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Leptin as a Potential Biomarker for Childhood Obesity

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Received: February 20, 2017; **Published:** February 23, 2017

Abstract

Background: Leptin is a hormone that is crucial to appetite and weight control. It is a cell-signaling hormone vital in the regulation of appetite, food intake and body weight.

Methods: Scientific databases search in MEDLINE (PubMed search from 1994 to 2016), for researches studying the relationship between leptin and pediatric obesity as well as the impact of exercise intervention programmes on leptin concentrations. 65 studies have met the inclusion criteria, 12 of which were detailed.

Results: The present review demonstrated that leptin directly interacts with the hypothalamus for energy balance regulation and the measurement of free, bound and total leptin and soluble leptin receptor concentration play a key role in the understanding of obesity in pediatrics which is crucial for determining intervention programme responsiveness in pediatric obesity.

Conclusion: Leptin plays a key role as a biomarker for childhood obesity since considerable evidence showed that leptin operates directly with the hypothalamus for energy balance regulation. Leptin can help in the prediction of weight gain in obese children as well as its important interrelationship with other parameters, such as insulin, lipoproteins, exercise, and growth hormone.

Keywords: *child; control; obesity; prevention; systematic review; Lifestyle; intervention*

Introduction

Childhood obesity is a major public health crisis nationally and internationally. The prevalence of childhood obesity has increased over few years. It is caused by imbalance between calorie intake and calories utilized. One or more factors (genetic, behavioral, and environmental) cause obesity in children [1]. Childhood obesity is primarily a result of energy imbalance, whereby ingested calories exceed energy expended [2]. Obesity has a central role in metabolic syndrome [3]. 'Metabolic syndrome' is characterized by a clustering of

metabolic abnormalities which leads to increased cardiovascular disease and all-causes mortality. The five generally accepted features of metabolic syndrome are obesity, insulin resistance, dyslipidemia [including increased triglycerides and decreased HDL], impaired glucose tolerance, and hypertension [4].

Lifetime eating and physical activity habits are commonly developed in childhood. Recognizing this, it is important to acquire insight into adiposity and energy balance regulation during this period of development [5].

The rise in childhood obesity dictates that early intervention becomes a priority due to the significant acute and future chronic health consequences. Obesity can affect the child's physical, emotional and social maturity and ultimately can lead to serious health concerns and early mortality, whether or not the child remains obese as an adult [6-8]. Identification and validation of novel biomarkers for detecting children who may be at risk of being overweight or obese is of paramount importance. The discovery of the gene associated with obesity, the ob gene, and its protein leptin provided the first physiological evidence of a regulatory system controlling body weight. Since its discovery, leptin has been reported to function within the long-term energy balance system and it regulates fat and glucose metabolism [9].

Leptin, the product of the ob gene, is a single-chain proteohormone produced by adipose tissue, but also by placenta (syncytiotrophoblasts), ovaries, skeletal muscle, stomach, mammary epithelial cells, bone marrow, pituitary, and liver, with multiple functions through various receptors located centrally and peripherally [10]. Centrally, leptin acts particularly on the hypothalamus to suppress food intake and stimulate energy expenditure [11]. Leptin receptors belong to the cytokine class I receptor family [12] and are found all over the body [13], indicating a general role of leptin. A circulating form of the leptin receptor exists, which acts as one of several leptin-binding proteins [14]. Several alternatively spliced isoforms of the leptin receptor have been identified (Ob-Ra, Ob-Rb, Ob-Rc, Ob-Rd, and Ob-Re) [15].

Biochemistry of Leptin

Leptin, or OB protein, is a unique protein in that it has no strong sequence similarity with any other protein, so it is difficult to make a model structure as other known structures cannot be used as references. Luckily, through the use of a mutagenic form of leptin which has a substitution of Glu for Trp at position 100, an accurate model of the crystalline structure could be derived. It contains four anti-parallel α-helices that connected by two crossover links, along with one short loop [16]. These are arranged in a left-hand twisted helical bundle, in which, a large hydrophobic core is parallel to the helical bundle that is formed from the conserved residues of the four α-helices that face each other. Specifically, the four α-helices (A, B, C, D) are composed from the following residues in the 146 sequence: A, Pro 2-His 26; B, Leu51-Ser67; C, Arg71-Lys94; D, Ser 120-Ser 143. The last residues in the sequence make a kinked helix off of helix D. These helices are very super-imposable, which allow them to join to their receptor in a signal transduction pathway. OB protein, or leptin, also has a disulphide bond between the Cys 96 and Cys 146 residue and connects the last turn of the D α-helix to a loop that extends from the C to D helix. The only β-strand identified is in residues 47–50, though no connections are able to be identified to connect it to any other strand, so it is unlikely that any β-sheets exists in the OB protein [17].

The leptin receptor, also known as LEP-R, is a production of the db gene and is a member of the cytokine receptor family. Out of six different LEP-R isoforms, only one of these forms, OB-Rb, is fully functional in a signal pathway. Each isoform has identical extracellular and trans-membrane domain. The extracellular domain of the leptin receptor has two cytokine resembling binding sites. Another form of the leptin, receptor OB-Re, does not play a direct role in leptin signaling but is likely important in determining the amount of leptin that is present in the bloodstream. It is important for leptin action to only have certain amounts of free in circulation and another proportion of leptin to be bound to its receptor on cell membranes for the signal pathway to occur [18]. The main transduction pathway of leptin is the JAK/STAT, and is the major transduction signal pathway leptin uses to exert its effects. While leptin is also used in other pathways, like AMPK and insulin signaling, the JAK/STAT pathway will be concentrated on [19].

The JAK/STAT pathway, as shown in Figure 1 [64], has a critical role in mediating the effects of many other cytokines besides leptin as well as other growth factors. JAK is the shortened name for Janus kinase, and STAT is short for signal transducer and activator of transcription. JAK/STAT takes chemical signal information from outside the cell, has the signals sent through the cell membrane, and then has the

signals put into the cell nucleus where they are added onto gene promoters in the DNA. This causes DNA transcription and cell activity. Receptors of leptin have no intrinsic tyrosine kinase activity, and depend on kinases, like JAK, for certain cell signal pathways to take place. Ligand binding to OB-Rb activates JAKs by causing them to combine and phosphorylate each other. With leptin, the OB-Rb form reacts and has its tyrosine phosphorylated. Therefore, the leptin receptor uses the JAK complexes in order to phosphorylate themselves as well as certain proteins in the STAT complex. The produced transcription factors from STAT are used by activated OB-Rb/JAK complexes to cause certain factor proteins to become active with the tyrosine phosphorylation. Activation of these factors causes them to dissociate from the OB-Rb and make dimers that move into the nucleus. These hetero-dimers interact with specific DNA elements in the promoter sequences of target genes to regulate gene expression [19].

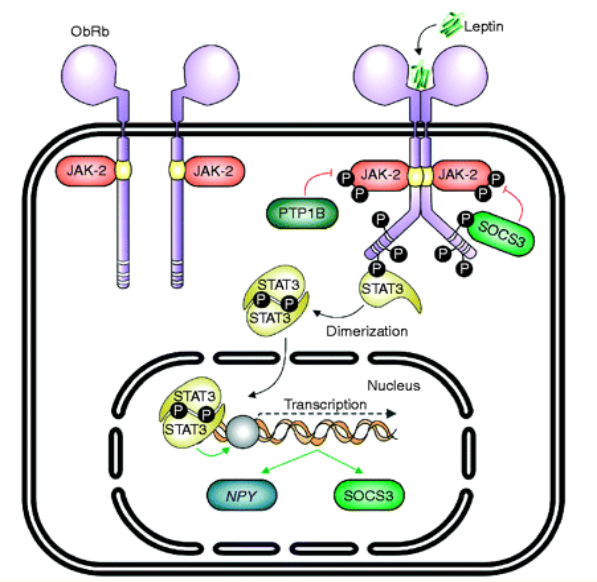

Figure 1: *Leptin binding to its receptor activates the associated JAK-2 tyrosine kinase, which subsequently phosphorylates intracellular tyrosine residues of the receptor. This leads to the activation of STAT3, which dimerizes and migrates to the nucleus, where it works as a transcription factor, promoting the expression of genes like neuropeptide Y (NPY). STAT3 also induces the expression of SOCS3, a protein that acts as a negative regulator of the JAK/STAT pathway. Likewise, PTP1B is another protein that negatively regulates the JAK/STAT route [64].*

The soluble leptin receptor

Higher sOb-R concentrations are found in lean compared to obese individuals [19]. Two recent studies postulated that when leptin binds to the sOb-R, there may be a delay in leptin clearance and degradation from circulation and this increases the concentration of available circulating leptin [20,21]. It is important to remember that bound drugs or hormones, in this case sOb-R bound to leptin, are pharmacologically or physiologically inactive; only free leptin can act on target sites to elicit biological responses [22]. When leptin is bound, it is prevented from being degraded and cleared from the body. Suppression of leptin action or partial peripheral leptin resistance, as found in common obesity, has been postulated to occur when there is a two-fold or greater increase of sOb-R [20]. This supports the pharmacological principle of sOb-R acting as a potential reservoir or sink for bioactive leptin in humans. When sOb-R concentrations decrease, there would be higher concentrations of liberated leptin and an overall higher than normal circulating leptin concentration with obesity. This results in the significantly elevated leptin to sOb-R ratio seen in obese individuals [15]. Consequently, leptin circulates mainly in its bound form in lean individuals, yet mainly in its free form in obese individuals [20,23]. The low sOb-R concentration found in obesity

may be related to a stabilizing feedback mechanism trying to reduce the escalating leptin concentrations [15]. Free and receptor-bound leptin heritability in twin studies has been examined. Jordan., *et al*. [24] showed that there is a strong heritability influence for the Ob-R and bound leptin and only a weak genetic influence for free leptin; however, dominance or recessive genetics were not assessed. Additionally, free leptin concentrations were positively correlated with AA Venner., *et al.* / Clinical Biochemistry 39 (2006) 1047–1056 1049 BMI and fat mass, yet sOb-R and bound leptin concentrations were negatively correlated to BMI and fat mass [24,25]. This supports the notion that free and bound leptin concentrations have different and not entirely understood regulatory mechanisms. Additional monozygotic and dizygotic twin studies have examined the general genetic influence on leptin concentrations [26,27]. Although leptin concentrations initially showed genetic influence, this was no longer evident following BMI adjustment. It is possible that free leptin concentrations are secondary to body weight gene effects. Leptin, sOb-R concentrations and the ratio of sOb-R and leptin change during child and adolescent development [68]. Specifically, there are higher sOb-R concentrations compared to leptin concentrations in children [61]. In addition, obese children have higher leptin, but lower sOb-R concentrations relative to lean controls [28,29]. A decrease in sOb-R concentrations could indicate a decrease in functional Ob-R and be a sign for leptin resistance [15,28]. Leptin resistance in obese children has been postulated by Cinaz., *et al.* [29] to be a defect of sOb-R production. Furthermore, sOb-R concentrations have been found to increase and stabilize in obese children when they have a significant reduction in weight, relative to children with little weight loss [30]. Reinehr., *et al.* proposes that because of this stabilization in sOb-R, these concentration changes are the consequence, rather than the cause, of obesity. The low sOb-R concentrations in morbidly obese individuals are actually a sign of decreased functional leptin receptors, which would support the theory of leptin resistance in this population.

Leptin mediation

It appears that leptin acts as a "satiety signal" to prevent obesity in times of energy excess, and as a "starvation signal" to maintain adequate fat stores for survival during times of energy deficit. Data suggest that the leptin system may be more efficient in signaling a decrease in fat mass and lack of nutrients (low leptin state) and triggering a compensatory increase in food intake and a decrease in energy expenditure than as a satiety signal when its serum levels are elevated. In addition, recent evidence suggests that the neurobiology of leptin signaling in obesity appears to involve central leptin insufficiency, as opposed to the previously postulated notion of leptin resistance [31,32].

The arcuate nucleus (ARC), ventromedial (VMH), dorsomedial (DMH), and lateral (LH) hypothalamic nuclei are important regions regulating food intake and energy expenditure. Disrupting lesions in the ARC, VMH, and DMH of rats resulted in hyperphagia and obesity. Besides, lesions in the LH result in decreased food intake. Binding of leptin to its hypothalamic receptors activates a signaling cascade in the ARC that results in inhibition of orexigenic pathways as indicated by decreased mRNA expression of neuropeptide Y (NPY) and agouti-related peptide (AgRP), and stimulation of anorexigenic pathways as suggested by increases in the mRNA levels of alpha-melanocyte-stimulating hormone (α-MSH) and cocaine and amphetamine regulated transcript (CART). Activation of POMC/CART-expressing neurons by leptin results in release of α-MSH, which subsequently binds to melanocotin receptors (MCRs) and leads to anorexia and increased energy expenditure. At the same time, leptin inhibits NPY/AgRP neurons, which stimulate orexigenic responses and directly inhibits POMC neuron expression as indicated by POMC mRNA expression [32,33].

Recent data in mice show that leptin acts solely in the hypothalamus to control glucose homeostasis independent of its effects on appetite, by increasing non-thermogenic energy expenditure and glucose disposal in peripheral tissues by action on POMC neurons [34].

In humans, decreasing leptin concentrations in response to food deprivation are responsible for the starvation-induced suppression of the hypothalamic-pituitary-gonadal axes as well as the malfunction of several other neuroendocrine axes [32]. It seems that leptin may act as the link between adipose tissue, hypothalamic centers regulating energy homeostasis, and the reproductive system.

The human placenta express the leptin and leptin receptor gene implying that it is a site production of the hormone as well as a target of its action (autocrine effect). During pregnancy, leptin production by the fetus and the placenta can signal fetal nutrient status. It may also provide a mechanism whereby maternal fuel reserves are more readily mobilized, favoring utilization by the fetus rather than build-

ing maternal reserves. In the case where maternal leptin concentrations are low owing to limiting nutrition, the proportional importance of fetal and placental leptin in mobilizing fuel for use by the fetus may be greater [35]. Neonatal leptin levels are higher in females and are associated with adiposity, and are independently correlationed with newborn length, IGF-I levels and formula feeding. Leptin clearly plays an important role in neonatal energy homeostasis and metabolism [36].

Synthesis of leptin is also modulated by several hormonal variables. Stimulators include insulin, catecholamines, and glucocorticoids [37]. Studies demonstrated that meals and insulin acutely affect leptin concentrations [38]. Suppressors include fasting, cAMP, and β3-adrenoreceptor agonists [39]. It has been demonstrated that leptin production occurs after increases in insulin in response to feeding, and a decrease in leptin concentrations follows decreases in insulin during fasting (Table 1).

Conditions with increased leptin secretion	Conditions with decreased leptin secretion
Obesity	Congenital leptin deficiency
Overfeeding	Lipodystrophy
Emotional Stress	Protein energy malnutrition
Chronic hepatitis-cirrhosis	Short-term fasting (24-72h)
Congestive heart failure	Sleep deprivation
Rheumatoid arthritis	Physical exercise training
Insulin	Testosterone
Estrogen	Growth Hormone
Glucocorticoids	
TNF-alpha	

Table 1: *Conditions with Changes of Serum Leptin Concentrations.*

Clinical significance of leptin in Obesity, Linear Growth, and Insulin Resistance Syndrome

In the majority of obese individuals, serum leptin concentrations are increased [40], and leptin administration shows only very limited effects [41] due to leptin resistance. Low soluble receptor concentrations and a high fraction of free to bound leptin are markers of leptin resistance. Leptin resistance is associated with insulin resistance and abdominal obesity and constitutes an additional component of the metabolic syndrome [42]. When free-leptin concentrations are compared between lean and obese individuals, even more pronounced hyperleptinemia in obesity is observed than that reported by measuring total leptin concentrations. Recent evidence suggests that the neurobiology of leptin signaling in obesity appears to involve central leptin insufficiency, as opposed to the previously postulated notion of leptin resistance [31,32].

Apart from leptin's mandatory regulatory role in energy intake and expenditure, independent participation of leptin in the hypothalamic integration of insulin–glucose homeostasis has been documented. Various lines of evidence show that (a) under the direction of leptin two independent relays emanating from the hypothalamus restrain insulin secretion from the pancreas and mobilize peripheral organs---liver, skeletal muscle and brown adipose tissue---to upregulate glucose disposal, and (b) leptin insufficiency in the hypothalamus produced by either leptinopenia or restriction of leptin transport across the blood brain barrier due to hyperleptinemia of obesity initiates antecedent pathophysiological sequalae of diabetes type 1 and 2. The efficacy and preclinical safety of leptin replenishment in vivo, especially by supplying it to the hypothalamus with the aid of gene therapy, in preventing the antecedent pathophysiological sequalae---hyperinsulinemia, insulin resistance and hyperglycemia---in various animal models and clinical paradigms of diabetes type 1 and 2 with or without attendant obesity have been documented [31,43].

The role and Implication of Leptin on Childhood Obesity

During the phase of normal or accelerated height velocity in obese children, plasma GH levels remain low and measurements performed during sleep and following pharmacological stimulation as well as spontaneous 24h of GH secretion are reduced [44,45]. Despite the reduction in GH levels, obese children may have normal, increased or reduced, plasma IGF-I and GH-binding protein levels [46]. The mechanism whereby obese children continue to grow despite the low levels of GH is not known. Several explanations have been postulated [46,47]. Maor., *et al*. [48] reported the presence of leptin receptors in growth plates. Leptin induces both proliferation and differentiation of chondrocytes. It stimulates the width of the proliferative zone of the epiphysial growth plate and increases the expression of chondroitin sulfate within the cartilaginous matrix. Apparently, leptin acts as a direct skeletal growth factor in obese children. It is suggested that in humans, obesity is associated with differential sensitivity to circulating leptin with central resistance and peripheral sensitivity (epiphysial growth plate) to the effect of leptin.

Both leptin and insulin resistance are strongly related to adiposity and other cardiovascular risk factors [49]. Studying these relations in childhood may help clarify some aspects in the development of the insulin resistance syndrome. However, conflicting results are published about the dependent versus independent associations between body fatness, leptin levels, and insulin resistance in obese children [50]. A clearer understanding of the leptin-obesity–insulin resistance relationship is still required during childhood and adolescence relative to the development of risk factors and type 2 diabetes.

In two studies on infants and children with mild and severe forms of protein energy malnutrition (PEM), leptin concentrations are significantly decreased and positively correlated with triceps, scapular, and abdominal fat thickness [51]. In severe PEM cases, concentrations of IGF-I are significantly low, whereas basal cortisol and GH concentrations are significantly high versus normal children. The BMI is correlated significantly with leptin, insulin and IGF-I. These findings suggest that during prolonged nutritional deprivation, the decreased energy intake, diminished fat mass, and declining insulin (and possibly IGF-I) concentrations suppress leptin production.

On the other hand, during recovery from malnutrition, leptin concentrations increase in relation to fat mass. During recovery from severe PEM, an increase in leptin concentration was observed only in children who showed catch-up growth. More interestingly, malnourished children with catch-up growth had higher serum leptin concentrations compared to healthy children. This suggested that leptin affects nutritional status during catch-up growth as a dynamic process, rather than merely being an index of body fat content [51].

Humans and mice lacking leptin (ob/ob) or leptin receptor (LepR, db/db) are infertile. Leptin administration to leptin-deficient subjects and ob/ob mice induces puberty and restores fertility. Recently, it has been made clear that leptin acts indirectly on gonadotropin-releasing hormone (GnRH)-secreting cells via actions on interneurons [52]. Data from two longitudinal cohorts suggest a role for leptin in the normal regulation of childhood weight gain, maturation, and the development of secondary sexual features and body composition [53].

Significantly, higher serum levels of leptin are detected in children with congenital heart disease (CHD), particularly in patients with cyanotic CHD. CHD patients with SpO2 < 90%, pulmonary hypertension (PH), severe pulmonary stenosis (PS), detectable collaterals, cardiomegaly and/or heart failure showed significantly higher levels of leptin than those with higher SpO2 or those without these findings. Elevated plasma leptin levels and its soluble receptor in these patients with CHD suggest that leptin may participate in the catabolic cardiac cachexia and failure to thrive in these patients [54]. It is possible that this catabolic state, affecting body fat and muscle, may be useful to secure calories to spare the mechanically compromised heart. Moreover, elevated leptin may modify the process of angiogenesis that could be essential to enhance renal perfusion in some cases of CHD [55].

Patients with congenital leptin deficiency are severely hyperphagic from early infancy and, although birth weight is normal, they rapidly become obese during early childhood. An increased susceptibility to infections has also been reported in these infants and appears to be associated with reduced numbers of circulating CD4+ T cells, and impaired T cell proliferation and cytokine release. Other features

of the disorder include hyper-insulinaemia, advanced bone age, hypothalamic hypothyroidism and hypogonadotropic hypogonadism leading to a failure to undergo puberty.

Congenital leptin deficiency can be successfully treated with daily subcutaneous injections of recombinant human leptin. Leptin replacement therapy is undertaken at low physiological doses, starting at 0.02 - 0.04 mg/kg/day given subcutaneously at 6 pm. The child's dose is adjusted to increase the peak serum leptin to 70 ng/mL. Treatment results in sustained weight loss, and reduces appetite, hyper-insulinaemia, and hyper-lipidemia, and attains appropriate pubertal development. In addition, leptin administration corrects abnormal thyroid biochemistry and allows the withdrawal of T4 treatment. The white blood cell count (lymphocytes, neutrophils, and monocytes) all increase and remain elevated for the first 3 months. There is no evidence of concomitant infection at the time of therapy.

Results

Leptin, energy balance and exercise intervention

The change in energy balance in lean and obese children has been assessed through exercise intervention programmes. These interventions, with and without diet education, elicit a number of key findings (Table 2).

Study	Population	Duration of the study	Serum/Plasma Leptin
Moro., *et al*. (1998)	Obese Children	Not Clear	Decreased
Reiterer., *et al*. (1999)	Obese Children	3 weeks	Decreased
Nakane., *et al*. Nakane., *et al*. (1999)	Obese Children	Not Clear	Decreased
Holub., *et al*. (1999)	Obese Children	3 weeks	Decreased
Gutin., *et al*. (1999)	Obese Children	4 months; training, 4 months; no training	Decreased
Sudi., *et al*. (2001)	Obese Children Obese prepubertal and pubertal girls	5 weeks	Decreased
Sramkova., *et al*. (2002)	Obese children and adolescents	5 weeks	Decreased
Miraglia del G.. *et al*. (2002)	Obese children and adolescents	6 months	Decreased
Pilcova., *et al*. (2003)	Obese children and adolescents	5 weeks	Decreased
Celi., *et al*. (2003)	Overweight children and adolescents	12 months	Decreased
Souza., *et al*. (2004)	Obese Children	One graded treadmill run	No Change
Bini., *et al*. (2004)	Obese prepubertal children	10–16 months	Decreased

Table 2: *Summary of exercise intervention studies and their effect on leptin concentration [65].*

Celi., *et al.* [56] has found that the lower the serum leptin concentration after previous weight excess reduction and/or the greater its decrease, the greater the probability for weight excess relapse. This was furthered by Gutin., *et al.* [56], who examined leptin during 4 months of physical training and 4 months without. This study found greater leptin reductions during physical training in children with

higher pretraining leptin and in those whose total fat mass increased least [56]. In addition, Miraglia del Giudice., *et al.* [57] found that individuals with relatively high or low leptin are less likely to lose body fat, compared to obese children with appropriate baseline leptin concentrations. The researchers suggest that the obese individuals with appropriate baseline levels are more sensitive to environmental factors; therefore, they are more likely to respond to intervention programmes. Overall, leptin changes during interventions are best determined by initial leptin concentrations [56-60]. This insight is important in understanding the predictive ability of leptin for an individual's ability to lose body fat and to act as a biological marker in childhood obesity. Hulver and Houmard [61] provide appropriate and well reviewed conclusions about exercise and leptin. Single, short duration (41 min or less) non-exhaustive exercise bouts do not appear to alter leptin concentrations significantly, yet leptin concentrations may be affected by short duration, exhaustive exercise. Studies of long duration exercise bouts (one to multiple hours) have a greater tendency to reduce serum leptin concentrations than do short duration bouts. Subsequently, exercise-associated reductions in leptin may be due to alterations in nutrient availability or nutrient flux at the level of the adipocyte. The overall training intensity will therefore have an effect on leptin concentrations. According to a recent meta-analysis [62], major predictors in percent body fat at a one-year follow-up after an exercise programme are longer exercise duration, longer training length and a combination of exercise modalities (aerobic and resistance training). Maziekas., *et al*. [62] proposed that the longer duration exercises are accompanied by lower exercise intensity; therefore, the body is using β-oxidation rather than glycolysis as the primary energy system. An increase in β-oxidation would result in a decrease in fat mass and a corresponding decrease in leptin concentration. Interestingly, Desgorces., *et al.* [63] has proposed that long duration training improves fuel homeostasis recovery in trained athletes and it controls the response of leptin to an acute bout of prolonged exercise. This study specifically found that during early season training, leptin concentrations were lower at both 120 min (1.28 ng/ml) and after a 24-h recovery (1.11 ng/ml) relative to pre-exercise concentrations (1.75 ng/ml). In addition, during late season training, leptin concentrations were lower at 120 min (1.38 ng/ml), but not after 24 h recovery, relative to pre-exercise concentrations (1.69 ng/ml). This further supports the premise that leptin responds to the balance between energy intake and expenditure. Another study by Laessle., *et al.* [64] demonstrated that in prepubertal obese girls, restrained eating was negatively correlated with leptin concentration. If lower leptin concentrations, therefore, decrease energy expenditure, then paradoxically, restrained eating might lead to weight gain in obese individuals because it promotes a positive energy balance [64]. Exercise intervention programs should focus on a variety of longer bouts of exercise at greater intensities, in addition to accurately calculated caloric intake. This will result in positive leptin and overall health effects in the child participants [65].

Conclusion

In facing the growing childhood obesity epidemic, innovative treatments have become necessary to make progress against this ubiquitous disease. Leptin plays an important role as a biomarker for childhood obesity since Considerable evidence for systemic effects of leptin on specific tissues and metabolic pathways indicates that leptin operates both directly with the hypothalamus for energy balance regulation, hence the measurement of free, bound and total leptin as well as soluble leptin receptor concentration are critical for our understanding of obesity in children; and leptin concentration may be an important factor for determining intervention programme responsiveness in pediatric obesity.

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