depends on comorbidities, age, psychological status, and aerobic capacity [179].

**5.1. Growing Up.** One of the main issues about pediatric obesity is the age of appearance and growth sprouts throughout adolescence until adulthood. We have already discussed the intrauterine milieu in previous sections, and 3 outcomes can be concluded: the growth restricted, a normal weight, and the macrosomic newborns. The small baby and the big baby are at high risk for early infant growth which is associated with subsequent obesity in adulthood [180]. In babies fed with milk-formulas, rapid weight gain during the first weeks of life is determinant for obesity several decades later [181]; meanwhile breast-fed babies are inversely correlated with adult obesity regardless of the mother's weight or glucose tolerance, highlighting the protective effect of breast milk [182]. BMI increases steadily and rapidly as the baby grows into a toddler and towards infancy reaching a minimum plateau at around 5–6 years of age, which is denominated *BMI rebound* (or adiposity rebound (AR)). Several studies have linked early rebound to increase risk of obesity in later life [183–186], especially in children who were tall at 3 years of age [187]. The third critical period phase is adolescence, which is elementary to determine the probability of adult obesity. During this phase, gender takes its toll in risk assessment, and girls are in a bit more danger than the boys to become obese, since sexual maturation comes with fat increase. Around 80% overweight adolescents will become obese adults, and in light of this data, intervention measures must be installed.

Adiposity rebound has gathered a fair amount of attention since the mid 80s when the first associations were made with obesity [188]. The phenotype of early rebounders is characterized by different velocities for height and weight gaining, varying in each child, with basic features as advanced bone age [189], early menarche [190], and later obesity [191]. Whitaker et al. [192] conducted a retrospective cohort study with 390 patients and their parents, reporting that the mean age for AR was 5,5 years, and by adulthood, 15% of the subjects were obese—with higher rates in those who were earlier and heavier rebounders and those who had heavier parents. The following year, Eriksson et al. [193] published that the highest death rates occurred in boys who were SGA at birth but had an early catch-up phase with normal or above average rates when compared to normal counterparts. Later, Velasquez-Mieyer et al. [194] undertook a cohort study analyzing 25 risk factors for AR, determining that 8 were the most prevalent among 909 subjects from Great Britain: parental obesity, very early AR (by 43 months), more than 8 hours spent watching

television per week at the age of 3, presence of catch-up growth, weight gain during the first year, birth weight, short sleep duration at age 3, and standard deviation score at age 8 and 18 months. These features are in agreement with factors used to identify high-risk youngsters, as published by Velasquez-Mieyer et al. [194]: placental insufficiency, gestational diabetes, maternal overweight/obesity and weight gain during pregnancy, SGA, LGA, infant overnutrition, bottle feeding, drug induced weight gain, early AR, and overweightness during adolescence.

Yet, the question rises, during which phase must intervention be applied? Several studies have proven that BMI rebound is in fact the most critical and determinant phase of the 3, and measures should be taken to improve adiposity in this children [187, 189, 192, 195–197], since early intervention is the best option to void adolescence obesity, and later adult obesity. According to the Physical Activity and Health CDC report [198] all people above 2 years of age should do at least 3 minutes of endurance-type of physical activity, at least of moderate intensity, preferably every day of the week. The problem in this statement is that children below 6 years old might not comprehend the object of physical activity; so planned sequential exercise should be substituted with programmed school activities which guarantee moderate activity for over 30 minutes. Young children are not physically adept to be subjected to adolescent or adult physical activity regimes; therefore the guidelines must be developed in accordance with this fact. The Framingham Children' Study [199–201] revealed several aspects that need to be addressed during this period: parental involvement in the physical activities and nutritional intervention, elevated TV viewing time, and nutrient tracking.

**5.2. The Benefits of AMPK.** Exercise has several advantageous properties which makes it appropriate to include it in the day-to-day life of a high-risk child/adolescent. The primary effects of exercise include enhanced GLUT4 translocation via insulin-independent pathways which include Nitric Oxide synthesis and AMPK activation (see Figure 7). AMPK is activated via phosphorylation of Thr<sup>172</sup> by AMPK kinase or Calmodulin dependent kinase (CaMKK). Once this enzyme is activated, it phosphorylates atypical Protein Kinase C (PKC) which stimulates phosphatase that will act upon IRS1, leaving the insulin pathway unopposed to induce Akt and glucose transporter translocation. Moreover, AMPK induces the expression of GLUT4 gene through MEFA2A and MEFA2D (factor 2a myocyte enhancer). During AMPK activation, it will inhibit AcetylCo~ACarboxilase 2 (ACC2), lowering Malonyl~CoA concentrations, spiking  $\beta$ -oxidation of fatty acids [202].

It has also been suggested that exercise exerts anti-inflammatory effects which are effective in aiding the low-grade inflammation that characterizes adult obesity [203], and it is not different in childhood/adolescent obesity [204, 205]. Weiss et al. [206] published that adiponectin inversely correlates with C-Reactive Protein (CRP) levels, while the latter and IL-6 were in direct relation to BMI. In children

between 8–16 year olds, being overweight is associated with elevated white blood count and CRP suggesting low-grade inflammation in these children [164]. Hypoadiponectinemia has been independently associated with metabolic syndrome in teenagers, which has upgraded adiponectin to a high CVD risk [207, 208], alongside with IL-6, and IL-18 [209–211]. When skeletal muscles exercise, they release a 100-fold of IL-6, with a concomitant release of IL-10 and IL-1 receptor antagonist [212, 213], serving as powerful immune modulators that interfere with the meta-inflammation that characterizes obesity.

## 6. Conclusions and Recommendations

Obesity in the pediatrics population has been a major public concern since the late 1970s [214]. Several steps have been taken to undermine the situation, but somehow it has gotten out of hand [215]. The Healthy People Program has a primary goal 5% or less prevalence of obesity in children and adolescents, increases school nutrition education, and increases the number (>75%) of primary care providers who are able to handle overweight reduction services [216]. Behavioral and motivational interventions have to go together with any of the primary tools: diet, exercise, and/or drug. The sticking to the program depends highly on this aspect, since children and adolescents are susceptible of depression, anxiety, impaired family functioning, poor psychological adaptation, and eating disorders behavior [216–218].

Understanding the etiology of a disease is the best way to conquer it: attacking key points in the natural history will help eliminate the progression of the disease. In this light it has been proposed that BMI rebound is the key aspect in high-risk children; nevertheless, the other two stages (prenatal and adolescent) are still important; yet the prenatal state depends on the mother's condition and comorbidities, while the adolescence phase is modulated by sexual hormones which will inevitably take its toll. So, success at halting obesity will be achieved with early interventions during infancy. School-associated programs for physical activity seem to be gaining popularity because they have been shown to reduce weight gain, visceral adipose tissue, and reduces remission of obesity [219–221]. Mallare et al. [222] recommended physical activity of 30–60-minute duration a day and lowering sedentary activities to less than 2 hours a day.

In the era of the “omics”, each treatment has to be individualized as much as possible, since each patient is a new case. A full history chart and complete blood and anthropometrical work-up will help to assess the main factors involved in the progression of the disease. Nevertheless, AMPK seems to be involved in virtually every aspect of the disease, serving a pivotal role. There is little doubt that common obesity is a multifactorial disease, and targeting the major intracellular components will benefit weight loss management and continuum of the program. More studies are needed to fully approve the use of Metformin as a weight-loss drug, like Orlistat and Sibutramine; yet its

pharmacological properties make it the drug of choice in obesity treatment. A nutri-genomically guided diet will aid in the reorganization of the cellular energy status, and exercise will enhance glucose uptake and lipid oxidation, improving the metabolic profile of these youngsters.

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