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Review

Evidence from clinical studies of leptin: current and future clinical applications in humans

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ABSTRACT

Leptin has been established as the prototype adipose tissue secreted hormone and as a major regulator of several human physiology functions. Here, we are primarily reviewing the findings from studies in humans involving leptin administration. We are describing the metabolic, endocrine and immunologic effects of leptin replacement in conditions of leptin deficiency, such as short-term fasting in healthy individuals, relative energy deficiency in sports (RED—S), congenital leptin deficiency (CLD), generalized (GL) and partial lipodystrophy (PL), HIV-associated lipodystrophy (HIV-L) and of leptin treatment in conditions of leptin excess (common obesity, type 2 diabetes, steatotic liver disease). We are comparing the results with the findings from preclinical models and present the main conclusions regarding the role of leptin in human physiology, pathophysiology and therapeutics. We conclude that, in conditions of energy deficiency, leptin substitution effectively reduces body weight and fat mass through reduction of appetite, it improves hypertriglyceridemia, insulin resistance and hepatic steatosis (especially in GL and PL), it restores neuroendocrine function (especially the gonadotropic axis), it regulates adaptive immune system cell populations and it improves bone health. On the contrary, leptin treatment in conditions of leptin excess, such as common obesity and type 2 diabetes, does not improve any metabolic abnormalities. Strategies to overcome leptin tolerance/resistance in obesity and type 2 diabetes have provided promising results in animal studies, which should though be tested in humans in randomized clinical trials.

1. Introduction

Leptin is a hormone, which is secreted predominantly by the adipose tissue in proportion to the amount of energy stored as fat and which is recognized as a key regulator of metabolism as well as of neuroendocrine and immune functions. Numerous studies have focused on defining the role of leptin in physiology and in different disease states, a fact that is vividly illustrated by the >44,000 available publications in Pubmed on leptin since its discovery in 1994 [1]. The vast majority of the reported findings have derived from cell culture and animal models, and secondarily from observational clinical studies. On the contrary, only a limited number of interventional, let alone placebo controlled leptin administration clinical trials (of the highest quality medical research in terms of methodology) have been performed to date. Based on the results from clinical studies, in the United States, metreleptin (a synthetic analog of leptin) was approved for the treatment of hypertriglyceridemia and diabetes due to congenital or acquired generalized lipodystrophy. In Europe, metreleptin is further approved for the treatment of familial or acquired partial lipodystrophy in adults and in children older than 12 years of age with metabolic abnormalities despite standard treatments [2]. Celebrating the 30 years from the discovery of leptin, we are going to discuss in this review, the results from clinical studies that have administered leptin in humans, compare them with the findings from preclinical experiments and present the main conclusions regarding the role of leptin in human physiology.

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2. Effects of leptin treatment in mice

In order to understand the role of leptin in human physiology and the path that was followed for the development of leptin-based treatments, it is important to summarize the main findings from animal studies evaluating leptin function.

Leptin treatment in mice has been assessed both in mouse models of leptin deficiency (ob/ob, aP2-nSREBP-1c transgenic mice), as well as in mouse models of leptin excess (diet-induced obese mice, DIO). The ob/ob mouse is characterized by lack of leptin due to a mutation in leptin gene [1]. Ob/ob mice develop severe obesity primarily due to hyperphagia and secondarily due to reduced energy expenditure and physical activity [3]. Additionally, they demonstrate several metabolic abnormalities, such as hyperglycemia, hyperinsulinemia, hyperlipidemia and liver steatosis [2,3]. They have impaired fertility and altered adaptive and innate immune responses. Altogether, they demonstrate a metabolic and endocrine phenotype that is very similar to the phenotype observed in humans with congenital leptin deficiency. Treatment with leptin of these mice resulted in reversal of all metabolic and endocrine abnormalities [2,3]. Specifically, it led to profound weight loss, mainly due to reduction of appetite by inhibiting Neuropeptide Y (NPY) and Agouti-related Peptide (AgRP) and by stimulating Proopiomelanocortin (POMC) neurons in the hypothalamus. Energy expenditure was also increased by activating sympathetic nervous system (SNS) and by promoting thermogenesis from adipose tissue [4–6]. A stimulation of lipolysis and an increased utilization of lipids as energy substrates was also reported with leptin treatment in these mice, which is thought to have contributed to the observed fat mass loss [4,5]. Glucose uptake and turnover were increased with leptin treatment in several organs, such as the brain, heart and brown adipose tissue [7]. Insulin resistance, hyperglycemia and hepatic steatosis were consequently reduced [2]. The reproductive function was corrected by restoration of the hypothalamic-pituitary hormones through leptin administration [8].

The aP2-nSREBP-1c mouse is characterized by failure of adipocytes to differentially fully, which results in a profound decrease of white adipose tissue mass, thus representing an animal model of lipodystrophy [9]. The mice are hyperglycemic, hyperinsulinemic, with marked hepatic steatosis and with mild hyperphagia. Treatment with leptin reduced appetite, body weight and hepatic steatosis. Additionally, it improved insulin sensitivity and glucose levels, with these effects being independent of the reduction of caloric intake [9].

Wild-type healthy C57BL/6 J mice, which their leptin levels reflect the leptin concentrations expected in healthy conditions, lost modestly body weight with the administration of high-doses of leptin due to a reduction in energy intake, while energy expenditure was not affected [10]. Furthermore, fasting of the above mice leads to profound reduction of leptin levels and downregulation of the gonadal, adrenal and thyroid axes, which are completely restored after leptin substitution [11]. During fasting, leptin substitution did not affect weight, glucose and insulin levels or ketone concentrations, but it led to lower food intake after refeeding [11]. In contrast, DIO mice, which have high body fat mass and high leptin levels, achieved minimal to no weight loss with high doses of leptin treatment [10,12].

In summary, mouse findings indicated that leptin treatment is more effective in restoring metabolic and endocrine abnormalities in conditions of leptin deficiency (congenital leptin deficiency, lipodystrophies, fasting - induced hypoleptinemia) than in normo- or hyperleptinemic conditions.

3. Effects of leptin treatment in humans

3.1. Conditions of acute energy deprivation in healthy individuals

Circulating leptin concentrations in humans, influenced by several hormonal and other factors, correlate strongly with body fat percentage and are thus elevated in obesity and reduced in leanness [2,13,14]. Furthermore, leptin concentrations are higher in women than men, which is only partially explained by the higher body fat percentage in women and may reflect the effect of sex steroids on leptin levels [2]. Soon after the discovery of leptin, it became apparent, that leptin levels can decrease rapidly (within 24 h) and profoundly (by >50 %) during fasting both in normal-weight and obese humans [15]. Since animal experiments indicated an appetite – suppressant role for leptin [16], the reduction of leptin levels during fasting in humans has been initially interpreted as a compensatory mechanism aiming to increase appetite and to signal the urgent need for higher energy intake [11].

Fasting is additionally accompanied by several metabolic and neurohormonal changes [17]. LH pulsatility and overall secretion as well as testosterone and estradiol levels are decreased with prolonged food deprivation to prevent procreation, which is an energy demanding process. Furthermore, energy fuel utilization gradually changes. The SNS activity is altered as is the release of catecholamines and cortisol as well as of thyroid hormone levels [18]. These promote lipolysis, glycogenolysis, gluconeogenesis and in more prolonged cases protein catabolism. Initially, hepatic glycogen stores are exhausted and subsequently ketone bodies deriving from β oxidation of free fatty acids, fat-derived glycerol and ketogenic aminoacids are used as main energy fuels [17,18]. Animal and observational human studies have suggested that the decrease in leptin during fasting might be responsible for all the above metabolic and neurohormonal changes [11,18].

Two randomized, placebo controlled cross over clinical trials performed by the Mantzoros Clinical Research group in individuals undergoing complete fasting for three days and receiving metreleptin (the synthetic analogue of leptin) or placebo provided compelling evidence about the physiologic role of leptin in starvation in humans [19–21]. The first study included 8 males and 7 females who were healthy and had a normal BMI. They underwent three hospital 3-day admissions in a cross-over study design: one under isocaloric fed-state and two during complete fasting-state. During fasting and in a double-blind random order, participants were treated either with placebo or with metreleptin, in a physiological dose that prevented fasting-induced hypoleptinemia [19–21].

The first important finding of this study was that the weight loss observed during the 3 day-fasting was similar under leptin replacement compared to placebo and was not related to the leptin levels at the start of the intervention. This argues against a significant impact of leptin on energy expenditure. In agreement with the above, although, as expected, catecholamines, cortisol and heart rate (markers of sympathetic nervous activity) increased during fasting, treatment with leptin had no impact on them or on blood pressure [19–21]. Additionally, treatment with leptin did not prevent lipolysis and the shift from glucose to lipid utilization, but it rather slightly stimulated them during the third day of fasting [21].

A second important finding of this study was that fasting-induced hypoleptinemia is associated with appetite in humans. Specifically, the lower the leptin levels after 72 h of fasting were, the higher the energy intake in a subsequent ad libitum meal was [21]. This inverse association was though blunted for leptin levels above 10 ng/ml indicating possible saturation of leptin regulatory effects on appetite above a certain threshold [21].

The third important finding was that fasting-induced hypoleptinemia contributes to the suppression of the pituitary-gonadal axis. Specifically, maintenance of normal leptin levels during fasting, using metreleptin administration, prevented the loss of LH pulsatility both in men and women that normally occurs during fasting and it even succeeded in preventing the concomitant fasting-mediated testosterone reduction in men [19,20]. In contrast, metreleptin administration did not prevent the loss of growth hormone (GH) pulsatility or the decline of IGF-1 observed during fasting. It restored only partially TSH pulsatility in men but improved neither TSH nor had any major effects on thyroid hormone levels in men or women during short term fasting lasting a few days.

The fourth important finding was that fasting-induced

hypoleptinemia affects the number of cells involved in adaptive immune response. Specifically, maintenance of normal leptin levels during fasting with metreleptin partially prevented the decline of total CD3+, CD4+ and CD8+ T lymphocytes and CD19+ B lymphocytes that occurs during fasting. On the other hand, leptin did not affect the number of natural killer (NK) cells, representing innate immunity, and the stimulated cytokine production by peripheral blood mononuclear cells (PBMCs) [19,20].

In the last 15 years, a series of new hormones have been identified, the blood levels of which drastically change during fasting. These include: a) activins and follistatins, which are involved in reproductive function and glucose homeostasis as well as maintenance of muscle and bone mass [22–26], b) GDF-15 a mitokine which has been linked to appetite regulation, energy expenditure and immune response [27–31] and, c) PCSK9 and ANGPTL3 which are involved in lipid metabolism [32]. Maintenance of normoleptinemia with metreleptin administration did not prevent the fasting-induced changes in the concentrations of the above hormones, indicating leptin-independent mechanisms of function for them [25,28,33–36].

An important question remaining after the first study was whether administration of leptin in a very high dose, that not only prevents fasting-induced hypoleptinemia but increases leptin concentrations above the normal range, might be needed to observe more pronounced effects on metabolic, immune and neurohormonal changes occurring in starvation. This question was answered by a second clinical trial which included lean men and women, as well as obese men undergoing again a 72 h - fasting, but being this time treated in each admission with a different leptin dose (physiologic, supraphysiologic and pharmacologic) [21,37]. Higher doses of leptin administration resulted in leptin concentrations up to 150 ng/ml, but they still had no impact on body weight loss, energy expenditure, SNS activity or fuel utilization during fasting [21,37].

In summary, based on the results of several randomized human clinical trials, hypoleptinemia during fasting serves two main purposes. The first purpose is to induce appetite as a signal for the urgent need to increase energy intake. The second purpose is to conserve energy by inhibiting energy demanding biological functions such as procreation in states of starvation or by regulating immune cell function.

3.2. Conditions of chronic energy deficiency

3.2.1. Relative energy deficiency in sports (RED—S)

RED-S is a condition characterized by chronic low energy availability due to intense exercise that can induce a wide spectrum of abnormalities in multiple organs [38]. These include neuroendocrine abnormalities that are similar to the changes observed during acute complete fasting, such as the insufficiency of the hypothalamic - pituitary – gonadal, – thyroid and – somatotropic axis and the stimulation of the – adrenal axis [38]. RED-S can also have detrimental effects on bone health and on immune cell responses and it can promote anemia, endothelial dysfunction and gastrointestinal symptoms, as recently reviewed elsewhere [38].

An important aspect of RED-S is the limited amount of energy stored in adipose tissue due to energy deficiency leading to low body fat mass [38]. Since leptin levels correlate strongly with fat mass, people with RED-S demonstrate a chronic mild or significant hypoleptinemia corresponding to the amount of negative energy balance. Women with RED-S often develop a secondary amenorrhea due to the insufficiency of the hypothalamic – pituitary – gonadal (HPG) axis but the latter remains frequently undetected among men. Since it was shown that acute hypoleptinemia during short-term fasting is causally related with the inhibition of HPG-axis, an important question was whether HPG-axis insufficiency can be restored in women with RED-S with leptin administration. This question was addressed in two clinical trials [21,39,40].

In the first open-label study, eight women with amenorrhea due to RED-S were treated with leptin for up to three months [40]. Mean LH levels increased, LH-pulse patterns improved or normalized in six women and three women developed an ovulatory menstrual cycle. A significant fat mass loss also occurred when leptin levels exceeded the upper limit of normal range. As we mentioned previously, in an ad libitum meal after three days of complete fasting in healthy individuals, treatment with leptin led to 18 % less caloric intake compared to placebo. Interestingly, the observed fat mass loss in women with RED-S treated with metreleptin matched the expected fat mass loss based on a 18 % reduced caloric intake [21]. This suggests that the fat mass loss due to leptin administration is explained exclusively by reduced energy intake and not increased energy expenditure.

The second study was a double blind placebo-controlled trial of longer duration [39]. Eleven women with RED-S were randomized to receive metreleptin and nine placebo over a 36-week period with an additional 16-week follow up after treatment completion. Similarly to the open – label study, levels of reproductive hormones improved and 7 participants from the metreleptin group developed menstruation [39]. Although the treatment dose was adjusted in each visit on the basis of attained body weight (but not fat mass) in order to prevent weight loss in the study participants, metreleptin administration led to supraphysiological circulating leptin levels and thus significant fat mass loss during the 36 weeks of treatment, which was regained after treatment discontinuation [21]. In this study, three of the women with RED-S underwent a brain fMRI one week and 24 weeks after treatment and were matched with nine normoleptinemic women [41]. The one-week leptin treatment enhanced the activation of brain areas involved in salience and rewarding of food during fasting. The 24-week treatment had though the opposite effects, i.e. it decreased the activation in brain areas related to food attention and rewarding value of food after feeding.

In both studies, a transient mild increase in free fatty acids was observed with leptin treatment, indicating a possible modest stimulation of lipolysis [21]. In agreement with the short-term fasting studies in healthy individuals, long-term leptin treatment in RED-S did not affect resting metabolic rate and markers of SNS activity [21], whereas it had significant effects on immune system [42]. Specifically, restoration of leptin levels with metreleptin administration in RED-S restored CD4+ T-cell counts and their in vitro proliferative response. Genes related to cell survival were upregulated and genes related to apoptosis were downregulated. Finally, the STAT3, AMPK, mTOR and ERK1/2 pathways, which are involved in cell proliferation and survival, were activated in CD4+ T cells [42].

Long-term leptin treatment in RED-S had also mild effects on somatotropic, thyroid and adrenal axis. Specifically, in the 3-month study, it increased transiently IGF-1 in the first month and IGFBP-3 during the second and third month, without affecting cortisol levels [40]. Moreover, leptin increased TSH pulse frequently and amplitude, as well as transiently free T3 and free T4. In the 36-week RCT, it increased fT3, total IGF-1 and tended to increase free IGF-1 and IGFBP-3, whereas it reduced cortisol levels compared to placebo [39].

Finally, long-term leptin treatment had beneficial effects on both health. Specifically, it increased the concentration of markers related to bone formation, such as osteocalcin, and decreased the concentration of markers related to bone resorption and osteoclastic activity, such as the RANKL/OPG ratio, CTX, intact PTH and the urinary N-Terminal telopeptide/creatinine ratio [39,43]. Notably, leptin treatment resulted in an increase in bone mineral content and bone mineral density of 2–3 % after 36 weeks of treatment. Six subjects who elected to continue on open-label metreleptin treatment for another 12 months demonstrated a 4–6 % improvement in bone mineral content and bone mineral density [43]. The restoration of the gonadotropic axis and secondarily the decline of cortisol levels are considered important contributors to the improvements observed in bone health in these patients [43].

In summary, the findings from the clinical trials in RED-S fully agree with the results from the short-term acute energy deprivation studies about leptin. Hypoleptinemia in both conditions may stimulate appetite and it inhibits the HPG axis and immune function. In the long term it

may have additional direct neuroendocrine regulating effects (e.g. cortisol, IGF-1, fT3 levels) and indirect effects regulating bone mass and density. All the above effects aim at preserving energy, maintaining body weight, muscle and bone mass while promoting the use of fat from lipolysis and glucose from glycogenolysis and gluconeogenesis as energy sources. Notably, all the studies in RED-S have been performed with female patients. Thus, whether leptin treatment exerts the same effects on males with RED-S remains unclear and has to be assessed in future RCTs. This is though highly likely, given the similarities in response to leptin during short-term fasting observed in healthy males and females [19,20].

3.2.2. Anorexia nervosa

Anorexia Nervosa (AN) is a life-threatening mental disorder characterized by severe undernutrition, beyond usual RED—S, leading to low body weight [44]. AN is associated with profound metabolic and endocrine alterations and is thus increasingly recognized as a metabo-psychiatric disorder [45]. Several studies have demonstrated that leptin levels in patients with AN are very low (often below 1 ng/ml) due to the almost complete absence of fat mass [46,47]. People with AN demonstrate frequently an insufficiency of HPG axis which leads to amenorrhea in women and to low testosterone in men [48]. Additionally, they demonstrate elevated GH but decreased IGF-1 concentrations, indicating resistance to GH possibly due to undernutrition. Patients with AN have also low total T3 levels and elevated cortisol levels and most importantly they suffer from low bone mineral density combined with altered bone microarchitecture and higher risk for fractures, which often persists even after weight recovery [49].

An interesting question is whether hypoleptinemia in AN might be responsible for some of the mental and somatic symptoms that patients with AN report [46]. In this context, case reports on seven patients with AN treated off-label with metreleptin have been published so far (reviewed in [46]). In all cases treatments were short, ranging from 9 to 24 days and uncontrolled. According to the results, metreleptin administration might be able to improve mood, sleep and body image disturbance within a few days but these findingsshould be viewed as preliminary data only raising hypotheses for future studies given their uncontrolled design. Additionally, in some cases, improvement of constipation, of low blood cell counts or of HPG-insufficiency were reported. Leptin administration was combined in several of these cases with efforts to induce weight gain, even with nasogastric feeding [50]. Thus, these results should be interpreted cautiously since it is difficult to dissect the effects of leptin from the impact of the general management which these patients received. Moreover, mechanistic evidence for the reported effects are currently limited.

Since leptin in humans acts not only on hypothalamus, but also on other centers related to reward system and even after exposure to stimuli unrelated to eating-behavior [41,51], leptin might have effects on mood and psychiatric disorders. This demands though further investigation in patients with AN. Finally, based on the findings from patients with RED—S, leptin administration is expected to induce weight loss in patients with AN, if used in the long-term. If it is used in the short-term, the question is whether any positive effects in mental symptoms observed during leptin treatment will remain after its discontinuation. Nonetheless, a Phase II RCT (NCT06305182) with metreleptin vs placebo in patients with AN has been recently registered, albeit not yet recruiting, in clinicaltrials.gov, which is expected to provide more evidence about the possible impact of leptin on mental symptoms in this disease.

In summary, AN is associated with severe hypoleptinemia. The evidence of the effects of leptin substitution in people with AN is very limited. Such studies are needed, but they should be performed cautiously to avoid any detrimental effects of leptin treatment, such as further weight loss in a population with underweight.

3.3. Syndromes of leptin deficiency

3.3.1. Congenital leptin deficiency (CLD)

CLD is a rare condition characterized in its classical form by very low leptin levels due to mutations in leptin gene, resulting in impaired synthesis and/or secretion of leptin [52]. People with CLD gain weight in very young age due to hyperphagia and become severely obese [53]. Additionally, they often develop insulin resistance, diabetes and dyslipidemia. Hypogonadotropic hypogonadism is frequently present as well as recurrent and/or severe infections, especially of the respiratory and gastrointestinal tract [52,54].

Since CLD is extremely rare, no RCTs could have been performed so far but several cases treated with metreleptin have been reported [55–58]. In all cases, treatment with leptin led to profound reduction in energy intake, resulting in significant weight loss and fat mass loss [56,57]. Leptin replacement in CLD was found to regulate neural activation in striatal regions of the brain, suggesting reduced perception of food reward as well as increased response to satiety signals after food intake in uncontrolled studies [55]. In contrast, no changes in energy expenditure or in cortisol levels were observed [56]. Additionally, restoration of LH and FSH pulsatility were observed, as well as an increase in CD4+ T cell population [56]. Leptin replacement induced also a change in lipidome profile consistent with increased lipolysis and fatty acid oxidation [58]. The slow fat mass loss led also to gradual improvement of insulin sensitivity and of dyslipidemia (reduction in triglycerides and LDL-cholesterol and increase in HDL-cholesterol). Interestingly and in contrast to RED—S, CLD is not associated with osteoporosis and treatment with leptin has no significant effects on bone mineral content [57,59].

In summary, leptin treatment in CLD is very effective leading to restoration of the observed profound metabolic abnormalities.

3.3.2. Non-HIV related lipodystrophy syndromes

Lipodystrophy syndromes comprise a rare heterogeneous group of disorders characterized by diminished subcutaneous adipose tissue and increased ectopic accumulation of fat, especially in visceral organs [60,61]. Lipodystrophy syndromes are classified in two major forms, the generalized lipodystrophy (GL) and the partial lipodystrophy (PL), which both can be congenital due to gene mutations or acquired. In GL, the absence or gradual loss of adipose tissue is severe and it affects the whole body, whereas in PL the adipose tissue loss is relative and it is related to specific body regions, such as the limbs or upper body [60,61]. People with GL and PL might be overweight or slightly obese, but they demonstrate often severe hypertriglyceridemia, insulin resistance, diabetes, liver abnormalities (steatosis and elevated liver transaminases) and reproductive dysfunction [60–62]. In GL symptoms are more profound and complications manifest earlier compared to PL. Leptin levels are severely reduced in GL (mean levels at 1–2 ng/ml) and modestly in PL (mean levels at 6–7 ng/ml) [63].

Similarly to CLD, GL and PL are rare syndromes and thus no RCTs have been performed to date. Nevertheless, prospective, single-arm open-label studies with continuous enrollment since 2000 have provided several evidence about the impact of leptin treatment in these patients. First of all, the findings from these studies fully agree with the conclusions from studies in women with RED-S and healthy individuals in acute fasting. Patients with GL and PL treated with metreleptin had a mild weight loss due to decreased appetite [63–65]. Leptin treatment did not increase energy expenditure, but rather modestly decreased it [66]. Additionally, leptin improved menstrual abnormalities and low estradiol levels and corrected the LH response to LHRH in young women with lipodystrophy [67]. Finally, it normalized both the absolute number and relative percentage of T lymphocyte subsets [68]. Leptin treatment had no effect on cortisol and ACTH secretion, on blood pressure and on thyroid hormones [67,69].

Notably, both patients with GL and PL demonstrate significant improvement in HbA1c (−2.2 % in GL and − 0.6 % in PL after 12 months

of treatments), triglycerides (−32.1 % in GL and − 20.8 % in PL) and liver volume (−33.8 % in GL and − 13.4 % in PL) with metreleptin [70,71]. Since weight loss is rather modest in these patients, the observed improvement in glucose homeostasis and lipid metabolism might be mediated by mechanisms that are at least partially independent of food intake [72]. According to a recent study, leptin might be able to decrease gluconeogenesis in patients with lipodystrophy by decreasing the availability of carbon sources deriving from glycerol, alanine and lactate [73]. Reduced gluconeogenesis is expected to decrease blood glucose levels and potentially decrease hyperinsulinemia and insulin resistance. In another study, leptin-mediated improvement in peripheral insulin sensitivity increased the uptake of glucose by peripheral tissues, which consequently reduces carbohydrate transport to the liver [74]. This event resulted in reduced de novo lipogenesis and might explain the improvement of dyslipidemia and of liver steatosis [74]. Furthermore, animal experiments suggest that leptin may act as an insulin-mimetic in muscle or it might stimulate lipid oxidation in muscle to produce energy while reducing intramuscular lipid accumulation [75].

Importantly, metreleptin can be an effective treatment not only to congenital but also to acquired GL and PL. Specifically, acquired GL is often accompanied by other autoimmune disorders, such as juvenile dermatomyositis, rheumatoid arthritis, Hashimoto thyroiditis or chronic hepatitis which manifest in young age [76]. Metreleptin administration in clinical case reports in pediatric patients with acquired GL, who were under immunosuppression due to autoimmune disorders, resulted in profound decrease of hyperglycemia, possibly due to the marked improvement of insulin sensitivity and reduction of hypertriglyceridemia, without altering the clinical course or the treatment response of the autoimmune diseases [77]. Childhood cancer survivors undergoing hematopoietic stem cell transplantation will often develop PL, characterized by impaired glucose tolerance or diabetes, hypertriglyceridemia and hepatic steatosis [78–80]. Metreleptin administration in such patient cases was also capable of reversing metabolic abnormalities [78–80].

Finally, as in CLD, patients with GL or PL demonstrate normal or even increased bone mineral density/content or bone mass [81,82], which do not change after restoration of leptin levels with metreleptin administration [57,81,82].

In summary, leptin treatment is very effective at improving insulin sensitivity, hyperglycemia, hypertriglyceridemia and hepatic steatosis in lipodystrophies, These beneficial effects of leptin treatment are observed both in congenital and in acquired lipodystrophies and are more profound in GL than in PL.

3.3.3. *Leptin deficiency due to human immunodeficiency virus (HIV) – Associated lipodystrophy (HALS)*

Patients with HIV treated with highly active antiretroviral therapy (HAART) often develop an acquired type of lipodystrophy, commonly referred as HALS. We have previously described four types of HALS depending on fat distribution and amount [83]. One of these types is the lipoatrophic HALS characterized by generalized fat depletion and very low leptin levels <1–2 ng/ml [83,84]. Patients with lipoatrophic HALS demonstrate insulin resistance, hypertriglyceridemia and hepatic steatosis. Three placebo-controlled trials (two performed by the Mantzoros Lab) and one open-label study evaluated the effects of metreleptin administration in lipoatrophic HALS [84–87]. The findings from the studies agree that leptin administration improves insulin sensitivity (both in terms of HOMA-IR as well as of hepatic insulin sensitivity) and hyperglycemia. Leptin treatment had minor effects on body fat composition (reduction in truncal fat mass in one study) and in lipid metabolism (improvement of HDL-C in one study and of non-HDL-C in the other study) and it had no effects on hepatic steatosis but the duration of the studies was not sufficient to fully study SLD in the long term. Finally, leptin administration had no effects on viral load and T – cell numbers.

3.4. *Overweight and common obesity*

Despite the elevated leptin levels in obesity, which reflect the increased fat mass, initially there was hope that administration of leptin in pharmacological doses might still be able to induce weight loss. This hope was based on the analogous example of insulin treatment, which is able to reduce blood glucose levels even in individuals with hyperinsulinemia due to insulin resistance. The first phase II randomized controlled trial (RCT) with leptin in people with obesity was published in 1999 [88]. The study failed to reach its primary outcomes, reporting non-significant differences between placebo vs different leptin doses. However, variability in treatment response and a somewhat higher weight loss with high doses of leptin (after 24 weeks ~8 % in on-treatment analysis but only ~4 % in intention-to-treat analysis) led the authors to conclude that leptin treatment in higher doses might be beneficial for a specific group of patients. A series of subsequent RCTs with metreleptin or pegylated human recombinant leptin (PEG-OB) in different doses did not show any significant effects of leptin on weight loss, body composition, energy expenditure, SNS activity, adrenal hormones, lipid profile and macronutrient utilization [89–93]. These negative results created the concept of “leptin resistance” or “leptin tolerance” to describe the lack of significant effects of leptin in obesity.

If leptin resistance in obesity exists, leptin administration should result in less activation of signaling pathways in targeted tissues in people with obesity compared to normal-weight controls. However, it seems that this is not the case. In vivo and ex vivo metreleptin administration resulted in similar activation of leptin-relevant downstream signaling pathways (STAT3, MAPK) in human adipose tissue biopsies and peripheral blood mononuclear cells (PBMCs) of obese versus lean people, which were saturated at 50 ng/ml of leptin, thus indicating leptin tolerance than leptin resistance [91]. Several strategies have subsequently aimed to overcome leptin tolerance or resistance.

The first strategy that was tested, was “leptin sensitization” by initial induction of weight – loss with diet followed by leptin administration. This strategy was mainly evaluated in two studies performed by the same group in people that lost initially 10 % weight with diet and were subsequently treated with leptin [94,95]. The first study was single-arm open label and led to a 2.1 kg weight loss within 5 weeks in patients treated with leptin [94]. The authors concluded that the weight reduction and not weight regain after discontinuation of diet was achieved by restoration of energy expenditure to pre-weight loss levels by leptin. In a subsequent single-blind placebo-controlled trial from the same group, again an increase of energy expenditure and also of satiety was reported with leptin administration for 5 weeks following an initial 10 % weight loss with diet, but paradoxically no differences in weight loss were observed between leptin and placebo [95,96]. Thus, the observed improvements in energy expenditure might simply reflect physiological restoration of metabolic rates after completion of the dynamic phase of weight loss and stabilization of metabolism to a new baseline weight, irrespectively of leptin administration. Similarly, two RCTs with a 3- to 4-week lead-in diet period with 500 kcal/day deficit did not show any differences on weight loss with subsequent leptin treatment compared to placebo [89,93]. Finally, another RCT evaluated leptin administration for 16 weeks in women that have undergone a Roux-en-Y Gastric Bypass at least 18 months before [97]. These women had lost in average 31 % of their body weight and their leptin levels were significantly lower compared to the pre-operation state. Even in this population, leptin treatment could not induce any significant weight loss compared to placebo [97].

Leptin binds to the leptin receptor in order to mediate its functions. Four membare-anchored isoforms of the leptin receptor have been described, which participate in downstream cellular signaling upon binding of leptin. Another leptin receptor isoform, the soluble leptin receptor (sOB-R), which derives in humans exclusively by proteolytic shedding of the membrane-anchored proteins, binds leptin in human blood [98,99]. High concentrations of sOB-R in most studies seem to

inhibit leptin's effects, but low concentrations of sOB-R may reflect low expression of the membrane-anchored isoforms [98,99]. In obesity, low concentrations of sOB-R are observed and in anorexia nervosa high concentrations. Weight loss results in an increase of sOB-R concentrations [98,99]. Thus, it has been suggested that sOB-R might be involved either directly in leptin tolerance/resistance observed in obesity, or it may serve as marker of leptin sensitivity. Different strategies aiming to regulate sOB-R levels [100], to increase intracellular trafficking of membrane-anchored isoforms of leptin receptor [101] or to improve leptin signaling have shown promising results in animal studies [102]. More recent studies in obese mouse models have also reported that partial leptin reduction by genetic manipulation or by use of neutralizing antibodies is able to reduce body weight and improve insulin sensitivity, possibly via restoration of leptin sensitivity in hypothalamus [103]. Such new approaches are attractive but evidence from non-human primate or human studies are currently lacking and they are needed in order to evaluate their translational potentials.

The second strategy was a combination treatment of leptin with an amylin analogue. Amylin is a hormone co-secreted with insulin from pancreatic β cells that reduces food intake and increases satiety [104]. In animal studies, amylin and leptin demonstrated synergistic effects in reducing energy intake (up to 45 %) and body weight (up to 15 %) [105]. A RCT (NCT00392925) was performed combining an amylin analogue (pramlintide) and metreleptin. The study included a 4-week lead in period with pramlintide and diet that led to 4.4 % weight loss followed by another 16 weeks treated either with metreleptin, pramlintide or both medications combined [104]. At study completion, patients treated with the combination of metreleptin with pramlintide lost significantly more weight (−12.7 %) compared to monotherapies (−8.4 for pramlintide and − 8.2 for metreleptin) [104]. These results justified further studies, which were initiated but early terminated due to findings suggesting the development of antibodies against leptin in the majority of patients [106]. These antibodies seem though rarely to impact efficacy or safety of the medication. In a post-hoc analysis of 134 patients with lipodystrophy and 579 with common obesity treated with leptin, only 4 patients with lipodystrophy and 3 patients with obesity may have developed neutralizing antibodies, indicated by worsening of their metabolic profile [106]. Meanwhile, novel and more potent amylin analogues (e.g. cagrilintide) have been developed, which are currently under evaluation as combined treatments with GLP-1 receptor analogues (e.g. Cagrilintide with Semaglutide) [107,108]. In a phase II study, the combination of cagrilintide with semaglutide resulted in almost 16 % weight loss within 32 weeks [107], thus leading to the current evaluation of the combination treatment in a Phase III trial. Whether a combination treatment with new generation leptin and amylin receptor analogues can be efficacious for the treatment of obesity, remains to be addressed in future studies.

The third strategy to maximize benefit from a potential leptin treatment focused on identifying and treating patients with common obesity that had relatively low leptin levels. The rational supporting this approach was based on a post-hoc exploratory analysis in people with obesity treated with leptin showing better response in terms of weight loss in men with leptin levels <5 ng/ml and women <16 ng/ml [109]. This was further supported by genetic studies suggesting that some of the observed variations in leptin levels in obesity might be the result of previous unknown genetic mutations controlling indirectly leptin gene expression and subsequently leptin blood concentrations [110]. This approach though does not take into consideration the findings from patients with relative leptin deficiency due to RED-S or partial lipodystrophy, which showed that the magnitude of response to metreleptin cannot be predicted by the endogenous leptin levels [21,111]. Nevertheless, a very recent study aimed to evaluate the above hypothesis by using a new monoclonal antibody (REGN4461, mibavademab) that activates leptin receptor and does not induce drug-related antibodies [112]. In this phase I double blind placebo controlled trial, overweight or obese patients with relatively low leptin levels were treated for 12 weeks [112]. The low leptin levels were defined in two cohorts as below 5 ng/ml and in two separate cohorts as 5–8 ng/ml for males and 8–24 ng/ml for females, with the upper limit corresponding to the 25th percentile for the respective gender. Placebo-corrected weight loss after 12 weeks of leptin treatment was significantly higher in patients with leptin levels <5 ng/ml compared to patients with >8 ng/ml, but in both groups the effects were marginal (−3.1 % vs +0.1 % weight change) [112].

Given that the new anti-obesity treatments (GLP-1 receptor agonists such as semaglutide and GLP-1/GIP receptor co-agonists such as tirzepatide) are leading to profound weight loss while demonstrating an acceptable risk/side effects profile, any monotherapies with leptin analogues or leptin receptor agonists have to be at least equally potent and safe as the above treatments in order to have chances to be included in the treatment armamentarium against obesity. This seems to be at the moment extremely challenging. Thus, the question is whether combination treatments with the new gut hormone (poly) agonists and leptin analogues might be able to demonstrate additive or synergistic effects. Treatment with GLP-1 receptor agonists has been associated with a reduction of leptin concentrations, including free leptin levels, and an increase in soluble leptin receptors [113,114]. Similarly, treatment with tirzepatide led to robust reduction of leptin concentrations [115]. Such changes are also expected, since leptin levels correlate strongly with fat mass, which decreases during the treatment with GLP-1 and GLP-1/GIP receptor agonists. Whether leptin analogues or leptin receptor agonists are affecting gut hormonal function remains unclear. Nevertheless, a phase study II (NCT06373146) that has recently been initiated, is planning to evaluate the effect of mibavademab in combination with tirzepatide, a GLP-1 and GIP receptor coagonist approved for obesity and type 2 diabetes on weight loss in people with obesity.

Altogether no study so far could demonstrate significant weight loss with metreleptin administration in common obesity which will justify its further clinical development. Strategies aiming to overcome leptin resistance have generated positive findings in animal studies, which need though to be confirmed in human trials. Similarly, combination treatments with leptin receptor agonists and anti-obesity drugs are attractive approaches, which have though to prove their superiority compared to monotherapies in RCTs.

3.5. Diabetes

The impact of leptin administration on glucose homeostasis and insulin resistance has been tested in patients with type 2 diabetes [91], with type 1 diabetes [116], with diabetes or hyperglycemia due to lipodystrophies [70,71,84–87] and in patients with insulin-resistant diabetes due to mutations in the insulin receptor gene (Rabson-Mendenhall syndrome, RMS) [117].

In a placebo-controlled trial performed from our group in obese patients with type 2 diabetes, metreleptin administration over 16 weeks reduced only marginally HbA1c (from 8.01 % to 7.96 %) [91]. Similarly, in another independent study in obese patients with newly diagnosed type 2 diabetes, in which hyperinsulinemic-euglycemic clamp and tracers were used, leptin treatment had no effect on insulin sensitivity [90]. Several other studies in obese insulin-resistant populations could not show any improvement on markers of insulin sensitivity with leptin treatment, even in obese patients with “relative” leptin deficiency [93,118,119]. Altogether, leptin treatment had no effects on glucose homeostasis in common, non-syndromic obesity with type 2 diabetes or insulin resistance.

In a small open – label single arm study, the effects of metreleptin on glucose homeostasis in patients with type 1 diabetes mellitus were tested [116]. Metreleptin did not improve HbA1c, but it reduced body weight by 6.6 % and total insulin dose by 15 % after 20 weeks of treatment. Metreleptin administration did not prevent hyperglycemia after intentional reduction of the dose of basal insulin by 50 % in these patients. Given the lack of a placebo group, results have to be interpreted

cautiously since they might simply reflect the effects of increased attention from patient or of more intensive provided care by examiner during the study.

As mentioned above, metreleptin administration demonstrated positive effects on glucose homeostasis in patients with lipodystrophies [70,71]. It could significantly reduce blood glucose levels and HbA1c both in GL and in PL. Postprandial glucose levels were also decreased in HALS. The effects of metreleptin on glucose homeostasis were mainly achieved by improvement in insulin sensitivity. The exact mechanisms responsible for this improvement are not clear. Metreleptin administration in people with lipodystrophies had no direct effects on insulin secretion or β-cell function, in contrast to the effects that have been previously reported in rodent studies [120].

Finally, leptin treatment was evaluated in people with RMS. This syndrome is caused by homozygous or compound heterozygous pathogenic variants in insulin receptor (INSR). People with RMS have dysfunctional adipose tissue development and low leptin levels (by 1–5 ng/ml) and they develop insulin-resistant type 2 diabetes [117]. In an open-label controlled study, treatment with leptin resulted in lower HbA1c levels compared to the untreated group. This reduction was attributed to the concomitant weight loss observed in these patients [117].

In summary, leptin treatment was efficacious in improving glucose homeostasis by reducing insulin resistance and promoting weight loss only in patients that demonstrated some degree of leptin deficiency.

3.6. Steatotic liver disease (SLD)

Steatotic liver disease (SLD) is a condition characterized by increased accumulation of fat in the liver [31,121]. This is often the result of high caloric intake leading to increased de novo lipogenesis from carbohydrates in the liver as well as to insulin resistance resulting in enhanced hepatic uptake of free fatty acids deriving from lipolysis of adipose tissue [121]. When fat storage capacity is exhausted in the liver, lipotoxic species are formed which can induce liver inflammation and in later stages liver fibrosis and cirrhosis [121].

As mentioned in the above relevant sections, both in non-HIV and HIV-related lipodystrophy syndromes, the presence of SLD is very common. Specifically, the subcutaneous lipoatrophy results in increased deposition of lipids in visceral organs, low leptin and adiponectin levels and severe insulin resistance, aggravating the elevated triglyceride concentrations and increasing the risk for development of diabetes [122]. In HIV-related lipodystrophy, either the virus itself or the antiretroviral treatment may additionally affect directly hepatocyte function by stimulating mitochondrial dysfunction and oxidative stress [122].

We have previously reviewed the effects of metreleptin administration on lipodystrophy syndromes [122]. The findings for non-HIV-related lipodystrophies derive exclusively from open-label uncontrolled studies – case reports and for HALS from two RCTs (described above in HALS section) [122]. Metreleptin administration for one- and up to three years decreased hepatic lipid content, liver volume and liver transaminases in most cases and hepatocyte ballooning and inflammation (in histology) in some cases of non-HIV-related lipodystrophy, with the effects being more profound in GL than in PL [118,122–124]. Metreleptin did not improve liver fibrosis [118,122–124]. In HALS, treatment with leptin did not reduce liver fat % and liver volume despite improving insulin sensitivity and decreasing body fat mass in the first RCT [84], whereas in the second RCT leptin did not improve liver transaminases [85].

The hepatic effects of metreleptin were also evaluated in an open-label study in patients with “relative leptin deficiency” (RLD) and biopsy-proven metabolic-dysfunction associated steatohepatitis (MASH) [118]. RLD was defined as leptin in the lower 25th percentile for BMI and patients with MASH and RLD were treated with metreleptin for one year. Paired liver biopsies existed for 7 of these patients showing improvement in steatosis and NASH score in 5 of them, in ballooning in 4, in lobular inflammation in 3 and in fibrosis in 1 one of them. The authors concluded that patients with MASH and RLD have reductions in hepatic steatosis and injury with leptin administration. However, a very important limitation of the study, apart from its small size, is its open-label uncontrolled character. According to RCTs evaluating medications for the treatment of MASLD, an improvement in NAS score and liver fibrosis is very frequent even in placebo group (up to 33 % of the population) [125]. Thus, the reported findings should be interpreted cautiously. Moreover, the mechanism mediating such effects remains largely unknown. A recent study has suggested that leptin can increase hepatic triglyceride export through vagal stimulation [126]. In this placebo-controlled study with cross-over design, a single leptin dose was administrated in lean individuals after overnight fasting which induced VLDL-TG export and tended to inhibit the fasting-induced increase in liver fat content. Furthermore, improvement in insulin sensitivity and reduction of appetite might reduce carbohydrate and free fatty acid flux to the liver, resulting in reduction of de novo lipogenesis and consequently of hepatic steatosis [74].

Nevertheless, even if such effects can be verified in larger studies, they may still not be sufficient for the approval of leptin or leptin receptor analogues in MASLD in patients with relative leptin deficiencies. The reason is that for such an approval, a medication has to show significant resolution of MASH without worsening of fibrosis or conversely improvement of fibrosis without worsening of MASH, which none of the studies with leptin were able to show it so far, even in an open-label design and even in severe leptin deficiencies.

In summary, leptin treatment is effective at reducing hepatic steatosis in lipodystrophies but not in people with common obesity. Leptin treatment might also reduce liver inflammation in lipodystrophies, whereas it does not improve liver fibrosis.

4. Mechanisms

Human interventional clinical studies in different metabolic conditions have provided robust and consistent evidence about the role of leptin in human physiology. Summarizing, restoration of hypoleptinemia observed by fasting or in syndromes associated with low and/or dysfunctional adipose tissue mass, leads to (s. Fig. 1):

4.1. Body weight loss due to reduction of appetite and consequently of energy intake

Animal studies have shown that leptin can act on the arcuate nucleus of hypothalamus to activate POMC neurons to produce αMSH and to inhibit AgRP and NPY neurons [127]. Thus, leptin may act directly on the homeostatic centers of appetite in hypothalamus. This is further supported by studies in humans with RED-S or lipodystrophy showing changes after treatment with metreleptin in hypothalamic activity, as well as in functional connectivity with other important feeding-related areas [41,128,129]. Mechanisms regulating appetite and energy intake are though much more complex in humans than in rodents, since they strongly involve the hedonic - and reward system - related areas of the brain. In individual cases and case series of patient with CLD and in response to food vs non-food images, administration of leptin was shown to decrease activity in regions related to hunger (insula, parietal and temporal cortex) as well as to modify the activity in several areas of reward system, i.e. decreasing activity in amygdala, the nucleus accumbens, caudate and putamen (areas related to perception of food reward) and increasing activity in prefrontal cortex (area of inhibition and satiety) [55,130,131]. Similarly, in women with RED—S, treatment with leptin reduced the activity in areas related to food attention and rewarding, such as the precuneus, bilateral parietal, dorsolateral, and midbrain cortices [41]. Treatment with leptin seems also to modify resting state connectivity in insula, superior temporal gyrus and medial prefrontal cortex in patients with lipodystrophy, thus also indicating decreased feeling of hunger and lower incentive value of food in these

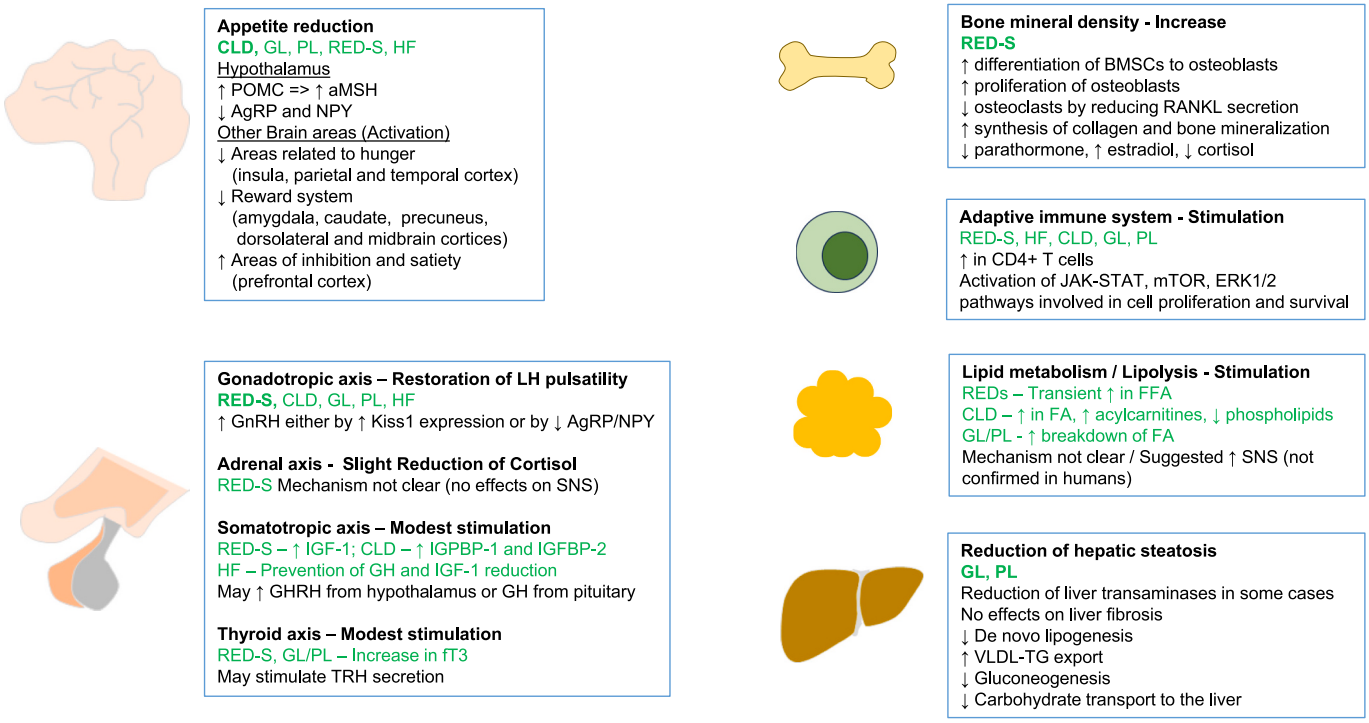

Fig. 1. Summary of the effects of leptin administration on humans

In CLD, metreleptin is a very effective treatment at reducing body weight through inhibition of appetite and consequently at improving metabolic abnormalities. Metreleptin has been also approved for the treatment of GL and PL, since it reduces hypertriglyceridemia, hyperglycemia and hepatic steatosis. In women with RED-S and hypothalamic amenorrhea, metreleptin improves the function of gonadotropic axis by restoring LH pulsatility leading to recovery of menstruation in these patients. Metreleptin did not improve body weight or glucose homeostasis in common obesity and type 2 diabetes, which are conditions characterized by elevated leptin levels due to leptin tolerance/resistance. Novel leptin receptor analogues, combination treatments with amylin-analogues or incretin-based therapies, genetic manipulation or use of neutralizing antibodies to target hyperleptinemia in obesity are novel strategies that have provided promising results in animal studies, but require further evaluation in clinical trials.

CLD: Congenital leptin deficiency, GL: Generalized lipodystrophy, PL: Partial lipodystrophy, RED—S: Relative energy deficiency in sports, HF: Healthy state during fasting, HALS: HIV-associated lipodystrophy, OB: Obesity, FFA: Free Fatty Acids.

Bold Green: Strong to very strong effects, Green: moderate to strong effects. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

patients [129].

4.2. Restoration of LH pulsatility leading to normalization of sex hormonal profile and recovery of ovulatory menstruations

Two main mechanisms have been proposed so far to explain the effects of leptin on LH pulsatility. Of note, GnRH neurons do not express the leptin receptor, which excludes direct effects of leptin on these cells [132]. The first mechanism involves the neuropeptide kisspeptin, encoded by *KISS1* gene, which can induce GnRH secretion from the hypothalamus. Leptin seems to stimulate neurons in the ventral premammillary nucleus (PMN) which are connected to kisspeptin neurons in the anteroventral periventricular and caudal arcuate nuclei, resulting in higher *Kiss1* expression [133,134]. Additionally, AgRP and NPY neurons, which their activity decreases with leptin, can inhibit GnRH and Kiss1 neuron activity [133,135]. Thus, leptin deficiency might result in reduced expression of Kiss1 both directly through less activation of PMN neurons as well as indirectly through increased activation of AgRP and NPY neurons. The second mechanism suggest direct effects of leptin on pituitary gonadotropes. According to this mechanism, gonadotropes express LEPR and its activation might lead to increased expression of GnRH receptor (GnRHR) and FSH, thus acting synergistically with GnRH pulses in gonadotropic pituitary function [133,136,137]. Nevertheless, it should be noted that leptin administration in RED-S restored HPG axis and menstruation in many but not all women. This indicates that additional mechanisms, independent of leptin, participate in the regulation of reproductive function in conditions of energy deficiency.

4.3. Improvement of immune system function by restoration of T cell populations

The main effect observed with leptin treatment is the restoration of CD4+ T cells. These cells express high levels of the long isoform of the leptin receptor, which activates the JAK – STAT pathway. Activation of these pathways in T cells increases their proliferation, survival, differentiation and cytokine production (reviewed in [138]). This might explain why people with lipodystrophies that have severe leptin deficiency also suffer frequently from respiratory and gastrointestinal infections. More recent studies have suggested that the effects of leptin on T-cells might expand also to follicular helper T cells, involving the STAT3 and mTOR pathways. Notably, lower leptin levels might be a risk factor for vaccine failure [139].

4.4. Modest and transient increase in lipolysis

The mechanisms behind these effects of leptin are unclear and may involve both direct and indirect effects of leptin. Of note, animal studies have suggested that hypoleptinemia due to fasting induces lipolysis by activating the hypothalamic-pituitary-adrenal axis [140]. This seems not to be the case in humans, since restoration of leptin levels in fasting-induced hypoleptinemia as well as in RED—S, CLD and in lipodystrophies did not inhibit lipolysis but it rather stimulated it, whereas it had mild to no effect on adrenal hormones.

4.5. Improvement in insulin sensitivity, glucose levels, triglycerides and hepatic steatosis (especially in leptin deficient GL and PL)

The mechanisms behind the regulatory effects of leptin on glucose and lipid homeostasis are not fully understood. In contrast to animal experiments, it seems that leptin has no direct effects on insulin secretion by pancreatic β cells. Leptin might inhibit gluconeogenesis by providing less carbon sources and thus decreasing blood glucose levels. Weight loss and fat mass loss with leptin might also improve insulin sensitivity resulting in reductions in glucose levels but also in carbohydrate and lipid fluxes to the liver [73]. This can lead to a decrease in de novo lipogenesis and consequently to reduced hepatic fat accumulation [74]. Additionally, leptin might stimulate VLDL-TG export which can also contribute to the reversal of steatosis [126].

Importantly, the effects of leptin administration on energy intake, HPG axis, T-cell composition, lipolysis, glucose and lipid metabolism are more profound in conditions of absolute/severe leptin deficiency (e.g. CLD, GL) than in conditions of severe/moderate leptin deficiency (RED—S, PL and HALS). However, baseline leptin levels in each condition cannot predict the level of response to leptin treatment.

4.6. Improvement in bone mineral density (in leptin deficient RED—S)

As described above, leptin treatment of women with RED-S led to an increase in bone mineral content and density. In contrast, leptin administration has no effects on bone health in patients with CLD, GL or PL. A possible explanation for this paradox is that patients with GL or PL have normal or even elevated bone mineral density and content, apparently due to their insulin resistance and the resultant hyperinsulinemia as well as higher IGF-1 levels, and thus no signs of osteoporosis as in RED—S. The increased lean mass, tall stature in CLD and lipodystrophies and overweight or even severe obesity in CLD provide higher mechanical loads, which might protect bones.

Leptin might regulate bone metabolism both through central and peripheral pathways [141,142]. Regarding the peripheral pathways, leptin might directly interact with bone marrow mesenchymal stem cells (BMSCs), osteoblasts, osteoclasts and chondrocytes. Through these interactions, leptin might stimulate BMSCs to differentiate to osteoblasts. Moreover, leptin might directly enhance the proliferation of osteoblasts, the synthesis of collagen and bone mineralization [143], whereas it might inhibit osteoclasts by decreasing RANKL secretion [144,145]. Metreleptin treatment has been also shown to decrease parathormone, a hormone that promotes bone absorption through indirect activation of osteoclasts [144]. Regarding the central pathways, restoration of HPG axis and consequently of estradiol levels by leptin is expected to contribute significantly to improvement of bone mass in women with RED—S. Additionally, leptin can modestly reduce cortisol levels, which might also act beneficially on bone mineral content. On the other hand, it has been also suggested that leptin may have detrimental effects on bone through its binding to hypothalamus. This has been suggested to stimulate sympathetic nervous system (SNS) which activates β2-adrenergic receptor on osteoblasts resulting in lower bone mass in mice [146]. However, metreleptin administration in patients with hypoleptinemia did not seem to stimulate SNS, thus questioning the importance of the above mechanism in humans.

4.7. No changes in energy expenditure, blood pressure, heart rate and body temperature.

These findings from human studies are in complete contrast to preclinical experimental data which suggested regulatory effects of leptin on energy expenditure and SNS activity and adrenal hormone secretion [5,21,66]. This is an important point to take also into consideration in the evaluation of any results from preclinical models with leptin in the future.

Finally, leptin treatment in metabolic diseases without leptin deficiency (common obesity, type 2 diabetes) has no metabolic effects. Similarly, leptin treatment in patients with common obesity and leptin levels below the 25th percentile of the BMI-corresponding population creates no significant metabolic benefit. Finally, approaches to improve leptin sensitivity before treating obese patients with leptin have failed so far.

5. Conclusion

Human clinical trials administering leptin have provided unique insights about the role of leptin in energy homeostasis, glucose and lipid metabolism, endocrine function, bone health and immune system response. Metreleptin has thus found its place in our therapeutic armamentarium as leptin replacement therapy for leptin deficiency states such as CLD and congenital lipodystrophies [35].

Given the limited translation of findings from animal studies with leptin to humans, more clinical trials are needed in order to further define the role of leptin in human physiology and in different disease states. The development of new leptin analogues and leptin receptor agonists that do not induce leptin antibodies offer a great opportunity for such studies. Thus, current efforts focusing on the evaluation of these medications alone or in combination with other drugs (e.g. incretin analogues) are of great importance.

CRediT authorship contribution statement

Nikolaos Perakakis: Writing – original draft, Investigation. **Christos S. Mantzoros:** Writing – review & editing, Investigation, Conceptualization.

Declaration of competing interest

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