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Review article

Leptin as a predictive marker for metabolic syndrome

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ABSTRACT

Metabolic syndrome poses a major threat on human health affecting the quality of life. Adipose tissue is an important organ which plays a crucial role in the pathogenesis of metabolic syndrome. Adipocytokines secreted by the adipose tissue plays a critical role in storage, food intake, energy expenditure, lipid and glucose metabolism. Leptin is primarily involved in regulating food intake, body weight and energy homeostasis through neuroendocrine functions. Contemporary research suggests that leptin also influences insulin sensitivity and lipid metabolism. High leptin concentrations are directly associated with the obesity subsequent development of metabolic disease sequelae such as insulin resistance, type 2 diabetes and cardiovascular diseases. Elucidation of the mechanism of action of leptin would help to develop novel therapeutic approaches for there metabolic disorders like obesity and diabetes. This review provides an updated 'state-of-the-art' about the leptin and its role in the pathophysiology of metabolic syndrome at the molecular level.

1. Introduction

Adipocytokines, secreted by adipocytes play a major role in whole body metabolism. Leptin and adiponectin are the two important adipocytokines involved in energy expenditure, lipid and glucose metabolism and inflammation [1,2]. Alterations in the levels of adipocytokines are associated with the risk of obesity, insulin resistance, type 2 diabetes mellitus (T2DM) and cardiovascular diseases [1]. Various reports suggest that adipocytokines can serve as predictors of metabolic syndrome in adults [3,4]. Due to the high prevalence of metabolic disorders, it is important to focus on the mechanistic aspects of adipocytokines and their regulation and reveal therapeutic targets [5]. Recent research has focused on leptin and its role in the energy balance and food intake and regulation [6]. However, the detailed mechanism of leptin action in metabolic diseases like obesity, T2DM and cardiovascular diseases (CVD) is poorly understood [7].

2. Leptin

The name "Leptin" is derived from the Greek word 'leptos' means 'thin'. Ob/Lep gene synthesizes this protein and is secreted by the white adipose tissue. It is known to regulate food intake, metabolism and energy expenditure through its receptor present in the hypothalamic region of the brain (Fig. 1) [8,9]. Leptin acts on the peripheral tissues and regulates metabolic activities [10,11].

A researcher from the Jackson laboratory USA first discovered (in 1950) the strain of obese mice. Recessive mutations in the mice were found to cause obesity and their weights were three times higher than normal mice with insatiable appetites. Friedman in 1994 first cloned the ob gene in mice and its homolog in humans [12]. Leptin was identified through the isolation of leptin receptor gene (LepR) via the expression cloning method [13]. Leptin gene was identified by positional cloning [14]. Obese (ob/ob) and diabetic (db/db) strains were developed by a single gene mutation in mice [15].

2.1. Leptin structure

Leptin gene codes for a polypeptide chain consisting of 167 amino acids, which further gets modified into the 146 amino acids. Leptin belongs to the type I helical family which is related to growth hormone, prolactin and interleukins. It comprises of four antiparallel helices, each around 5–6 turns long and shows, up-up-down-down characteristic arrangement of cytokines. This further forms two layer packing of the helices [12,16].

2.2. Leptin receptors

Different LepR isoforms such as Ob-Ra, Ob-Rb, Ob-Rc, Ob-Rd, Ob-

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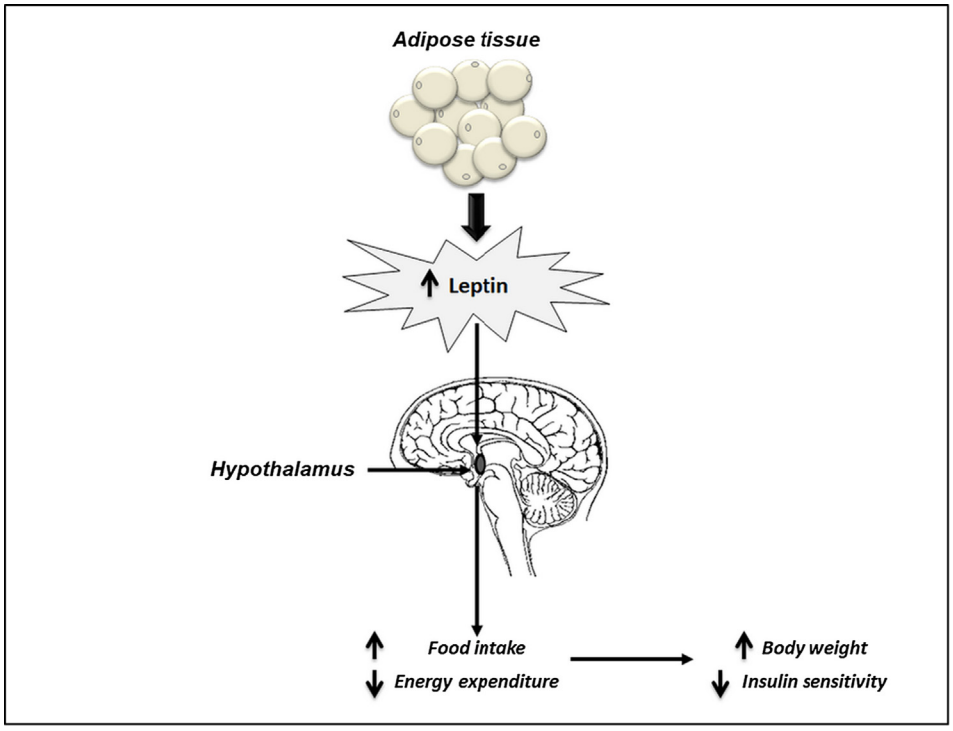

Fig. 1. Leptin and its targeted endocrine organ.

Re, Ob-Rf are formed due to the alternative splicing and represent variants, which differs at the −COOH terminus. All these receptors are truncated intracellular domains except for the 'long-form' leptin receptor (Ob-Rb) [17]. Isoforms of Ob-Rb are extensively expressed in the feeding centers of the hypothalamus, suggesting its role in regulating metabolic rate and feeding behavior [18]. Structure of leptin receptors and their signal response is summarized in Fig. 2.

Leptin receptors (ObRs) are expressed in brain and peripheral tissues. Binding of leptin leads to the activation of receptors associated with Janus kinase 2 (JAK2) pathway which in turn leads to phosphorylation of two tyrosine residues. Expression of leptin receptors such as ObRa and ObRb is observed everywhere in the mammalian tissues while ObRb is highly expressed only in the hypothalamus [19]. In humans, loss of total function mutations in ObRb gene is rarely observed; however, polymorphisms in the gene which codes for extracellular receptor domains are commonly observed which is associated with increased body weight and adiposity. In humans and rodents, it was found that mutations in the leptin or LepR genes lead to obesity, infertility and insulin resistance. In vitro studies also indicate that leptin has a direct effect on various tissues such as pancreatic β-cells, adipose and adrenal cortex [20].

3. Association of leptin with metabolic diseases

3.1. Leptin and obesity

Higher leptin levels were found to be positively associated with obesity. It has been suggested that obesity is associated with hyperleptinemia and leptin resistance in humans [21]. In contrast, a study in T2DM patients reports no changes in adiponectin or leptin concentrations [22]. A study from Romania investigating the relationship between markers of adiposity (leptin, adiponectin and high sensitivity C-reactive protein) in obese children reports that leptin levels were significantly higher in obese children with metabolic syndrome than obese children without metabolic syndrome suggesting that these markers can be used as predictors of cardiovascular risk in the pediatric population [23]. Obese females in the USA were reported to exhibit higher leptin levels as compared to the lean control subjects [24].

3.2. Leptin and T2DM

Increased leptin levels were reported in the type 2 diabetes patients with retinopathy in Iran, suggesting that leptin is a better marker to study the effect of obesity on diabetic retinopathy than the BMI and body adipose index [25]. It has been suggested that laparoscopic sleeve gastrectomy surgery in diabetic patients leads to decreased leptin and ghrelin levels, which may be beneficial in improving glucose homeostasis after surgery [26]. Testosterone replacement therapy has been shown to decrease leptin levels in the aging men with type 2 diabetes from Denmark. This study report that higher leptin levels are associated with the risk profile of cardiovascular diseases [27]. Higher leptin levels were observed in young adults with risk factors of metabolic syndrome and also showed a positive correlation with HOMA-IR, BMI, HbA1C in western Algeria [28]. Adela et al, carried out a study using different sets of serum markers such as cytokines/chemokines, metabolic hormones, adipokines and apolipoproteins for evaluation of pathophysiological conditions of T2DM, coronary artery disease and T2DM with coronary artery disease patients reports higher leptin levels in type 2 diabetic patients than coronary artery disease patients and type 2 diabetic patients with coronary artery disease [29]. A clinical study from Egypt report elevated serum leptin concentration and leptin-to-adiponectin ratio in metabolic syndrome patients suggesting to consider leptin-to-adiponectin ratio as a marker for early diagnoses of individuals exhibiting components of metabolic syndrome [30].

3.3. Leptin and CVD

A study investigating the association between circulating adipokine levels and cardiovascular risk factors and metabolic syndrome components in adults of Arab ethnicity reported a positive correlation of leptin with metabolic syndrome components, wherein subjects in the highest tertile of leptin increase the odds of having metabolic syndrome risk [31]. A recent report suggests that leptin has a potential mechanism of adverse cardiac remodeling in patients with coronary artery disease

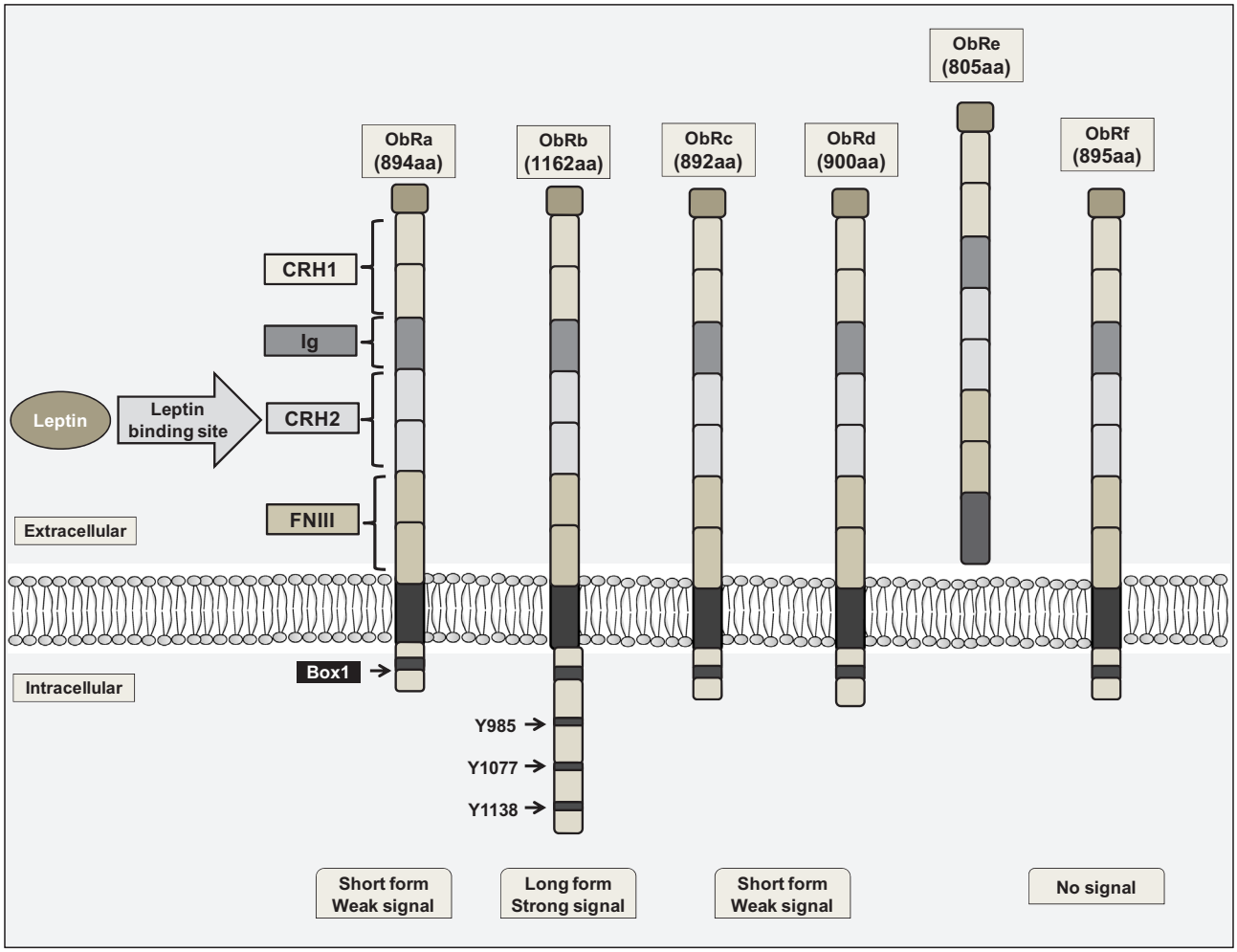

Fig. 2. Leptin receptors. ObRa: Leptin receptor a; ObRb: Leptin receptor b; ObRc: Leptin receptor c; ObRb: Leptin receptor d; ObRb: Leptin receptor d; ObRf: Leptin receptor f; aa: Amino acid; CRH1 & 2: cytokine receptor 1 & 2; Ig: Immunoglobulin; FNIII: Fibronectin type III; Y985, Y1077, Y1138: Tyrosine motifs.

[32]. It has been demonstrated that serum leptin concentrations are positively associated with the intima-media thickness of the common carotid artery indicating that higher leptin concentration is a risk factor for the development of atherosclerosis [33].

4. Ethnic variations in leptin levels and their association with metabolic markers

Studies have shown that South Asian women and men have significantly higher leptin concentrations than Aboriginal and European groups [34–36]. Aboriginal females were reported to have higher leptin levels as compared to European females with the same BMI [36]. It is also suggested that fat distribution and higher insulin do not explain increased leptin concentrations among South Asian women [36–38].

5. Mechanisms of action of leptin

5.1. Leptin and energy homeostasis

Leptin is a key regulator of food intake and its functions through activation of the hypothalamus in the brain. Several animal studies indicate that hypothalamus is the primary center for regulation of food intake and body weight [39,40]. Adipocytes release leptin into the bloodstream, which binds to leptin receptors in the hypothalamus and gives information regarding the status of body energy stores. After binding to leptin receptors, it regulates the activity of several hypothalamic neurons and expression of several anorexigenic and orexigenic neuropeptides. Leptin regulates the levels of orexigenic peptides such as neuropeptide Y, galanin, galanin-like peptide, orexin, melanin-concentrating hormone and agouti-related protein [41–43].

Studies indicate that the amount of leptin secreted by fat tissue is directly related to the mass of adipocytes under physiological conditions [44,45]. It functions as an 'adipostat' when the body has sufficient energy stores, by inhibiting appetite. In steady-state, secretion and expression of leptin reflects body adipocity in humans and rodents [46,47]. It is also associated with the size of adipose tissue in lean and obese mice [48]. Leptin gene expression was shown to be lower during food deprivation state [49,50]. Although leptin is known to increase sympathetic nerve activity [51] and activate brown adipose tissue thermogenesis in mice [52], these effects have not been confirmed in humans [53]. Further, a 53% reduction in serum leptin due to 10% reduction in body weight is reported in obese human individuals [54]. In contrast, a 300% increase in serum leptin due to the 10% increase in body weight has been observed in humans [55]. Thus, it is evident that leptin functions not only as an "adipostat" to signal the status of body energy stores to the brain, but also functions as a sensor of energy balance.

Patients with congenital leptin deficiency due to mutations in the leptin gene or leptin receptors are found to be obese and exhibit marked hyperphagia [56,57]. Various reports suggest that administration of leptin lowers the food intake through neural circuits, reduce the perception of food reward and improve the satiety signal response in

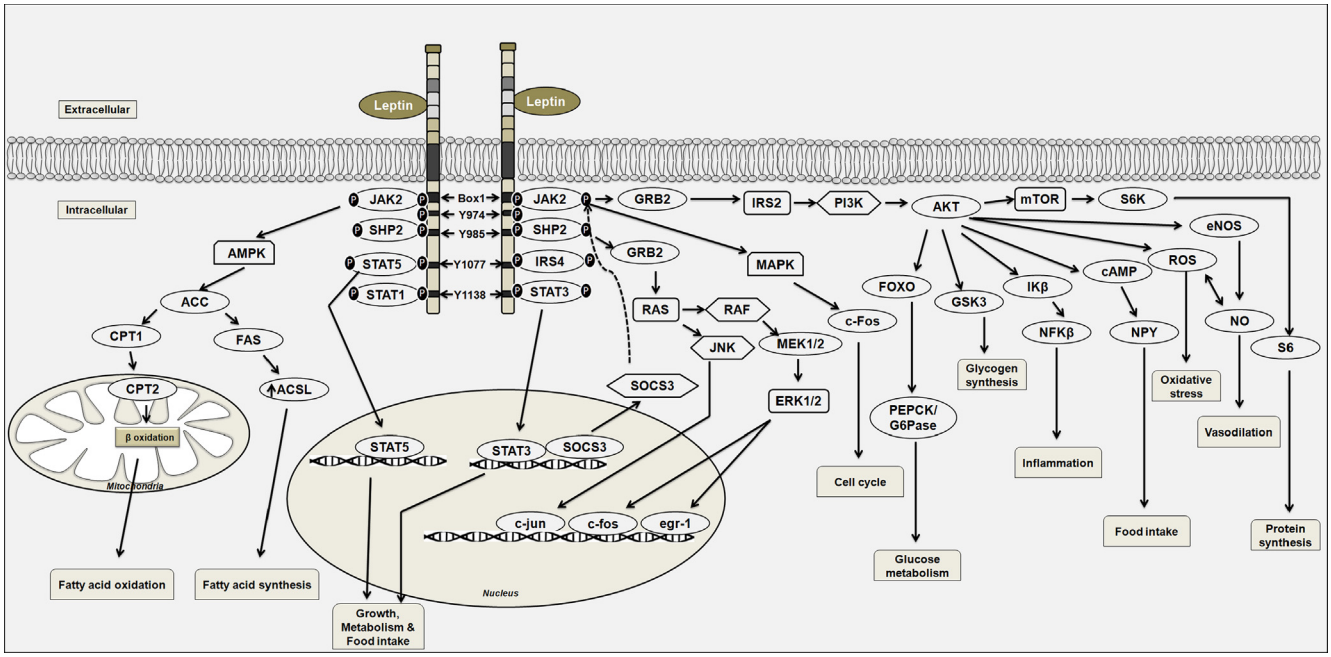

Fig. 3. Mechanism of action of leptin. JK2: Janus kinase 2; SHP2: Src homology 2 (SH2) domain containing non-transmembrane protein tyrosine phosphatase; STAT: Signal transducer and activator of transcription; IRS4: Insulin receptor substrate 4; AMPK: Adenosine monophosphate-activated protein kinase; ACC: Acetyl-CoA carboxylase; CPT: Carnitine palmitoyltransferase; FAS: Fatty acid synthase; ACSL: Acyl-CoA synthetase long chain family member; GRB2: Growth factor receptor-bound protein 2; IRS2: Insulin receptor substrate 2; PI3K: Phosphatidylinositol 3-kinase; AKT: Protein kinase B; mTOR: Mechanistic target of rapamycin; S6K: Ribosomal protein S6 kinase; S6: Ribosomal protein S6; eNOS: Endothelial nitric oxide synthase; ROS: Reactive oxygen species; NO: Nitric oxide; cAMP: Cyclic adenosine monophosphate; NPY: Neuropeptide Y; IkB: Nuclear factor kappa beta inhibitor; NFKB: Nuclear factor kappa beta; GSK3: Glycogen synthase kinase 3; FOXO: Forkhead box O; PEPCK: Phosphoenolpyruvate Carboxykinase; G6Pase: Glucose-6-phosphatase; MAPK: Mitogen-Activated Protein Kinase; c-Fos: Fos proto-oncogene; RAS: RAF: Serine/threonine-specific protein kinases; MEK1/2: Mitogen-activated protein kinase; ERK1/2: Extracellular signal–regulated kinases; JNK: c-Jun N-terminal kinases; SOCS3: Suppressor of cytokine signaling 3.

humans [56]. Low body weight is also found in patients with leptin deficiency [58]. Moreover, administration of leptin in a dose dependent manner is reported to reduce food intake, body weight, fat deposition and increase energy metabolism in animals [59,60]. It has been suggested that leptin treatment reduces body weight by enhancing the metabolic rate [18].

5.2. Leptin and glucose homeostasis

Leptin acts through receptors located in the central nervous system, and also has a direct action on different tissues. Studies demonstrate the presence of leptin receptors in pancreatic β cells, suggesting its involvement in endocrine function and its relationship with insulin [61,62]. Leptin is shown to inhibit insulin expression through the autonomous nervous system by influencing leptin receptors in pancreatic β cells. It also inhibits both basal and glucose stimulated insulin secretion through the ATP-dependent potassium channels. It is considered that leptin antagonises cAMP signaling and diminishes, increase in cellular cAMP levels in response to β cell stimulation. It is also possible that leptin antagonises insulin secretion from β cells, through AKT and protein kinase C pathways [63,64].

Leptin is involved in various processes like enhancing glucose utilization, preventing insulin hypersecretion and also involved in fat metabolism [65]. High fasting glucose is known to affect leptin levels in diabetic individuals [66]. Various reports suggest that leptin acts on pancreatic β cells and inhibits insulin secretion causing breakdown of insulin receptors, thereby promoting glucose synthesis in the liver [67–71]. It has been demonstrated that leptin or leptin receptor deficiency lowers insulin sensitivity, increases glucose levels and leads to the development of obesity in both ob/ob mice and humans [71–73]. Streptozotocin induced insulin deficiency is shown to reduce circulating concentrations of leptin and that suppression was also reversed by insulin treatment [74]. Insulin acts directly on the adipocytes by increasing leptin secretion and gene expression possibly due to increased glucose transport and metabolism [75,76]. Administration of leptin into wild-type mice is shown to increase glucose turnover and glucose uptake independent of increases in circulating insulin levels [77]. Reports also suggest that leptin has favorable effects on glucose homeostasis in T1DM mouse model [78–80].

It is demonstrated that humans with congenital leptin deficiency and mice (obese and lean) with the leptin receptor mutation exhibit insulin resistance [81]. Similarly, animal models of lipoatrophy, that lack adipose tissue, are called as hypoleptinemic [82]. They have metabolic abnormalities, including hyperglycemia, insulin resistance, and hyperlipidemia. However, administration of leptin in ob/ob mouse is shown to improve glucose and insulin levels before weight loss is achieved [81]. Leptin treatment is reported to improve the levels of insulin, LDL, HDL and triglycerides in individuals with congenital leptin deficiency [83]. Chronic leptin treatment is shown to improve glucose metabolism, triglycerides, insulin sensitivity and hepatic steatosis in insulin-resistant lipodystrophic patients [84,85]. Reports indicate that there is a link between insulin and leptin secretion in insulin resistant individuals [86,87]. Overall possible mechanism of leptin is summarized in Fig. 3.

5.3. Effect of drugs on serum leptin levels

Metformin is a biguanide hypoglycemic agent, acts by reducing insulin resistance without directly affecting insulin secretion [88]. Short term treatment with metformin is shown to lower serum leptin concentration without affecting body weight and body fat control in normal weight healthy men [89]. Long term use of metformin is reported to lower leptin levels in T2DM individuals [22]. We have earlier reported lower leptin levels in diabetic individuals undergoing oral

hypoglycemic agent treatment [90]. Second-generation sulfonylurea drug like glibenclamide is used for the treatment of diabetic patients, which improve insulin secretion by lowering glucose levels [91,92]. Reports indicate that sulfonylurea treatment increases leptin levels in obese patients with and without T2DM [93]. A study from Japan indicates that patients with type 2 diabetes have higher leptin levels than the control group, but after metformin treatment leptin levels significantly reduce [94].

6. Conclusion

Leptin acts as a key a signaling molecule of metabolic status and mediates various metabolic processes such as energy homeostasis and neuroendocrine functions. Hyperleptinemia and leptin resistance are closely associated with pathological conditions such as obesity and T2DM. Indeed, lower circulating leptin levels are positively correlated with improved insulin sensitivity, lipid metabolism and lower adiposity and inflammation. Thus, continuous monitoring of leptin may give a clear idea of the progress of clinical pathologies. Increasing leptin sensitivity could be an attractive target for the management of metabolic disorders.

7. Future perspectives

Literature is scarce on the levels of leptin in different ethnic groups suggesting a need to undertake epidemiological studies, which may give a clear idea of leptin cutoffs for healthy individuals and patients with metabolic disorders. Given the importance of leptin's actions in human health and diseases, it is of research priority to identify predictors of leptin responsiveness for various pathological conditions. Future studies should also explore leptin therapy along with healthy diet and lifestyle patterns which may positively influence leptin signaling in order to manage obesity and diabetes.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

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