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A Review on Congenital Leptin Deficiency: Phenotypes, Diagnosis and Management

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Abstract

Obesity commonly occurs as a result of environmental polygenic factors but it can be caused by a number of non-environmental non-polygenic conditions, the so called monogenic forms of obesity, which are rare causes of obesity, the treatable form of which is congenital leptin deficiency which is a clinical condition that arises due to genetic loss of leptin functions. It is distinguished by an early onset severe obesity as a result of uncontrolled appetite. Despite the fact that it is a rare condition, patients respond well to leptin replacement therapy.

Methods: In this review, data on the effects of leptin analogue was extracted from naïve leptin patients and six studies were included.

Results: As an overall trend leptin therapy has a powerful positive effects on body weight and associated abnormalities, a remarkable weight loss was observed among participants (mean weight reduction was 29.6 kg), reported cases were fifteen for LEP gene defects, twenty-one for LEPR gene mutations and three for functional leptin mutations.

Conclusion: This review will assess congenital leptin deficiency condition in terms of phenotypes, clinical consequences, diagnosis and management, and will evaluate leptin analogue therapy among different genetic phenotypes of leptin deficiency patients.

Keywords: Leptin; Congenital leptin deficiency; Lepr; Obesity; Metreleptin

Abbreviations

BFM: Body Fat Mass; BW: Body Weight; CLD: Congenital Leptin Deficiency; LEP: Leptin; LEPR: Leptin Receptors; FSH: Follicle Stimulating Hormone; LH: Luteinizing Stimulating Hormone; IGF: Insulin like Growth Factor; EE: Energy Expenditure; TGs: Triglycerides; R-metHuLeptin: Recombinant Methionyl Human Leptin (Amylin pharmaceutical Inc, San Diego, CA, USA and Amgen, Inc, Thousand Oaks, California, USA)

Introduction

In 1994 leptin was identified in the ob/ob gene in mice by positional cloning. Mice models of congenital leptin deficiency known to have morbid obesity, diabetes and infertility [1], in humans it leads to severely increased food intake and early onset morbid obesity with abnormal metabolic and neuroendocrine functions, and defective immune response that renders patients, mainly children, at increased risk of severe infections and death [2]. At birth, serum leptin levels are higher in neonates than in adults. After birth, leptin is mainly provided to neonates and infants through maternal breast milk that contains higher leptin concentrations (3.37 ng/ml) compared to formula milk (2.2 ng/ml) [3], the fact that may explain the timing of clinical presentation, within the first few months of life and linked to introduction of bottle feeding [4] or food. Autosomal recessive homozygous defective mutations in the leptin gene (LEP gene) are the main cause of genetic leptin deficiency and minor cases are due to the leptin receptor gene (LEPR gene) defects [5]. Prevalence of leptin mutations among patients with early onset severe obesity and non-satiable appetite from consanguineous parents is around 1% [6], LEPR gene mutations represent around 2-3% of genetic leptin mutations [7]. Leptin replacement therapy normalizes the abnormal clinical phenotype and the associated metabolic, hormonal and immune function disturbances [8,9]. So what is congenital leptin deficiency and what are the effects of leptin analogue administration? This review aims to describe congenital leptin deficiency, its phenotypes, clinical significance, consequences, and the impacts of leptin replacement therapy.

Methodology

Aim

This review aims to identify frequency of congenital leptin deficiency and its clinical and genetic phenotypes. Explore the clinical consequences of congenital leptin deficiency. Explore the effects of leptin analogue.

Objectives

General objectives:

What is congenital leptin deficiency?

How to identify patients with congenital leptin deficiency and how is it frequent?

Specific objectives:

What are the clinical consequences of congenital leptin deficiency?

What are the different clinical and genetic phenotypes?

How congenital leptin deficiency is diagnosed?

Is leptin analogue safe? Is it effective?

Would some patients benefit more than others from leptin replacement therapy i.e. children or adults, those with complete leptin deficiency or relative one?

Literature review strategy

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines a literature review

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was conducted. The literature review search strategy has two objectives: (1) to identify data that described the basic science of leptin, the frequency and the consequences to health of congenital leptin deficiency and (2) to identify studies on the impacts of leptin replacement therapy. Relevant studies were retrieved from January 1997 to January 2018 from Cochrane Library of Clinical Trials (n=84), PubMed (n=1045), BMC (n=16) and ClinicalTrial.gov (n=5) with the use of the following synonyms for searching: congenital leptin deficiency, insufficiency, leptin resistance, leptin replacement, metreleptin and r-metrHuLeptin with no restriction of language. Abstracts and titles of identified articles were screened for eligibility criteria for inclusion. Studies were eligible if they: (1) assessed congenital leptin deficiency (2) clinical trials on human participants (3) studies that included outcomes of systemically administered leptin. Studies were excluded if they were: (1) studies evaluating outcomes other than congenital leptin deficiency (2) incomplete or active trials.

Data abstraction

The review primary outcome was to quantitatively evaluate and compare the effects of leptin analogue administration on body weight, fat mass percentage, energy intake and serum concentrations of leptin, follicle stimulating hormone, luteinizing hormone, blood sugar, insulin, triglycerides, and cholesterol. Data extracted was that relating to the design of study including population, patient sampling, time length of follow up and leptin replacement dosage. Baseline characteristics of study participants included age, sex, body fat mass percentage, genetic leptin deficiency phenotype, serum leptin levels, metabolic and hormonal parameters (lipids profile, blood sugar parameters and gonadotropic hormones). Quality assessment was done using The Centre for Evidence-Based Medicine (CEBM) of Oxford checklist (Figure 1). Abstracted data is summarized in Table 1 and 2.

Literature Review

Leptin basic physiology

The word leptin means thin, originally derived from the Greek word leptos. Leptin is a prototype adipocyte derived adipokine, encoded in the LEP gene in humans. A 16 KDa protein that consists of 167 amino acid polypeptide chain [10], produced by white adipocytes, and is expressed in a number of peripheral and central tissues [11]. Serum leptin levels are higher in females than in males, probably due to gender body fat mass (BFM) differences and/or hormonal impact of progesterone and estrogen on leptin production [12], and are closely related to BFM content e.g. high in adiposity [13].

Leptin main function is appetite control and energy regulation, mediated through binding to leptin receptors (LEPRs) expressed

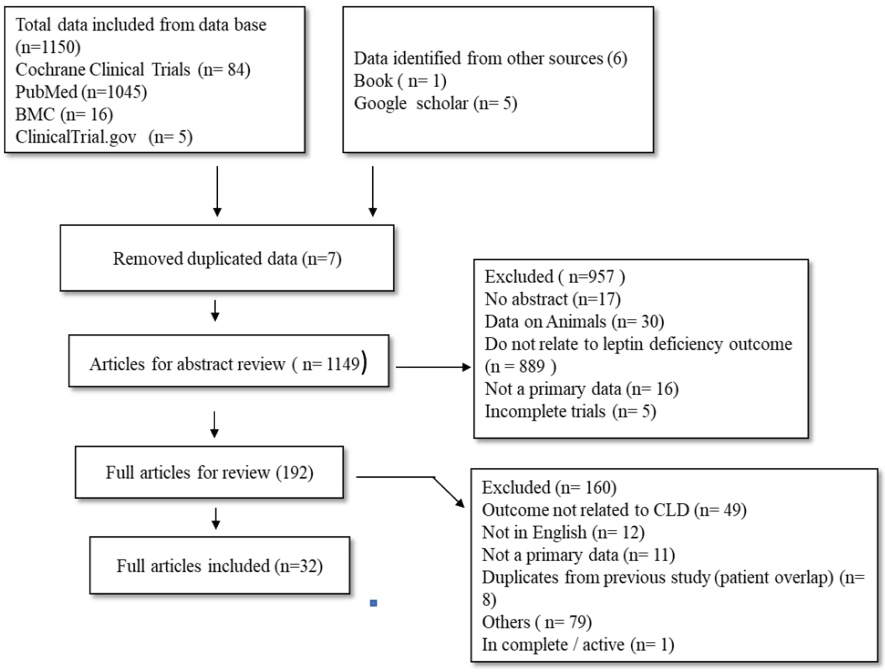

Figure 1: A flow diagram outlining literature strategy and study selection.

Reference	N	Age	Male	Female	Leptin deficiency Genetic phenotype	Ethnicity	Leptin treatment Dose	Study design	Study follow up duration
Farooqi et al. [17]	1	9 years	-	1	ΔG133	Pakistani	0.028mg/kg	Case study	12 months
Frank et al. [30]	1	14 years	-	1	L72S	Austrian	1.2 mg/day	Case study	24 months
Gibson et al. [1]	1	5 years	-	1	ΔG133	Pakistani	0.028mg/kg	Case study	48 months
Licinio et al. [10]	3	Mean 34 years	1	2	C105T	Turkish	0.01-0.04mg/kg	Case study	18 months
Wabitsch et al. [21]	1	3 years	1	-	D100Y	Turkish	0.03mg/day	Case study	18 weeks
Wabitsch et al. [4]	2	Mean 7.5 years	1	1	C309c>A	German	N-R	Case study	8 weeks

Table 1: Data extracted was related to the design of study including population, patient sampling, time length of follow up and leptin replacement dosage.

Reference	Fat mass%		BW		EI		Insulin		Glucose		LH		FSH		Cholesterol	
			Kg		kcal/day		µU/ml		mg/dl		mIU/ml		mIU/ml		mg/dl	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	pre	Post	Pre	Post	Pre	Post	pre	post
Farooqi et al. [17]	59	52	94.4	78	1500	1000	41	34	78	85	0.2	0.3	0.3	2.9	193	182
Frank et al. [30]	50.1	30.8	N-R	N-R	N-R	N-R	N-R	N-R	N-R	N-R	N-R	N-R	N-R	N-R	N-R	N-R
Gibson et al. [11]	53.4	38.1	64.4	48.4	N-R	N-R	27.4	6	66.7	N-R	<1.0	<1.0	<1.0	2	162	124
Licinio et al. [10]	47	22.9	125	66.3	2330+/_322	N-R	5.4	2.2	103.3	82.7	0.75+/-0.04	2.75 ± 0.07	N-R	N-R	156.3	110.3
Wabitsch et al. [21]	N-R	N-R	43.4	35	N-R	N-R	19.2	4.8	N-R	N-R	<0.1	N-R	0.79	N-R	N-R	N-R
Wabitsch et al. [4]	N-R	N-R	64.15	59.15	N-R	N-R	26.15	16.75	N-R	N-R	0.1	0.1	0.45	1.4	N-R	N-R

Table 2: Baseline characteristics of study participants.

in central and peripheral tissues. In humans, single LEPR gene is responsible for the production of six LEPRs isoforms (a, b, c, d, e and f) which are different in their C -terminal intracellular domains, in contrary to the four receptor isoforms produced in murine models. All LEPRs isoforms belong to IL-6 cytokine receptors family, the most active receptor isoform is the ObR long form which is abundant in hypothalamus and is linked to body weight (BW) control [1].

Leptin regulates lipid metabolism, hematopoiesis, immune function and angiogenesis [14], and plays a vital role in hormone and hypothalamic functions [15,16]. Leptin secretion is affected by sex and age, and BW accounts for 50-60% of its variability [14]. It is directly influenced by BFM, fat distribution, overfeeding, blood levels of sugar, proteins, insulin, glucocorticoids, estrogen and agonists of the transcription factor peroxisome proliferator-activated receptors gamma (PPARγ). As basics of leptin has been outlined, the coming section will describe what is leptin deficiency and its phenotypes.

Leptin deficiency

Leptin is a satiety hormone and its absence is responsible for uncontrolled appetite and morbid obesity in obese ob/ob mice [17], the fact that raised concern for a new era in obesity genetics. Lack of leptin can be congenital, acquired, or may occur as a part of a physiological adaptive response [12].

Congenital leptin deficiency (CLD): Bioactive leptin deficiency: CLD represents the genetic causes of loss of leptin functions either due to defective secretion (leptin gene defects) or defective receptor binding (leptin receptor gene mutations). LEP gene defect is a condition in which patients are born with normal birth weight after which they start to gain weight rapidly and present with early onset severe obesity due to impaired satiety control and constant food seeking behavior, this presentation is termed as classical phenotype of CLD [6].

Reported LEP gene mutations according to the most recent data were found in patients from Pakistani (4), Turkish (3), Turkmenian, Egyptian (2), Austrian (1) and Indian (1) ethnicity [18]. Reported deaths were nine, all belonged to one Turkish family but one, who was Egyptian, the main cause of death was lethal infections [2,19]. Most identified patients are a product of a consanguineous heterozygous parents, except one recently discovered boy with unipaternal disomy whose father is heterozygous and his mother is normal [20]. In addition to consanguinity LEPR gene mutations are reported to occur in common with certain ethnic groups, as follows: Turkish (3), Bangladesh (3), Norwegian (1), Iranian (1), white British (2), South European (3), Algerian (3), Dutch (2) and Kabilian (3) [5].

Bioinactive leptin or functional leptin deficiency: is a recently discovered phenotype of CLD. Patients present with the classical CLD clinical phenotype, but their circulating serum leptin levels are appropriate for their BFM content, yet the mutant leptin is unable to bind to receptor, and it may be missed for LEPR gene mutations [21].

Other forms of leptin deficiency: Leptin Resistance: patients with common obesity is known to have hyperleptinemia, as expected, in relation to increased BFM content, as a result they may develop a state of leptin tolerance, evident by hyperphagia. Leptin resistance is defined as inability to control appetite and weight gain due to leptin insensitivity, it is a leading cause for overweight and obesity [13,17]. Reported mechanisms in animal models: abnormal transport across blood brain barriers, defective signaling and disordered target neural circuits. Leptin sensitivity may be restored through: suppression of leptin production, increase kidney excretion, and by physical activity [1].

Relative leptin deficiency: it describes a state of inappropriate serum leptin concentrations in relevance to BFM content. It has been linked to insulin resistance observed in individuals with morbid obesity with uncontrolled blood sugar, and in weight reduction states [17]. A target treatment analysis from a small sized long term prospective case control study conducted by Löfgren et al. [17] concluded that reduction of BW in obese subjects (induced by life style modification or gastric banding) is correlated to an increase in subcutaneous adipocytes cell size, in spite of their normal BFM, which can affect the production of baseline leptin and hence a relative reduction in its fasting serum levels in relation to BFM content. The above study is limited by the fact that leptin secretory behavior was examined in vitro omitting the effect of hormonal regulation on leptin release and leptin circadian rhythm in humans. Having reviewed CLD and leptin deficiency variants, the coming section will discuss clinical phenotypes of CLD and how they are identified.

Phenotypes of congenital leptin deficiency

Clinical phenotype: the hall mark of CLD is early onset severely increased appetite and morbid obesity within the first few months of life. Children may develop skeletal deformities of the lower limbs mainly knees by the age of five to six years [14], present with recurrent childhood infections and atopic diseases due to abnormalities in T cell number and function [9]. Hyperinsulinemia with euglycemia is a common metabolic presentation as well as hypertriglyceridemia. According to Fischer-Posovszky et al. [16] patients with CLD typically present with hyperinsulinemia and/or type 2 diabetes mellitus.

Patients with LEPR gene mutations present with classical CLD phenotype with selective adipocyte mass distribution (hyperphagia confirmed by ad libitum energy intake test which is a standardized meal test after a period of fasting, mainly breakfast) in children with no major changes in basal energy expenditure (EE). Patients are also subjected to fatal infection due to disturbed T cell response [5,22].

Patients with LEP and LEPR gene defects present with delayed puberty due to deranged hypothalamic gonadotropic axis [10].

However, some female cases have spontaneous menses despite of their under developed secondary sexual characteristics (reported in the third and fourth decades in adults with LEPR gene mutations), which is linked to the large adiposity that may stimulate estrogen production which is sufficient to cause uterine development and hence menses [2].

In general patients with LEPR mutations have less severe phenotype presentation, that may be referred to the older age at which they are identified compared to LEP gene mutations, or to the presence of unknown other leptin receptors that may mediate leptin function [5].

Genetic mutations: LEP gene mutations: identified gene mutations according to the most recent data are: homozygous frameshift mutation (Δ133G), nonconservative missense mutation (C105T), homozygous missense mutation (L72S), homozygous non-missense mutation (c.2236.A) and homozygous missense p.N103K substitution, and identified cases are fifteen. The first cases to be identified were two children from a related Pakistani parents in 1997, they presented with classical CLD phenotype, screening for central and endocrine causes was negative, leptin deficiency was suspected and confirmed by undetectable serum leptin levels. Genetic study revealed homozygous frameshift mutation in the LEP gene with premature stop codon (Δ133G) [15]. Since then a number of affected subjects is being identified, based on the unique medical history. One Austrian young girl was reported with a milder clinical phenotype, she possessed L72S gene mutation [16].

Patients with CLD of same genetic phenotype and ethnic backgrounds have varied presentations, for instance two girl patients with (Δ133G) LEP gene mutation, the younger patient has recurrent infections, a history of atopic and autoimmune disease (the latter might be linked to her maternal autoimmune conditions: SLE and hypothyroidism), on the contrary to the older one who hasn't reported the same immune phenotype [9].

Shabana and Hasnain [18] conducted a case control observational study (2011-2014) aimed to screen prevalence of (p.N103K) mutation among Punjab Pakistani population as no carrier of this mutation has been identified in Pakistan. The study discovered only one Pakistani boy with such mutation. Retrieving his medical history, parents stated that their son has been obese since infancy due to non-satiable appetite. Parents examination reported a heterogenous allele of same mutation. P.N103K missense mutation leads to undetectable leptin levels and low functional activity.

LEPR gene mutations: reported cases are twenty-one and identified mutations are eight: homozygous missense, nonsense, frameshift, compound heterozygous, abnormal splicing of leptin receptor transcripts [5,10,22], and chromosome-1 unipaternal disomy [20]. Farooqi et al. [5] screened for LEPR gene mutations among three hundred severely obese children below ten years of age, 3 % of cases reported LEPR gene mutations (four adults and six children) and matched CLD phenotype. Homozygous frameshift mutation (c.1604-8A>G) has been discovered recently and affected children are at increased risk of diabetes [22].

Functional leptin mutations: the most recently discovered phenotype, three children were identified (one Turkish and two German). Identified gene mutations are two: homozygous transversion (c.298G → T) and homozygous substitution (C.309c>A) [4,21].

Variants of leptin gene mutation: Murray et al. [23] reported one lean Caucasian boy who had poor appetite and low serum leptin levels. Moreover, he had marginal adrenal insufficiency, low testosterone level, delayed puberty that responded to testosterone administration. In addition to prolonged recovery from minor viral infections, he had low C3/C4 levels. Gene sequence revealed a LEP gene sequence variant mutation with normal leptin binding protein levels. The boy status of leptin deficiency was linked to poor intake. As clinical phenotypes have been discussed, what are the clinical significance and consequences of CLD?

Consequences of leptin deficiency

- Lack of leptin known to have significant impacts on neuroendocrine, immune and metabolic functions. Low serum concentration of follicle stimulating hormone (FSH) and luteinizing hormone (LH) are reported to occur in patients with LEP gene mutations, in contrary to patients with LEPR gene mutations who have normal FSH and LH levels [5]. CLD is associated with complete loss of LH pulsality, in addition to under developed secondary sexual characteristics, with primary or secondary amenorrhea. Leptin is linked to initiation of puberty, based on data from normal physiological studies that demonstrated a rise in serum leptin levels (almost the double) before puberty in healthy boys, and prior to any observed changes in sex hormones levels, that fall down to baseline levels after the start of puberty [24].
- Effects on growth is more evident in rodents than in humans. Children with CLD have normal IGF-1 (insulin like growth factor) levels hence normal linear growth [5], in spite of the reported increase in bone age, which is usually observed among subjects with common obesity, yet it usually increases by less than three years [9,22]. Adult patients with LEPR gene mutations have reduced final height as a consequence of absent pubertal growth spurt [5]. A small case control study demonstrated that among adult individuals with leptin deficiency compared to heterozygous and normal ones, growth hormone secretion is influenced by adiposity not by leptin status [25].
- Effects on thyroid functions are contradicted, adults with CLD reported central hypothyroidism [2]. On the other hand some children reported normal thyroid functions [15] and others reported hypothalamic hypothyroidism [9,16,22] whether these effects are based on age differences, or genetic phenotypes is not well understood. A small observational case control study conducted by Mantzoros et al. [24] in four Caucasian family members, with different leptin deficiency genetic status (one homozygous, two heterozygous carriers and one normal) revealed that there is close relation between leptin and hypothalamic axis and that leptin did affect the circadian pattern of thyroid axis, yet patients had normal thyroid functions.
- Ob/ob leptin deficient mice demonstrated decreased adrenocorticotropic hormone (ACTH), in contrast to humans, among whom adrenal functions are not significantly affected [15,24]. Impaired adrenal function has been observed in five Turkish adults with leptin deficiency (40% reported high serum cortisol levels, and 60% have elevated serum ACTH levels, disordered circadian pattern and low 17 hydroxyprogesterone concentrations) [2].
- According to available data, patients with leptin deficiency and patients with common obesity are at increased risk of infection. Animal model (ob/ob mice) of CLD showed an impaired T-cell immunity. In humans, defective immunity has been reported in children, whereas intact immune functions have been reported in adults [18]. Mackey-Lawrence and Petri [11] stated that LEPR

gene mutations render affected patients at an increased risk of lethal respiratory infections. Compared to LEP gene mutations, LEPR gene mutations lead to mild reduction in absolute CD4+ T-cell counts [5]. Moreover, children with biologically inactive CLD are at increased risk of infection, although they may have intact normal T cells number and function [21]. Leptin may protect against parasitic infections, Mackey-Lawrence and Petri [11] have linked hypoleptinemia to an increased risk of amebiasis among malnourished children based on immunohistochemistry results that revealed increased expression of intestinal LEPRs during acute infection in a three years prospective study among 2-5 years old children in Bangladesh. In addition, they linked leptin insufficiency to increased susceptibility to *E. histolytica* (through expression of one copy of Q223R SNPs in LEPR gene) in a nine years prospective cohort.

- Ob/ob leptin deficient mice, expressed hypoventilation (impaired hypercapnia ventilation response) and obstructive sleep apnea (OSA). In humans, a link between OSA and low leptin levels have been demonstrated but the exact mechanism is not fully known. Subjects who have OSA and treated for six months with positive ventilation pressure and responded well to therapy, had hypoleptinemia which is linked to decreased levels of stress and visceral adiposity, besides low muscular sympathetic nerve activity and amended insulin response [12].
- Ozata et al. [14] conducted a small sized case control trial to examine effects of leptin deficiency on platelet aggregation. The study concluded that both obese (due to leptin insensitivity) and leptin deficient individuals are at increased of platelet aggregation, hence vascular events, however, there is no enough data on role of leptin in the prevention of cardiovascular disease.
- Children with CLD may develop bone deformities that may require surgical intervention [15]. Affected adult women are at increased risk of osteoporosis as a consequence of leptin resistance. Male subjects are subjected for osteopenia due to low testosterone levels that suggests a defective combined testosterone leptin effect [2].
- Total EE is not affected, yet after treatment, EE rises as a result of increased physical activity among both children and adult patients [8,15]. As clinical consequences of CLD has been discussed, the following section will outline diagnosis of CLD.

Diagnosis

Patients with early onset morbid obesity with non-satiable appetite and associated neuroendocrine dysregulation, in absence of dysmorphic and developmental features should be screened for genetic nonenvironmental causes of obesity. Serum leptin levels are detectable and adequate for BFM content in LEPR gene mutations, as well as functional leptin deficiency, the fact that may render affected subjects under diagnosed [15], therefore both conditions cannot be excluded by measurement of serum leptin levels only, Further, genetic sequence and functional studies are needed [4]. A cohort study aimed to investigate whether bioactive to immunoreactive ratio can be used as a screening tool for functional leptin deficiency, conducted among seventy children and adolescence with early onset obesity, however, all identified patients had homogenous bioactive to immunoreactive leptin ratio, and those with low bioactive to immunoreactive ratios (<90%) were negative to LEP gene mutations on genetic sequence [27].

Hyperphagia is a prominent feature in the identification of CLD, it's reported to occur in early neonatal life among patients with defective LEP gene mutations, whereas among subjects with LEPR gene mutations it's reported beyond neonatal period [5].

An European multicenter cohort population based trial (2007-2010) demonstrated that normal weight girls have higher serum leptin levels (as well as adiponectin) than boys (both aged ≥ 3.0 - ≤ 9.0 years) ranged from 2.2- 4.8 ng/ml for the 97th percentile for leptin, and positive trends in variance for both gender above the 50th percentile for leptin. Extracted reference values for age and sex as follows: girls serum leptin levels ranged from 0.9- 0.5ng/ml for the 3rd percentile and 6.2-11.3 ng/ml for the 97th percentile for leptin, on the other hand for boys, serum leptin levels for the 3rd percentile was 0.4 ng/ml and ranged from 4.0-9.2 ng/ml for the 97th percentile. Enzyme linked immunosorbent assay (ELISA) are more accurate in measurement of serum leptin levels than radio-immunoassay, as it detects wider leptin range [26].

Genome DNA isolation and sequence: genome DNA is extracted from peripheral white blood cells. The target intron and exon are amplified by polymerase chain reaction, resultant product is subsequently sequenced and compared to a reference sequence [5]. Having outlined how CLD can be identified, the coming section will discuss available treatment modalities and evaluate efficacy and safety of leptin replacement therapy.

Management

Conventional treatment: no data on effects of diet control and exercise on CLD subjects. Adiposity and bone deformities may restrict movement and further worsen obesity [15], one reported case of in-patient and out-patient diet control measures that only lead to limited success [4] and another reported child who failed to response to diet restriction and exercise program [22].

On the other hand one reported adolescent girl with a milder CLD phenotype was started on low calorie diet by her parents since infancy in order to counteract her insatiable satiety, whether this played a role in her milder clinical phenotype presentation or the mutation itself, is not well understood [16].

Leptin replacement therapy: Recombinant methionyl human leptin (R-metHuLeptin), the only leptin analogue, is produced in *Escherichia coli* through recombinant techniques, it consists of 147 amino acid polypeptides with a terminal methionine, found in a freeze-dry formulation stored in glass vials. To be used should be reconstituted with sterile water [28].

A single center study conducted among healthy individuals (men, postmenopausal or women underwent hysterectomy) to assess safety and pharmacodynamics, demonstrated that R-metHuLeptin was well tolerated with no reported life threatening side effects during the follow up period. The most relevant side effect was mild sensitivity reactions at site of injection. No reported significant clinical effects on vital signs (as temperature) or electrical impulses of heart or on laboratory measures (as blood count) [28].

Recombinant methionyl human leptin (Myalept or metreleptin) was approved by US Food and Drug Administration in 2014 for the management of the complications arising from leptin deficiency in patients who have congenital or acquired generalized lipodystrophy based on two approved clinical trials (NIH 991265/20010796 and FHA101) that included ninety patients with generalized lipoatrophy [29]. It is metabolized in liver and excreted through kidneys. Recommended doses are 0.06 mg/kg to 5 mg per day based on patient's BW and gender, and dose prescription is guided by risk benefit assessment (Risk Evaluation and Mitigation Strategies, REMS)

for lymphoma, diabetes and neutralizing antibodies, the health care prescriber and pharmacy provider should be certified and the prescriber should attest an approved indication.

Common reported side effects were: hypoglycemia (13%), headache (13%) and abdominal pain (10%). Other side effects: lymphoma (7.9%), pancreatitis (22%), hypersensitivity reactions (47%), autoimmune diseases (36%), nonalcoholic steatohepatitis (>50%) and neutralizing antibodies. Reported deaths were 15%. It was utilized for treatment of common obesity, with no reported significant effects on BW, therefore trials were discontinued. A combined therapy with pramlintide was investigated in obese individuals and was stopped due to commercial reasons.

Leptin administration in lean subjects with relative leptin deficiency (induced by acute fasting) revealed variable outcomes, lean women expressed neutral effects on growth hormone axis, while men participants has an improved IGF-1 (reflects adrenal, somatic and growth hormone function) and IGF binding Protein 3 levels. This variation could be due to gender difference that might affect degree of hypoleptinemia [25].

Metreleptin effects

A nine years old girl with a frameshift homozygous mutations received R-metHuLeptin for one year. The main and early observed effect of leptin was regulation of appetite. The child food seeking behavior improved and energy intake decreased in terms of quantity and speed. At baseline, the child blood pressure, temperature, lipid profile, blood glucose, growth velocity and IGF-1 were normal. After one year of treatment, BW started to decrease (within two weeks of therapy and lost weight was 1-2 kg/ month), hyperinsulinemia improved, BFM decreased with a positive pulsatile gonadotrophins stimulation test. The drug was well tolerated, the only adverse effect observed was the production of neutralizing antiLeptin antibodies within two months of treatment and continue throughout the whole treatment period. Total EE was normal with a reduced basal metabolic rate, and increased EE in response to increased physical activity level (1.6-1.9) suggests that leptin effects were due mainly to reduced energy intake [15].

A 5 years old girl with a frameshift homozygous mutation treated with leptin therapy for four years. Weight loss was observed within two weeks of therapy, the patient had some refraction to treatment evident with relapses, this refractory periods was managed with an increase in leptin dose. Hypertriglyceridemia was normalized within the first month of treatment, whereas hyperinsulinemia reported to improve after six months. Her white blood cell count with immature band forms was elevated by two folds within the first four weeks of therapy and continued to be high for three months, with no evidence of concurrent infection. The patient has recurrent perineal dermatitis and asthma, both were resolved after therapy. Dermatitis disappeared by the end of the first year of treatment, on the other hand asthma became worse at the start after which it began to improve and totally resolved by the second year, and reported no history of hospital admissions. The patient has subclinical hypothyroidism with low antithyroid microsomal antibodies levels and responded well to therapy, as a result thyroxine was stopped [9].

A three years old child with bioinactive CLD (D100Y mutation), received leptin therapy for eighteen weeks, demonstrated an immediate improvement of food intake behavior followed by a fall in total energy intake that led to reduced BW. An interesting observation was decreased mutant leptin levels (48.7 to 14.5 ng/ml). Hyperinsulinemia was normalized as well as liver transaminases, IGF-1 levels showed a mild increase from baseline (36 to 57 ng/ml). LH levels were low up to week nine where they rose to 0.14 from <0.1 mlU/l. On the other hand, FSH levels rose from 0.79 to 1.39 mlU/l) at week nine [21]. Same results were observed among two siblings (9.8 years, 6.3 years) with (C.309c>A) homozygous missense mutation, a drop in serum mutant leptin levels was reported in the girl patient by day nine of treatment from 59.7 to 46.9 ng/ml after which a rebound increase occurred and reached 64 ng/ml by the end of trial. Hyperinsulinemia was observed in both children that was normalized by the eighth week of therapy. Cortisol serum levels showed contradicted results, the older girl showed a dramatic increase in cortisol levels from 4.8 to 16.8 µg/dl while on the hand the young boy has a decreased cortisol levels (8.8 to 5.1 µg/dl) by the eighth week [4], whether this depends on serum cortisol status, or gender differences is not well known.

Licinio et al. [8] studied effects of R-metHuLeptin among adult subjects, appetite and food behavior improvement were observed within two weeks of therapy. One woman has been diagnosed with type 2 diabetes mellitus and dyslipidemia, required high doses of leptin suggesting a leptin resistance state due to common obesity. Hypertriglyceridemia, hyperglycemia and hyperinsulinemia were normalized by eighteen months of therapy. Central hypogonadism was reversed, besides emergence of secondary sexual characteristics and menarche in both adult female participants [8].

A follow up case study on an Austrian young girl with CLD demonstrated that leptin administration led to acute changes in food reward, preference and intake. These changes resulted in high palatability to high caloric food. Long term effects observed were maintained cognitive food behavior and reward that was linked to maintained weight loss. Data was extracted from brain functional magnetic resonance imaging [30].

Results

Table 1: Gives information on leptin deficient participants (number of participants, age, sex and genetic phenotype) and studies characteristics (design and duration). N: number of participants.

Table 2: Describes participants main basic characteristics prior to and in response to R-metHuLeptin therapy. BW: body weight, EI: energy intake, LH: luteinizing hormone, FSH: follicle stimulating hormone, Pre: pre-treatment, Post: post-treatment, N-R: not reported.

Six studies were eligible for inclusion criteria (five case studies and one case series). Number of total participants was nine (three adults and six children). Follow up period was variable, ranged from few weeks to four years. R-metHuLeptin dose ranged from 0.01-0.04 mg/kg/day in either single or twice a day regime. Dose was adjusted to reach 10% of predicted normal serum leptin levels for the patient's age, sex and body composition. Dose adjustments during treatment were made according to body composition and weight changes [17] i.e. excessive weight loss or weight gain (if BW continued to increase for two consecutive months, leptin dose will be increased to reach 20, 50, 100, 150 % of serum leptin levels).

BW

All but one trial reported changes in BW. All patients had marked weight loss (mean weight reduction was 29.6 kg) ranged from 3.8 to 78.7 kg. The largest mean weight loss was observed by Licinio et al. [8], around 78.7 kg among adult participants within eighteen months of treatment. In addition, even short term trials showed BW changes, for example Wabitsch et al. [21] demonstrated a remarkable mean weight loss of 9.3 kg within eighteen weeks of therapy.

BFM

Only four studies assessed BFM percentage. Mean reduction was 19.03 %, ranged from 7.0% to 33.7%. Remarkable BFM reduction was observed among one male adult participant (from 43.8 % to 10.1%) [10].

Hypoleptinemia

Four studies reported changes on serum leptin levels. They were observed to be amended in two participants with LEP gene mutations and two participants with bioinactive leptin deficiency. The girl serum leptin concentrations rose from below 0.04 to 19.8 ng/ml by one year of therapy [17]. Among adult patients a mean increase of leptin levels was observed from 0.77 (+/- 0.01) to 12.67 (+/- 0.83) ng/ml [8]. On the other hand, participants with biologically inactive leptin deficiency showed contradicted results, two children reported reduced mutant leptin levels with a mean reduction of 44.2 ng/ml and one child showed a rebound increase from 59.7 to 64.0 ng/ml by end of trial [4,21].

Metabolic abnormalities

Hyperinsulinemia: Insulin was entirely normalized in five studies, mean reduction was 11.8 μU/ml ranged from 7.0 to 21.4 μU/ml. The largest reduction was observed by Wabitsch et al. [21], fasting insulin was decreased from 19.2 to 4.8 μU/ml by eighteen weeks of therapy among children patients. On the other hand among adult participants only one adult female has fasting hyperinsulinemia and has shown marked reduction from 7.5 to 3.1 μU/ml by end of trial [8].

Hyperlipidemia: Five studies reported serum triglycerides levels, all participants have normal serum triglycerides except three participants. A remarkable improvement in hypertriglyceridemia was reported in one leptin deficient girl, serum levels were reduced from 240 to 52.2 mg/dl by four years of therapy [9]. Mean reduction of all three affected participants was 151 mg/dl ranged (125 to 187 mg/dl). Three studies reported serum cholesterol levels, all participants have normal cholesterol before and after treatment.

Hyperglycemia: Three studies assessed blood sugar. All participants have normal blood glucose at baseline except one adult female who was diabetic and her blood sugar parameters were totally normalized by eighteen months of therapy, her fasting blood sugar was reduced from 131 to 86 mg/dl. HbA1c values were not reported [8].

Hormonal abnormalities: Four trials reported LH and FSH. LH was static among all children participants (<0.1 mlU/ml) except for one children where it rose from 0.2 to 0.3 mlU/ml [15]. Among adult participants reported mean LH levels at baseline was 0.75 (± 0.04) mlU/ml reaching 2.75 (± 0.07) mlU/ml by end of study [10]. In the contrary to the mean FSH levels that showed a mild increase from < 0.3 to 1.9 mlU/ml among children participants [4,9,15].

Reported side effects were spontaneous self-limiting skin reactions at injection site within one week of leptin therapy in one adult female [10], and the production of neutralizing antiLeptin antibodies within two months that continued throughout the whole treatment follow up period [15], it has no effect on leptin therapy, although an elevated and delayed peak serum leptin levels were reported after leptin administration [15].

Discussion

The primary outcome of all included six studies was to examine the effects of leptin replacement therapy on leptin naïve patients, However, there was no definite baseline selection criteria for participants other than their clinical phenotype (being morbidly obese with a history of early onset increased appetite). No specific genetic mutations were selected for intervention, as such the outcome of studies cannot be generalized. Moreover, almost all studies retrieved patient's medical history data through interviews conducted with their families, thus subjected to recall bias. Quality assessment measures were not reported for the six included studies. On the other hand, data analysis was clearly described and the findings can be utilized for generalized group of patients.

Dramatic effects were reported on BFM content and BW. Food intake showed variable responses ranging from a rapid reduction to a rebound increase in energy intake that ended by a maintained controlled appetite. The observed maintained reduction in BW was referred to the fall in BFM content, that stimulated the sense of wellbeing and increased the ability for performing effective physical activity observed within six months of therapy [8,15]. On the hand, gradual improvement was observed in hyperinsulinemia and dyslipidemia that was linked to the change observed in BMI [8,31].

The nine years old girl with CLD entered puberty while on treatment, whether this occurred in response to leptin therapy or as a normal physiological response to her age, it cannot be determined. On the other hand the three adults with leptin gene defect received an evening programmed dose of leptin therapy to mimic the normal pulse pattern of leptin secretion and within six months of therapy they developed secondary sexual characteristics, one adult female started menarche and the other one had regular menses thereafter, whether these changes occurred as a direct effect of leptin or to the timing of dose administration is not fully understood. Static LH levels were observed in three children, this may reflect that leptin has no premature pubertal effects in young patients [4,9,21].

Moreover, not all participant were able to complete the whole follow up period and some trials didn't report most of patients basic characteristics, this can be referred to individual reasons (patient access to research center or noncompliance to self-administered metreleptin injections). Due to the lack of comparative studies it was also difficult to assess if administration of leptin therapy in childhood or adulthood has more powerful significant effects on CLD phenotype, but according to the reported comorbidities it would be of great benefit if treatment is started as soon as CLD is suspected.

This review has some limitations. Most importantly, the analysis was confined to clinical data from human trials utilizing exogenous leptin for management of CLD among patients who are naïve for leptin and didn't include effects of leptin analogue in other forms of leptin deficiency, which adversely affected the sample size and power of the study. Moreover, data was pooled from case studies and case series, that may appropriately reflect the reality of the treatment of leptin deficiency, however, case reports are less powerful compared to large cohort ones, and are subjected to increased bias.

All included studies revealed that leptin analogue has a powerful favorable effects on metabolic and neuroendocrine abnormalities linked to leptin deficiency, However, participants were of different ethnicity with heterogenous genetic phenotypes, thus the outcome of intervention may be influenced by individual variations. Furthermore, follow up period was variable, the fact that may affect validity of the results (underestimated or overestimated). In addition, data for this review was obtained from published available literature, thus subjected to selection bias. Furthermore, many studies has restricted access and primary data couldn't be extracted.

Bariatric surgery

There is limited data on effects of bariatric surgery on CLD. One reported young adolescent boy with unipaternal disomy LEPR gene mutation has underwent two adjustable gastric banding upon his family request for obesity management, due to disfiguring effects, the first banding led to loss of 28% of initial BW within one year, after which banding has slipped and removed. The patient regained 5 kg. A second banding was done one year later and the patient lost 20% of his BW. In the contrary to one adult female patient who underwent bariatric surgery but failed to lose weight due to non-adherence to diet and physical activity [20]. No available data on bariatric surgery effects on neuroendocrine and metabolic abnormalities.

Conclusion and Recommendations

This review has comprehensively presented data on congenital leptin deficiency among patients who have never been exposed to endogenous nor exogenous leptin, and did focus on certain body parameters. In patients with functional leptin deficiency, leptin replacement therapy was also effective in improving parameters of morbid obesity, hyperinsulinemia and hyperlipidemia as well as biologically inactive leptin levels. Although data suggests that R-metHuLeptin may be clinically efficient for patients with defective LEPR gene mutations, there is no available data.

Further studies is needed in the field, as congenital leptin deficiency is a treatable condition with good outcome. Exogenous leptin should be investigated for treatment of other forms of leptin deficiency such as leptin resistance. Primary health care facilities are the first healthcare line that deals with individuals with obesity, and many patients with congenital leptin deficiency can be identified there, if working personnel are well educated and equipped with necessary tools and skills.

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