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Review Article

Leptin, cardiovascular diseases and type 2 diabetes mellitus

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Abstract

Leptin, an adipokine that is implicated in the control of food intake via appetite suppression, may also stimulate oxidative stress, inflammation, thrombosis, arterial stiffness, angiogenesis and atherogenesis. These leptin-induced effects may predispose to the development of cardiovascular diseases. In the present review we discuss the evidence linking leptin levels with the presence, severity and/or prognosis of both coronary artery disease and non-cardiac vascular diseases such as stroke, carotid artery disease, peripheral artery disease (PAD) and abdominal aortic aneurysms (AAA) as well as with chronic kidney disease (CKD) and type 2 diabetes mellitus (T2DM). Leptin levels have been positively associated with the presence, severity, extent and lesion complexity of coronary atherosclerosis as well as with the presence, severity and poor clinical outcomes of both ischemic and hemorrhagic strokes. But conflicting results also exist. Furthermore, leptin was reported to independently predict common carotid intima-media thickness and carotid plaque instability. A link between hyperleptinemia and PAD has been reported, whereas limited data were available on the potential association between leptin and AAA. Elevated leptin concentrations have also been related to CKD incidence and progression as well as with insulin resistance, T2DM, micro- and macrovascular diabetic complications. Statins and antidiabetic drugs (including sitagliptin, metformin, pioglitazone, liraglutide and empagliflozin) may affect leptin levels. Further research is needed to establish the potential use (if any) of leptin as a therapeutic target in these diseases.

Keywords: leptin; coronary heart disease; stroke; peripheral artery disease; carotid artery disease; chronic kidney disease; abdominal aortic aneurysms; obesity

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Introduction

Leptin is a hormone mainly secreted by adipocytes that is involved in the control of food intake via its action on the hypothalamus, leading to the suppression of appetite[1]. Therefore, leptin is an "anorexigenic" hormone. However, obesity is characterized by hyperleptinemia due to the development of leptin resistance[2].

Apart from obesity, hyperleptinemia has been also associated with hypertension and insulin resistance[3-7]. The peripheral actions of leptin include stimulation of inflammatory reaction, oxidative stress, atherogenesis and thrombosis, thus promoting endothelial dysfunction, arterial stiffness, development and vulnerability of atherosclerotic plaques[8-10]. Furthermore, leptin regulates bone homeostasis, reproduction and angiogenesis[11]. Based on these leptin-induced effects, the role of leptin on the presence, severity and prognosis of both cardiac and non-cardiac vascular diseases are being investigated. Of note, chronic kidney disease (CKD) is characterized by increased cardiovascular (CV) risk[12-14]; leptin metabolism is also being evaluated in CKD patients. It should be stated that leptin may have a "protective" role against adiposity or pancreatic damage as shown in animal studies[15, 16]. Furthermore, leptin administration (within the subphysiological to physiological range) was shown to reduce atherosclerotic lesions in low-density lipoprotein receptor (LDLR) knockout mice deficient in leptin[17]. These effects were mainly attributed to improvements in hypercholesterolemia and liver steatosis, as well as upregulation of adiponectin mRNA expression in the adipose tissue, connected with increases in circulating adiponectin levels.

Apart from leptin, other adipokines such as adiponectin, resistin and visfatin may be involved in the pathogenesis of CV and metabolic diseases. In this context, adiponectin was shown to affect insulin resistance, atherosclerosis, inflamma-

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tion and oxidative stress pathways[18-20]. Hypoadiponectinemia has been linked to increased CV risk and T2DM[21-24], although conflicting results exist[25-27]. With regard to CKD, adiponectin levels are elevated and may predict disease progression[28, 29]. Resistin and visfatin have also been implicated in insulin resistance, T2DM, CKD and CV disease[30-32].

In the present narrative review, the associations of leptin levels with coronary heart disease (CHD) and non-cardiac vascular diseases including stroke, carotid artery disease, peripheral artery disease (PAD) and abdominal aortic aneurysms (AAA) are discussed. The links between leptin concentrations and CKD progression and complications are also commented. Finally, the potential use of leptin as a therapeutic target is reviewed according to available data.

Leptin and CHD

It has been reported that CHD patients have higher leptin levels compared with controls[33-35], as also supported by a meta-analysis[36]. Serum leptin concentrations are increased after myocardial infarction (MI)[37]; percutaneous coronary intervention can also raise its levels[38]. Six weeks of exercise prevented the increase of leptin concentrations in CHD patients following an acute MI[39]. However, conflicting results exist[40,41] with a recent meta-analysis reporting no relationship between leptin levels and the risk of CHD[42].

In CHD patients, elevated leptin levels were significantly associated with an increased risk of cardiac death, acute coronary syndrome, non-fatal MI, stroke and hospitalization for congestive heart failure (HF)[43,44]. However, in another study, increased leptin levels and body mass index (BMI) were predictors of a better prognosis in CHD patients[45]. Likewise, an inverse association between leptin concentrations and incidence of adverse events was observed in patients suffering an acute MI[46] as well as between leptin levels and CV morbidity and mortality in patients with stable CHD[47]. Furthermore, leptin concentrations may affect thrombolytic therapy (TT) outcomes as high leptin levels on admission within 6 h after an acute MI were related to reduced TT efficacy[48]. Of note, leptin correlated inversely with mortality in men with HF and positively with mortality in men without HF[49]. In the same study, overweight/obese men with HF had a lower mortality risk compared with normal weight ones; however, adjustment for leptin eliminated this association, possibly reflecting cachexia[49].

Elevated serum leptin concentrations and certain leptin gene polymorphisms have been related to the presence and severity of HF with normal ejection fraction in CHD patients[50]. HF patients also have higher leptin levels than controls[51] in both cases with preserved and reduced ejection fraction[52]. In such patients, gender differences exist with women having higher leptin concentrations than men[53]. Furthermore, a direct association between leptin levels and HF progression (i.e. cardiac dysfunction) has also been reported[54]. Leptin correlated with epicardial fat thickness in HF patients[55]. Of note, HF patients with cardiac cachexia had lower leptin levels compared with HF patients without cachexia [56].

Leptin to insulin ratio was linked to CHD severity assessed by the Gensini score in female CHD patients[57]. Similarly, higher serum leptin levels were significantly related to increasing number of stenotic coronary arteries and arterial stiffness in CHD patients[58]. Interestingly, plasma leptin concentrations were higher in patients with stable angina than in controls and were even higher in patients with unstable angina[59]. The presence, severity, extent and lesion complexity of coronary atherosclerosis has been associated with higher leptin levels in CHD patients[60]. Certain leptin gene polymorphisms were shown to independently predict the presence for coronary atherosclerosis[61-63].

Leptin may affect cardiac remodelling, metabolism and contractile function[64]. In this context, leptin levels were shown to correlate directly with left ventricular (LV) relative wall thickness, LV end diastolic diameter and impaired LV diastolic function in patients with CHD[65, 66]. Furthermore, in such patients, soluble leptin receptor and leptin content in epicardial adipocytes was higher by 56.9% and 28.6% than in subcutaneous adipocytes[67]. In another study, leptin expression was increased in the perivascular adipose tissue, leading to inflammation, fibrosis and vascularization, in patients undergoing coronary artery bypass surgery[68]. In this context, leptin levels were positively associated with the concentrations of myeloperoxidase and C reactive protein (inflammatory markers) as well as with raised factor VII activity in CHD patients (but not in healthy controls)[69-71]. Leptin gene expression was increased in the epicardial, paracardial and subcutaneous adipose tissue in CHD patients with metabolic syndrome (MetS)[72]. Leptin was also previously reported to enhance platelet activation in CHD patients[73] as well as the calcification of vascular cells *in vitro* by exerting pro-osteogenic differentiation effects [74]. Furthermore, leptin may directly affect coronary endothelial cells by increasing the expression of tissue factor and cellular adhesion molecules[75]. Apart from atherosclerosis, leptin can also enhance insulin resistance in CHD patients[76,77].

Statins can decrease leptin concentrations in CHD patients[78, 79]. Whether this statin-induced effect is involved in the atheroprotective properties of statins should be elucidated in future studies. Apart from statins, several other drugs including hypoglycemic, antihypertensive and antiobesity agents were shown to affect leptin levels[80, 81]. Leptin may be a target candidate for therapeutic intervention.

Overall, hyperleptinemia has been linked to the presence and severity of CHD and HF. Statins and other drugs may reduce leptin concentrations. It follows that in such patients, the selection of leptin-lowering therapies may contribute to minimizing their CV risk. However, there is a need for more evidence.

Leptin and stroke

Elevated leptin levels have been reported to predict stroke risk in both genders, even independently of traditional CV risk factors[82-84], as supported by a meta-analysis[36]. However, conflicting results exist with earlier meta-analyses[85-87] and a recent meta-analysis[42] reporting the absence of any significant

association between leptin and stroke risk. Furthermore, in elderly individuals (mean age=79 years; 62% women) from the Framingham Original Cohort (*n*=757) followed-up for 10 years, an inverse association was observed between the risk of both ischemic stroke and first-ever all-stroke with leptin concentrations in individuals with the highest waist to hip ratio[88]. However, in another prospective study with 3411 elderly men (aged 60–79 years), followed-up for 9 years, higher leptin levels correlated with an increased stroke risk[89]. Furthermore, in a substudy of the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, higher baseline leptin levels were protective of CV events (including strokes), especially in normal weight, overweight and obese patients (but not in severely obese ones)[90]. Ischemic stroke subtypes may affect the association between leptin and stroke[91].

Gender differences exist in stroke patients with women having higher leptin levels than men[92]. Certain gene polymorphisms of leptin receptors have been related to an increased risk of stroke as reported in previous studies and a recent meta-analysis[93, 94]. Furthermore, elevated leptin concentrations have been associated with worse cognitive, neurological and functional outcomes[95, 96].

It has been suggested that leptin may be involved in the neuroendocrine abnormalities that occur after stroke such as the regulation of cortisol axis and vascular tone[97]. Furthermore, leptin can stimulate endothelial dysfunction, angiogenesis, oxidative stress, platelet aggregation and atherothrombosis, thus triggering vascular stiffness as well as inflammatory and atherosclerotic responses[97-99]. Of note, leptin, apart from crossing the blood brain barrier, is also synthesized in the brain[100].

In states of leptin resistance such as obesity and type 2 diabetes mellitus (T2DM)[101, 102], leptin action is decreased in the brain parenchyma and vessels, despite its elevated levels in the plasma and cerebrospinal fluid[103]. It has been hypothesized that in such cases, lowering leptin concentrations may predispose to vascular events due to the loss of protection from oxidative damage and lipotoxicity in non-adipose tissues induced by leptin[103]. Nevertheless, further research is required to establish the pathophysiological mechanisms of leptin metabolism in the brain.

Both animal and *in vitro* studies have shown that leptin administration (intraperitoneal or intracerebral) at the acute phase of stroke exerted neuroprotective properties against ischemic stroke via leptin receptors[104-106]. However, when leptin was delivered 10 days after experimental stroke, no effect on functional outcomes was observed despite the induced neurogenesis and angiogenesis[107]. Based on these findings, it has been suggested that using leptin in tandem with tissue plasminogen activator (tPA) might be a promising approach to improve stroke outcomes[100]. This combination treatment may extend the efficacy of tPA and decrease reperfusion injury. However, in one study with patients with acute ischemic stroke, increased plasma leptin levels were associated with larger infarct volume following tPA treatment[108]. Further human studies are needed to elucidate whether leptin co-administration with tPA may be clinically useful in acute ischemic stroke patients.

With regard to hemorrhagic strokes, elevated plasma leptin concentrations have been associated with increased severity and poor clinical outcomes, predicting early neurological deterioration, hematoma growth and functionality following intracerebral hemorrhage due to both hypertension and aneurysms[109-112].

Overall, hyperleptinemia has been linked to the presence and severity of both ischemic and hemorrhagic strokes. Experimental studies have reported that leptin administration at the acute phase of stroke may improve outcomes. However, human trials are needed to establish the therapeutic role of leptin, if any, in such patients.

Leptin and carotid artery disease

In obese patients, leptin was an independent predictor of common carotid intima-media thickness (cIMT)[113]. A similar association has also been reported in healthy individuals of both genders[114], obese children[115] and patients with psoriasis[116, 117]. Furthermore, the presence of carotid plaques correlated with hyperleptinemia in patients with systemic lupus erythematosus (SLE)[118]. Of note, both psoriasis and SLE have been linked to increased CV risk[119-122]. In contrast, data from the community Carotid Atherosclerosis Progression Study did not support any association between leptin levels and cIMT[123]. Leptin to adiponectin ratio has also been linked to cIMT[124].

With regard to the severity of carotid disease, high leptin concentrations were related to features of plaque instability in patients scheduled for carotid endarterectomy[125]. It has been shown that leptin was locally overproduced in the macrophages and smooth muscle cells of the carotid plaques in symptomatic compared with asymptomatic patients, thus potentially contributing to lesion instability via paracrine or autocrine effects[126]. Furthermore, leptin receptor gene was overexpressed in advanced carotid atherosclerotic lesions[127]. However, a previous study reported lower leptin concentrations in symptomatic carotid artery disease patients compared with asymptomatic ones[128]. Of note, genistein (an isoflavone) was shown to attenuate neointima formation that was induced by leptin in a rat carotid artery injury model[129].

Overall, hyperleptinemia was associated with increased cIMT and carotid plaque instability. However, further evidence is needed to evaluate the clinical implications of these associations.

Leptin and PAD

A link between hyperleptinemia and PAD has been reported[130]. In this context, higher leptin levels predicted PAD in hypertensive patients[131]. In another study among PAD patients, diabetic women with CHD had greater leptin concentrations than their non-diabetic counterparts[132]. Furthermore, gender differences were observed in African Americans PAD patients, with women having higher leptin levels than men[133]. Overall, more studies are required to further explore the role of leptin in PAD development.

Leptin and AAA

There are limited data on any potential link between leptin and AAA. The Health in Men study (involving 12 203 men 65 to 83 years screened with ultrasound; 875 had an AAA ≥30 mm) reported no association between serum leptin levels and AAA[134]. However, there is evidence that leptin is synthesized locally in the wall of AAA in humans[135]. Furthermore, animal studies showed that leptin accelerated the growth of both AAA and ascending aortic aneurysms[135,136]. Further research is needed to elucidate the relationship between leptin and aortic aneurysms.

Leptin and CKD

A link between increased plasma leptin concentrations and CKD has been reported possibly due to a reduced renal clearance[137-140]. In this context, leptin has been recognised as an "uremic toxin", being involved in both the progression of renal disease (via pro-hypertensive and pro-fibrotic effects) and the development of CKD-related complications (such as chronic inflammation, protein energy wasting, cachexia, bone and CV disorders)[137]. Leptin levels are elevated not only in the earlier stages of CKD but also in patients on hemodialysis or peritoneal dialysis, as well as in kidney transplant recipients[141-144]. Interestingly, leptin concentrations gradually increased with severity of CKD, from stage 1-2 to stage 3-4 and, finally stage 5[145]. In chronic hemodialysis patients, elevated serum leptin levels correlated with increasing age, female gender, obesity and good nutritional status[146]. In hemodialysis patients, fistula maturation failure rate was higher in those patients at the highest leptin tertile, independently of gender, age, obesity and diabetes[147]. Furthermore, certain leptin gene polymorphisms correlated with obesity and survival in peritoneal dialysis patients[148]. It has been reported that leptin concentrations may decrease with time in chronic hemodialysis patients (n=101; follow-up=24 months), but this change seems not to affect body composition or nutritional status[149].

In CKD patients, plasma leptin levels have been inversely associated with GFR and directly associated with urinary albumin levels as well as age and obesity markers (BMI and waist circumference)[150, 151]. Similarly, in kidney transplant recipients, serum leptin concentrations negatively correlated with GFR and positively with BMI[152]. However, in these patients, elevated leptin levels were associated with a lower risk of all-cause mortality and death with a functioning graft, whereas the risk of graft loss was higher in patients with low serum leptin concentrations[152]. A similar association between low serum leptin levels and increased all-cause death has been reported in hemodialysis patients[153, 154]. It was suggested that this may not be related to CV mortality[153]. Interestingly, adiposity may affect the relationship between leptin and mortality (both total and CV)[155]. In this context, leptin levels were directly associated with risk for CV and all-cause death in hemodialysis patients with an increased waist circumference (and not in those with smaller waist circumference)[155].

Epicardial adiposity has been linked to increased CV risk[156, 157]. In this context, increased epicardial fat was associated with a higher risk for CV events in CKD patients; a direct association between epicardial fat and leptin levels was also observed[158]. Likewise, increased visceral adiposity has been associated with elevated leptin concentrations in non-dialysis dependent CKD patients[159].

Apart from obesity, hyperleptinemia has been related to metabolic disorders such as MetS and non-alcoholic fatty liver disease (NAFLD)[160-163], which are associated with increased CV risk[164-168]. MetS and NAFLD may co-exist with CKD[169, 170]. In this context, elevated leptin levels correlated with the presence of MetS in CKD patients[171]. Furthermore, in CKD men, hyperleptinemia was related to hypogonadism[172], a disorder that has been linked to CV morbidity and mortality[173, 174].

In CKD patients, lifestyle modifications, including diet and exercise, led to weight loss and a decrease in leptin levels at 12 weeks[175]. Relative interdialytic weight gain, a predictor of long-term adverse CV outcomes, was inversely related to leptin concentrations in chronic hemodialysis patients[176]. Of note, in vitamin D deficient patients with end-stage renal disease (ESRD), vitamin D supplementation significantly reduced serum leptin concentrations[177]. However, the association between leptin and vitamin D supplementation remains unclear[178].

Overall, hyperleptinemia has been linked to the presence, severity and progression of CKD. In contrast, an inverse association between leptin levels and all-cause mortality was reported in hemodialysis patients and kidney transplant recipients. However, the role of leptin in the treatment of CKD patients has not been established yet.

Leptin and T2DM

Elevated leptin levels are associated with insulin resistance and T2DM development[179]. In T2DM, a link between high leptin concentrations and increased CV risk, as well as the presence of microvascular complications and cardiac autonomic dysfunction, has also been reported[180-183]. In this context, leptin concentrations correlated with the presence and severity of silent MI as well as with carotid atherosclerosis (assessed by cIMT) in T2DM patients[184, 185]. Furthermore, obesity, hypertension, MetS and endothelial dysfunction are more frequent in T2DM patients with increased leptin levels[186-188]. Of note, leptin was shown to decrease after an oral fat tolerance meal in both T2DM patients and healthy individuals[189]. Certain leptin gene polymorphisms have also been related to T2DM presence[190-193]. Leptin replacement therapy has been reported to improve muscle and liver insulin resistance in patients with lipodystrophy as well as to suppress liver gluconeogenesis, lipolysis and fasting hyperglycemia in animal diabetic models[194].

Among dipeptidyl peptidase-4 (DPP-4) inhibitors, data exist only for sitagliptin which was shown to reduce serum leptin levels in both animal and human studies[195-197]. Metformin can also decrease leptin concentrations in T2DM patients[198, 199] and upregulate the expression of leptin receptors in the liver of mice[200]. Improvement in leptin hypothalamic sensitivity was reported in relation to metformin therapy[201, 202]. Furthermore,

in vitro studies showed that metformin reduced leptin-related reactive oxygen species production, smooth muscle cell proliferation and matrix metalloproteinase-2 expression[203]. Of note, metformin was reported to decrease leptin concentrations in women with polycystic ovary syndrome (PCOS) in a meta-analysis[204]. Pioglitazone therapy may lower leptin levels[205], although conflicting results exist[206].

Reductions in leptin concentrations were observed following treatment with liraglutide (a glucagon-like peptide-1 receptor agonist, GLP-1 RA) in PCOS women[207]. Furthermore, *in vitro* studies showed that liraglutide improved endothelial dysfunction and reversed leptin resistance[208], whereas in animal models, liraglutide and leptin co-administration suppressed food intake and reduced weight loss[209]. However, data in T2DM patients are lacking. It should be noted that liraglutide has been approved for the treatment of both T2DM (at a dose up to 1.8 mg) and obesity (at the dose of 3 mg)[210]. Furthermore, liraglutide may lower the risk of CV morbidity and mortality[211, 212] as also shown in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial[213]. Based on these results, liraglutide was approved for CV benefit by the US Food and Drug Administration (FDA)[214]. Whether leptin is implicated in these liraglutide-induced CV effects remains to be established in future trials.

With regard to the other commercially available GLP-1RAs, there are no data on leptin for both lixisenatide and dulaglutide. Limited evidence exists for exenatide; when leptin was co-administered with exenatide, body weight and food intake were decreased and hyperglycemia was improved to a greater extent than either monotherapy[215]. Of note, both lixisenatide and exenatide did not affect CV morbidity and mortality in the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial[216] and the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) study[217], respectively. Regarding dulaglutide, its CV outcome clinical trial, the Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) study, is still ongoing[218].

Empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, was shown to reduce plasma leptin concentrations in an animal study[219]. No data exist for dapagliflozin and canagliflozin in relation to leptin. Of note, SGLT2 inhibitors have been reported to beneficially affect CV risk and renal function[220, 221]. In this context, both empagliflozin and canagliflozin significantly decreased the composite endpoint of CV morbidity and mortality as well as hospitalization for HF in T2DM patients with established CV disease [in the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial][222] and at elevated CV risk [in the Canagliflozin Cardiovascular Assessment Study (CANVAS) program][223], respectively. However, only empagliflozin was shown to significantly reduce CV and total mortality, whereas only canagliflozin therapy was associated with a significantly increased risk of amputations and bone fractures. Empagliflozin has been approved by the FDA for lowering the risk of CV death in T2DM patients with established CV disease[224]. Regarding dapagliflozin, its CV outcome clinical trial, the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE) trial, is still ongoing[225]. Whether leptin is involved in any of the observed effects of these drugs remains to be elucidated in future trials.

Overall, hyperleptinemia has been linked to the presence of insulin resistance, T2DM and diabetic vascular complications. There are antidiabetic drugs that can lower leptin levels, including metformin, pioglitazone, sitagliptin, liraglutide and empagliflozin, although the clinical implications, if any, of this drug effect have not been clarified yet.

The abovementioned associations of leptin with cardiometabolic and non-cardiac vascular diseases may be, at least partly, explained by the pathophysiological mechanisms affected by leptin that predispose to these diseases, including vascular inflammation, oxidative stress, endothelial dysfunction, cardiac remodelling and insulin resistance[226] (Figure 1).

Overall, the presence, severity and extent of CHD have been associated with leptin levels. Elevated leptin concentrations were also related to the presence, severity and poor clinical outcomes of both ischemic and hemorrhagic strokes. However, conflicting results also exist. Furthermore, carotid ath-

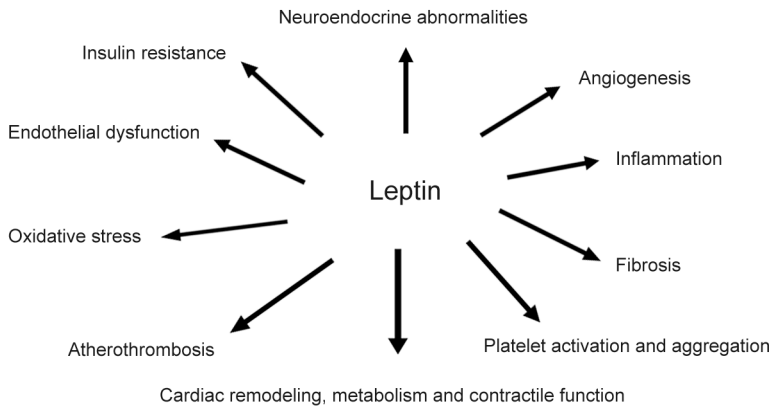

Figure 1. Pathophysiological mechanisms affected by leptin.

Table 1. Associations of leptin levels with cardiac and non-cardiac vascular diseases, chronic kidney disease and type 2 diabetes mellitus.

Diseases	Leptin levels
CHD	Increased leptin levels have been associated with the presence and severity of CHD and HF, as well as with CV morbidity and mortality in CHD patients.
Stroke	Increased leptin levels have been associated with the presence and severity of both ischemic and hemorrhagic strokes.
Carotid artery disease	Increased leptin levels have been associated with the presence and severity of carotid artery disease.
PAD	Increased leptin levels have been associated with the presence of hypertension and T2DM in PAD patients.
AAA	Increased leptin levels have been associated with accelerated growth of AAA and ascending aortic aneurysms.
CKD	Increased leptin levels have been associated with the presence, severity and progression of CKD.
T2DM	Increased leptin levels have been associated with the development of T2DM as well as with micro- and macrovascular diabetic complications.

CHD: coronary heart disease; PAD: peripheral artery disease; AAA: abdominal aortic aneurysm; CKD: chronic kidney disease; T2DM: type 2 diabetes mellitus; HF: heart failure; CV: cardiovascular

erosclerosis (assessed by common carotid intima-media thickness and carotid plaque instability) was linked to hyperleptinemia. Elevated leptin levels have also been related to CKD incidence and progression as well as with insulin resistance, T2DM, micro- and macrovascular diabetic complications. Limited data exist with regard to the associations of leptin with PAD and AAA. Further evidence is needed to elucidate the clinical implications of these associations.

Statins and antidiabetic drugs such as sitagliptin, metformin, pioglitazone, liraglutide and empagliflozin were shown to reduce leptin levels. Whether these drug-induced effects may affect clinical practice remains to be elucidated in the future. Table 1 summarizes the associations of leptin levels with cardiac and non-cardiac vascular diseases, CKD and T2DM.

Conclusions

There is evidence linking leptin levels with the presence, severity and/or prognosis of CHD, stroke, PAD, carotid artery disease, CKD and T2DM. Leptin promotes inflammation, thrombosis, arteriosclerosis, angiogenesis and atherosclerosis. Lifestyle measures and several drugs, including statins and antidiabetic drugs, may affect its levels. Further research is needed to establish leptin as a potential therapeutic target.

Declaration of interest

Niki KATSIKI has given talks, attended conferences and participated in trials sponsored by Amgen, Angelini, Astra Zeneca, Boehringer Ingelheim, MSD, Novartis, NovoNordisk, Sanofi and WinMedica. Dimitri P MIKHAILIDIS has given talks and attended conferences sponsored by MSD, AstraZeneca and Libytec. Maciej BANACH declares advisory boards fees from Abbott Vascular, Amgen, Daichi Sankyo, Esperion, Lilly, MSD, Resverlogix, Sanofi-Aventis, Speakers Bureau from Abbott/Mylan, Abbott Vascular, Actavis, Akcea, Amgen, Biofarm, KRKA, MSD, Sanofi-Aventis, and Valeant and grants from Valeant, and Sanofi-Aventis.

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