

ORIGINAL RESEARCH ARTICLE

Effect of leptin on aortic dissection

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The most important clinical features of aortic dissection (AD) are its acute onset, rapid progress, and high fatality rate. The exact pathogenesis of AD is unclear, and the focus of current research on the mechanism of AD has been primarily on hypertension and changes in metalloproteinases, among which leptin plays an important role. The purpose of this study is to evaluate the effect of leptin on AD. We conducted a computerized literature search on animal studies related to leptin and dissecting aortic aneurysm in PubMed, EMBASE, Cochrane Library, MEDLINE, and other databases from their inception to present. Meta-analysis was conducted to compare the changes in aortic diameter, aortic dilatation, and the incidence of AD in mice under the local intervention of leptin or leptin antagonist (LepA). A total of four studies were included, involving five batches of animal experiments. According to the results of the meta-analysis, the increase in local leptin content led to the enlargement of aortic diameter (relative risk [RR] = 0.18; 95% confidence interval [CI]: 0.09 – 0.27; $P < 0.0001$) and increased aortic dilatation (RR = 0.11; 95% CI: 0.01 – 0.22; $P < 0.0001$). This meta-analysis showed that local leptin administration increased the aortic diameter and aortic dilatation. However, due to high heterogeneity between the results, it is difficult to draw a clear conclusion on the effect of leptin on AD.

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1. Introduction

Aortic dissection (AD) is an acute cardiovascular disease that is caused by high-speed blood flow impacting the aortic intima, resulting in a break or tear in the middle layer of the aortic wall, and separating the inner and outer layers, thus forming a true lumen (the original aortic cavity) and a false lumen (a gap formed between the inner and outer layers by the tearing of the middle layer). AD patients rely on the outer structure of the torn aortic wall to withstand the aortic pressure that should be borne by the entire aortic wall. This outer structure is vulnerable to rupture, which may lead to death within a short period of time. If a patient is not diagnosed and treated in time, the mortality rate within 1 week is about 37%, while the mortality rate within 2 weeks is as high as 75%^[1,2]. There are about 12 new cases of AD in developed countries per million people per year^[1-3], and up to date, no large-scale epidemiological studies have been reported in China. With the improvement of living standards and the progress of diagnostic technology, the number of AD patients in China is increasing at an explosive rate^[4].

Stanford classification divides AD into two types. In type A, the rupture of intima may be located in the ascending aorta, aortic arch, or proximal descending aorta. The scope of dissection involves the ascending aorta, the aortic arch, descending aorta, and even the abdominal aorta. In type B, the rupture of intima is often located in the proximal descending aorta. The scope of dissecting aneurysm is limited to the descending aorta or extends into the abdominal aorta; it does not affect the ascending aorta. The most important clinical features of Stanford type A dissection are its acute onset and rapid progress. In clinical practice, we have found that the early diagnosis rate of AD is low, and some patients die of an aortic rupture before a definite diagnosis is made. Emergency surgery is the only effective treatment for acute Stanford type A dissection. Although the surgical technology for acute Stanford type A dissection has made significant advancements in recent years with the continuous progress of science and technology, such as the three-branch vascular stent technology used in aortic arch reconstruction and other technologies^[5] that improve the safety of AD surgery and the prognosis of patients, the difficulty of surgery still poses a challenge, and the risk of mortality is still high. Usually, only large, well-equipped heart centers are able to carry out such emergency operations. The majority of patients need to be transferred to large heart centers for surgical treatment after a concrete diagnosis is made, among which some patients may die during the transfer. Therefore, it is of great significance to explore the molecular mechanism of AD and find potential therapeutic targets for the prevention and treatment of this life-threatening disease.

The exact pathogenesis of AD is unclear. At present, it is generally believed that AD is formed on the basis of the internal causes of the arterial wall itself in addition to a series of external factors, such as hypertension, trauma, and so on. AD often occurs in patients with idiopathic degeneration of the middle layers of the aorta and certain hereditary diseases, such as Marfan syndrome, Ehlers-Danlos syndrome, Turner syndrome, and other connective tissue disorders. This is due to the internal factor of weak aortic wall in these patients. In the process of AD formation, the external factors that cause tearing of the intima and promote high-speed blood flow into the middle layer play important roles. These external factors include arterial blood pressure, wall shear stress, and hemodynamic status^[6,7]. However, AD is not caused merely by the stimulation of these external factors; instead, the primary cause of AD is the weakness of the aortic wall itself. The weakness of the aortic wall has been relentlessly investigated. Some studies have pointed out that the weakness of the aortic wall may be closely related to abnormal glucose and lipid metabolism^[8-11], which

are the main types of metabolic syndrome (MetS). MetS is characterized by abdominal obesity and abnormal metabolism of lipids, glucose, and carbohydrate, which may cause a series of cardiovascular and cerebrovascular diseases^[12].

In recent years, research on the mechanism of AD has mainly focused on hypertension and changes in metalloproteinases, among which leptin plays an important role. Leptin is a hormone that is mainly secreted by adipocytes and involved in the control of food intake through its action on the hypothalamus, leading to the suppression of appetite^[13]. Further research on leptin has found that the hormone not only has a variety of endocrine functions but also participates in immune and inflammatory responses, hematopoiesis, angiogenesis, reproduction, gene expression of cell cycle regulation, and regulation of cell matrix remodeling^[8,9,14]. Leptin also participates in the decomposition of the extracellular matrix (ECM), promotes angiogenesis, and improves the mitotic activity of vascular endothelial cells by regulating the expression of matrix metalloprotein (MMP)-9 and tissue inhibitors of metalloproteinases (TIMPs)^[15]. This suggests that leptin may be involved in the occurrence of AD. However, only a number of clinical trials have studied the role of leptin in AD thus far. Therefore, the role that leptin plays in AD patients remains unclear.

Several research groups all over the world have adopted animal models to study the impact of leptin on the occurrence and development of AD. The results of these pre-clinical studies are often derived from a relatively small sample, and there is no objective or quantitative way to systematically evaluate and summarize all the studies. Therefore, we present a systematic review and meta-analysis of leptin in AD animal models to clarify the relationship between leptin and AD.

2. Materials and method

2.1. Materials

We conducted a computerized literature search on animal studies related to leptin and AD in PubMed, EMBASE, Cochrane Library, MEDLINE, and other databases from their inception to present. The keywords used were “Leptin,” “Obese Protein,” “Obese Gene Product,” “Gene Product, Obese,” “Ob Gene Product,” “Gene Product, Ob,” “Ob Protein,” “Aneurysm,” “Aneurysms,” “Fusiform Aneurysm,” “Aneurysm, Fusiform,” “Aneurysms, Fusiform,” “Fusiform Aneurysms,” and “Saccular Aneurysm.”

The titles and abstracts of the identified studies were scanned to exclude any study that was irrelevant. The full texts of the remaining articles were read to determine

whether they contained information on the topic of interest. The reference lists of the articles with relevant information were reviewed to identify citations to other studies on the same topic.

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria

To prevent bias, the inclusion criteria were as follows: (i) The effect of leptin on AD tested in animal models; (ii) sufficient data, such as the increase in artery diameter and the comparison with animals receiving leptin or leptin antagonist (LepA); and (iii) original data, independent of other studies.

2.2.2. Exclusion criteria

The pre-defined exclusion criteria were as follows: (i) Specific article types including case reports, abstracts, reviews, editorials, and clinical trials; (ii) outcome variables that were not caused by leptin or LepA; (iii) literature without full text or available review and main outcome indicators; and (iv) repetitive publications.

2.2.3. Data extraction and quality assessment

The Chinese and English literature retrieved, according to the retrieval strategy, were screened by two researchers independently. The screening process was as follows: First, literature that were repeatedly searched were excluded; second, titles and abstracts were read to eliminate irrelevant studies; full texts were read to identify studies that met the criteria, and data extraction was carried out; cross-checks were carried out among researchers, and if there were any disagreements, a third researcher was consulted.

The following research design details were extracted from each study: (i) Year of publication, first author's name, and experimental model; (ii) individual data of each animal, including number, species, gender, *etc.*; (iii) treatment information, including treatment time, route of administration, and dosage; and (iv) result measurement and evaluation time. For results that were obtained from animal studies at different time points, we extracted the data at the time before killing. For data that were missing or presented graphically, they were measured using a digital scale software. In addition, we attempted to contact the author for more information or calculated on our own (if any); otherwise, we excluded it. For each comparison or each treatment and control group, we extracted data for the mean and its standard deviation. The time of the lesion was set to zero and the administration time was expressed relative to this. All data were extracted independently by two participants.

Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 (Higgins, 2006)^[16] was used as a quality

assessment tool in this study. The Cochrane Quality Rating Form contains a total of seven items, with each item given 1 point for "low risk" and 0 point for "high risk." Independent evaluations were made by the two researchers and were then integrated. If there were any disagreements, another evaluation was made by the third researcher.

2.3. Statistical analysis

We separately pooled relative risk (RR) estimates from each study for each outcome using random effects meta-analysis. The statistical heterogeneity of the RRs was evaluated using the χ^2 test, with significance set at $P < 0.01$, and the I^2 statistic was calculated. To evaluate whether there was publication bias in the included articles, we used R software to draw funnel plots for qualitative analysis and Egger's test for quantitative analysis. If $P < 0.05$, it indicated that there was publication bias. Low, moderate, and high degrees of heterogeneity corresponded to I^2 values of 25%, 50%, and 75%, respectively. Sensitivity analyses were conducted to evaluate whether the results could have been markedly affected by a single study. All data (except age) were expressed by $\bar{x} \pm s$.

3. Results

3.1. Search results

The references ($n = 72$) were retrieved by the original search strategy or manual searches. The abstracts were reviewed, and eight articles were selected for full-text evaluation after excluding repetitive literature and preliminary screening. After applying the inclusion and exclusion criteria, four articles were included. The flowchart of the study inclusion process is shown in [Figure 1](#).

3.2. Research quality assessment results

The Cochrane scoring system was used to evaluate the quality of the included literature. The results showed that the lowest score was 6, while the highest was 10, with an average of 4.25 ± 0.96 , which was in the upper-middle level ([Figure 1](#)).

3.3. Meta-analysis of studies on aortic diameter

The changes in mouse aortic diameter were reported in four studies (inclusive of five animal experiments). The mice in the experimental group of three animal experiments were intervened with leptin. It is worth noting that the results of two of these studies showed that there was a statistical difference in the enlargement of aortic diameter compared with the blank control group. However, one study reached the opposite conclusion, in which the diameter of the mouse aorta was smaller than that of the control group. The mice in the experimental group of the other two

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Danny Ben-Zvi et al2016	⊖	⊕	?	?	⊕	⊕	⊖
Ming Tao et al2012	⊖	⊕	⊕	⊕	⊕	⊕	⊕
Sudeshna Fisch et al2020	⊖	⊕	⊕	⊕	⊕	⊕	⊕
Ying Zhang et al2018	⊖	⊕	?	?	⊕	⊕	⊕

Figure 1. Risk of bias summary: Review authors’ judgments about each risk of bias item for each included study.

animal experiments were intervened with LepA, and the results showed that there was a statistical difference in the reduction of aortic diameter compared with the control group. The meta-analysis of all four studies (inclusive of five animal experiments) showed that an increase in local leptin content had a statistically significant effect on the enlargement of aortic diameter, with a combined RR of 0.18 (95% CI: 0.09 – 0.27; $P = 0.0001$; random effects model) and statistical heterogeneity ($P < 0.0001$; $I^2 = 96.9\%$). The increase in local leptin content promoted the enlargement of mouse aortic diameter. The forest plot is shown in Figure 2.

3.4. Meta-analysis of studies on aortic dilatation

The changes in aortic dilatation in mice were reported in four studies (inclusive of five animal experiments). The mice in the experimental group of three animal experiments were intervened with leptin. It is worth noting that the results of two of these studies showed that there was a statistical difference in the increased aortic dilatation compared with the blank control group. However, one study reached the opposite conclusion, wherein the aortic dilatation of the experimental mice was lesser than that of the control group. The mice in the experimental group of the other two animal experiments were intervened with LepA, and the

results showed that there was a statistical difference in the reduction of aortic dilatation compared with the control group. The meta-analysis of all four studies (including five animal experiments) showed that the increase in local leptin content had a statistically significant effect on aortic dilatation, with a combined RR of 0.11 (95% CI: 0.01 – 0.22; $P = 0.0001$; random effects model) and statistical heterogeneity ($P < 0.0001$; $I^2 = 95.7\%$). The increase in local leptin content promoted the dilation of mouse aorta. The forest plot is shown in Figure 3.

3.5. Publication bias results

First, a funnel chart was used to conduct a qualitative analysis of publication bias (sensitivity analysis based on the difference in artery diameter) for the included literature, showing that the distribution was asymmetric. For further verification, Egger’s test was conducted, and the results showed that there was no publication bias, $P = 0.988 (>0.05)$ (Figure 4 and Figure S1).

3.6. Sensitivity analysis

Due to the differences in the quality and sample size of the studies, the heterogeneity among the studies was significant. A sensitivity analysis was conducted to verify the reliability of the data. The difference in arterial diameter between the leptin enhanced group and the leptin weakened group was used for sensitivity analysis. The results showed that the study conducted by Ying *et al.*^[17] was the most important factor affecting the effect scale and the main reason for the existence of heterogeneity (Figure 5).

4. Discussion

Aortic vascular remodeling is one of the key factors in the pathogenesis of AD, and the severity of the disease is closely related to the abnormality of glucose and lipid metabolism. The main physiological and pathological changes in AD include the degeneration of the aortic middle layer, the imbalance of ECM synthesis and degradation, the rupture of elastic fibers, the deposition of collagen fibers, and the transformation of cell phenotype^[9]. The ECM is a dynamic network structure, mainly composed of a series of biological macromolecules, such as collagen, elastin, proteoglycan, and structural glycoprotein. Collagen and elastin are the main components of the aortic wall, accounting for 50% of the dry weight of normal arteries. They play an important role in maintaining the integrity of the aorta and withstanding the stress of blood flow on the wall^[10]. A large number of studies have shown that in patients with AD, the arterial wall is thinner, elastic protein fragments can be seen in the middle layer, elastic protein and collagen are significantly reduced, elastic fibers (composed of elastic protein and tropocollagen)

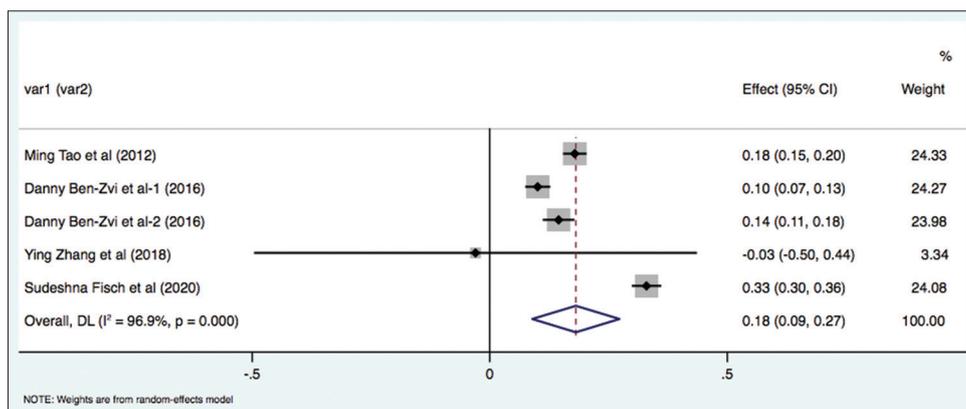


Figure 2. Forest diagram of the effect of leptin on aortic diameter.

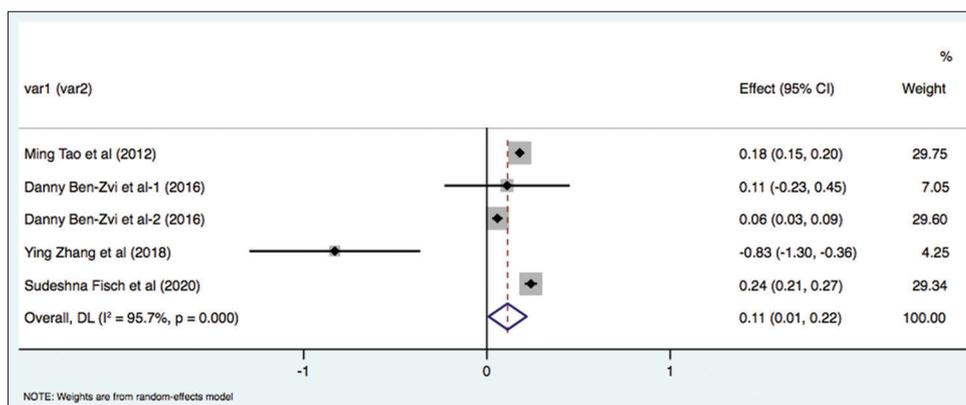


Figure 3. Forest diagram of the effect of leptin on aortic dilatation.

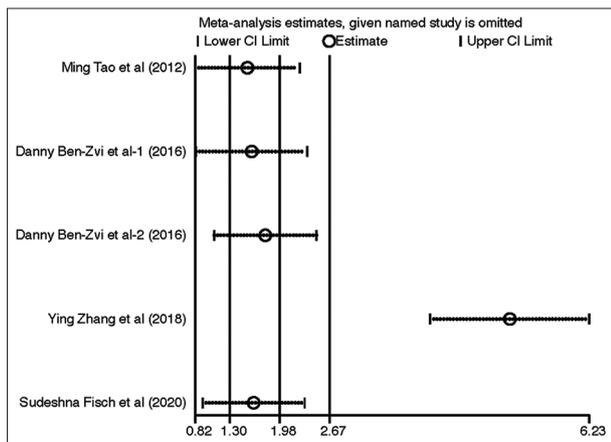


Figure 4. Results of sensitivity analysis (leptin enhanced group and leptin weakened group).

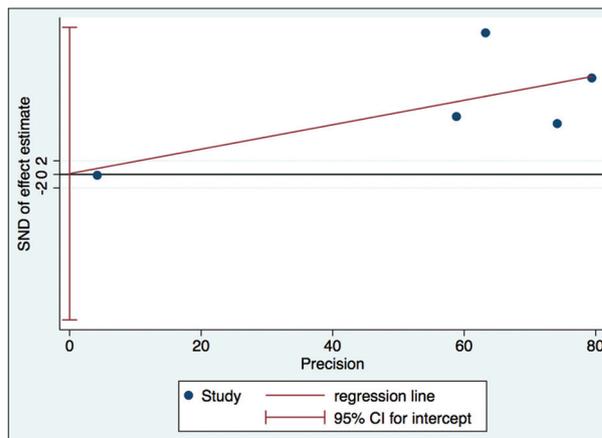


Figure 5. Egger's test plot.

are arranged in a disorderly fashion, and type IV collagen defects can be observed in the basement membrane of smooth muscle cells (SMCs), along with other pathological changes^[9-11]. These pathological changes will increase the compliance of the aortic wall; a high compliance can cause degeneration of SMCs in the middle layer, further lead to

elastic fiber defect, and eventually result in the degradation of the basement membrane, thus providing a pathological basis for the occurrence of AD^[9].

Abnormal glucose and lipid metabolism are mainly characterized by abdominal obesity and metabolic disorders of lipid, glucose, and carbohydrate, which can cause

serious cardiovascular and cerebrovascular diseases^[6]. In a study, abundant inflammatory cytokines were detected in adipocytes, and adipose tissue was found to have an effect on the oxidative stress reaction in AD patients by releasing large amounts of polypeptides and cytokines into the blood circulation, thus inducing the occurrence and development of various diseases^[15]. A number of studies have also pointed out that lipid metabolism is involved in aortic vascular remodeling and further confirmed that obesity has a strong correlation with the occurrence and development of abdominal aortic aneurysm and AD^[18-20]. Relevant research has confirmed this hypothesis laterally. Studies have found that insulin resistance ($5.5\% \leq \text{HbA1c} \leq 6.5\%$), caused by abnormal glucose metabolism, had significantly increased the cardiovascular incidence rate in this population^[21,22]. The studies have also pointed out that insulin resistance is the main feature of pre-diabetes, which can cause hyperlipidemia syndrome with elevated plasma triglyceride (TG), reduced human low-density lipoprotein (HDL), and elevated very low-density lipoprotein (VLDL). Obesity is one of the main risk factors for insulin resistance^[19]. The inflammatory reaction caused by excessive fat accumulation and abnormal lipid metabolism may eventually lead to insulin resistance. It is evident that there is a close relationship between lipid and glucose metabolism.

Relevant studies have shown that glucose and lipid metabolism play an important role in the phenotypic transformation of SMCs^[22-24]. The phenotype of aortic SMCs in AD patients changes from contractile to secretory, which is accompanied by increased glycolytic flux, decreased glucose oxidation, and increased cholesterol^[19,24,25]. Moreover, the increase in insulin resistance and lactate dehydrogenase A (LDHA) levels can induce the phenotypic transformation of SMCs and promote the occurrence of AD. However, the study also found that the occurrence and development of AD are greatly inhibited by drug intervention or the inhibition of these processes^[20,26].

In addition, abnormal glucose and lipid metabolism also affect a variety of physiological processes, including autophagy, inflammatory reaction, and vascular fibrosis, all of which play an important role in the progression of AD. The abnormal metabolism of glucose and lipid plays different roles in different stages of arterial dissection. Hyperglycemia in patients (diabetes), to a certain extent, provides the energy source for blood vessels. In some ways, this is beneficial to the stability of the disease, but long-term hyperglycemia promotes vascular inflammation and fibrosis and ultimately leads to vascular abnormalities. The abnormality of glucose and lipid metabolism will

inevitably lead to a series of changes in cell function, which will have an irreversible impact on cell metabolism, cell self-renewal, and cell life cycle^[27-33]. For example, in AD, the expression of autophagy in the middle layer was found to be significantly higher than that in the control group, thus suggesting the overactivation of autophagy in AD^[27]. Studies have confirmed that MYH11, a myosin marker of SMCs, leads to autophagic conversion through the ubiquitin-proteasome system after being stimulated by the external environment^[28,29]. In a study, adult mice that lack autophagy died of hypoglycemia 24 h after starvation, indicating that autophagy plays a key role in glucose homeostasis^[30]. In addition, studies have shown that the phenotypic transformation of SMCs, induced by PDGF, can be inhibited by inhibiting autophagy levels^[27]. Moreover, glucose is known to regulate the autophagy level in organisms by controlling glucagon/insulin secretion^[31]. The inflammatory reaction and vascular fibrosis that are induced by abnormal glucose and lipid metabolism can promote the occurrence and development of AD. It has been found that macrophages can infiltrate the aortic wall and release matrix metalloproteinases that degrade the elastic fibers of the aortic wall, which, in turn, decreases the elasticity of the vascular wall. Eventually, the middle layer of the aortic wall degenerates and loses its elasticity, causing vascular tears under the stimulation of hypertension^[32]. In view of the excessive fibrotic and brittle nature of the aortic wall as a result of the stimulation of inflammatory factors, the aortic wall is unable to withstand the shear force generated by blood pressure, which eventually causes dissection^[33].

Leptin is closely related to glucose and lipid metabolism. Leptin plays an important role in the regulation of glucose and lipid metabolism, energy metabolism, reproductive development, and immune regulation by acting on the central nervous system and peripheral tissues. Leptin is an independent predictor of carotid intima-media thickness (cIMT) in obese patients^[34]. Similar associations have been found in healthy male and female individuals^[35], obese children^[36], and psoriasis patients^[37,38]. In addition, the presence of carotid plaque is associated with hyperleptinemia in patients with systemic lupus erythematosus (SLE)^[39]. With regard to the severity of carotid artery disease, high leptin concentration has been found to be associated with plaque instability characteristics in carotid endarterectomy patients^[40]. Furthermore, the overexpression of leptin receptor gene (*LEPR*) has been observed in advanced carotid atherosclerosis^[41]. The previous studies, however, have reported that leptin concentration in symptomatic carotid artery disease patients was lower than that in asymptomatic patients^[42]. In a rat carotid artery injury model, genistein (an isoflavone) has been found to

reduce leptin-induced neointima formation^[43]. Overall, hyperleptinemia is associated with increased cIMT and carotid plaque instability.

Elevated leptin level is related to the development of insulin resistance and type 2 diabetes mellitus (T2DM)^[44]. In T2DM, the relationship between high leptin concentration and increased cardiovascular risk, microvascular complications, and cardiac autonomic dysfunction has been reported^[45-48]. Other studies have also reported that the concentration of leptin is associated with the occurrence and severity of asymptomatic myocardial infarction (MI) and carotid atherosclerosis (assessed by cIMT) in T2DM patients^[49,50]. In addition, obesity, hypertension, MetS, and endothelial dysfunction have been found to be more common in T2DM patients with elevated leptin levels^[51-53]. In both T2DM patients and healthy individuals, leptin decreases following an oral fat-tolerance meal^[54]. Other than that, certain leptin gene polymorphisms have been found to be associated with the presence of T2DM^[55-58]. It has been reported that leptin replacement therapy can improve muscle and liver insulin resistance in patients with lipodystrophy as well as inhibit liver gluconeogenesis, fat decomposition, and fasting hyperglycemia in animal diabetes models^[59].

Leptin may affect cardiac remodeling, metabolism, and systolic function^[60]. According to a study, the soluble leptin receptor (LepR) and leptin content in epicardial adipocytes are 56.9% and 28.6% higher, respectively, than those in subcutaneous adipocytes^[61]. In patients with coronary heart disease (CHD), leptin levels have been found to be positively correlated with myeloperoxidase and C-reactive protein (an inflammatory marker) concentrations as well as the increase in factor VII activity^[62-64]. There is also increased expression of leptin gene in the epicardium, pericardium, and subcutaneous adipose tissue of CHD patients with MetS^[65]. It has been previously reported that leptin enhances platelet activation in CHD patients by promoting bone differentiation^[66] and calcification of vascular cells *in vitro*^[67]. In addition, leptin may directly affect coronary artery endothelial cells by increasing the expression of tissue factors and cell adhesion molecules^[68]. Leptin can also increase insulin resistance in patients with CHD^[69,70]. Statins, on the other hand, can reduce the concentration of leptin in patients with CHD^[71,72]. Future research should clarify if this induction is related to the atherosclerotic protective properties of statins. In addition to statins, several other drugs, including hypoglycemic, antihypertensive, and anti-obesity drugs, have also shown effects on leptin levels^[73,74]. Leptin may be a target drug candidate for therapeutic intervention. Hyperleptinemia, in general, is related to the existence and severity of CHD

and heart failure. Statins and other drugs may reduce leptin concentration. Therefore, in patients with CHD and heart failure, the choice of leptin-lowering therapy may help reduce their cardiovascular risk.

Leptin can stimulate atherosclerosis, inflammatory responses, oxidative stress, and thrombosis, thereby promoting endothelial dysfunction, arterial stiffness, and the development of atherosclerotic plaques^[75-77]. In addition, leptin regulates bone homeostasis, reproduction, and angiogenesis^[78]. At present, there are many ongoing studies based on the physiological effects of leptin. Research has shown that leptin can regulate vascular remodeling *in vivo*^[79] and that the increase in leptin levels can significantly promote the growth of lesions after experimental vascular injury in mice^[67,80]. Leptin can also enhance platelet aggregation and stabilize arterial thrombosis, thereby increasing the possibility that elevated leptin levels in obese people may directly lead to an increased risk of cardiovascular disease associated with obesity^[81-86]. However, the evidence for any potential association between leptin and AD is limited, thus requiring further studies.

In our study, two pre-clinical studies were conducted on 88 animals that met the inclusion criteria. The results showed that leptin had a significant effect on the enlargement of aortic diameter and the increase in aortic wall compliance at the animal level. In animal models, the local application of leptin is sufficient to induce regional degeneration of ECM, thus increasing the risk of dissection. The local inhibition of leptin activity on the aorta may weaken the progression of AD and its related heart diseases to some extent. Based on its protective properties, we expect a positive response in local aneurysms when local LepA is used in various aneurysms (i.e., aortic, peripheral, and visceral lesions). It is evident that there is obvious heterogeneity in the research. Through sensitivity analysis, we found that the combined effect value reversed after excluding the study conducted by Ying *et al.*^[17], suggesting that this study is the reason for the heterogeneity in the meta-analysis. According to the study conducted by Ying *et al.*^[17], the reason for the contrasting experimental results may be related to the difference in drug dosage and the mechanism of action. Through meta-regression, we found that the mode of administration (local sustained-release and intraperitoneal injection), reagent dosage, and mouse type were not the reasons for heterogeneity. Leptin is known to play a key role in regulating energy balance and controlling body weight. Once it is released into the circulation, it may exert central and peripheral effects by combining with LepR, found in many tissues, thus leading to the activation of several main signal transduction pathways^[7,8,12,87]. We speculate that

intraperitoneal leptin injection may activate other signaling pathways, and leptin, as an upstream factor of the signaling pathway, may affect the occurrence of dissection in other ways. In a health study involving 12,203 men (screened by ultrasound; 875 aneurysms ≥ 30 mm), aged 65 – 83 years, it was found that there is no association between serum leptin levels and AD^[88]. However, it is still unknown whether there is a causal relationship between the systemic absorption of leptin and the formation of dissecting aneurysms.

The limitations of this study include the following: (i) There are some differences in the detection of indicators considering that each research institute is located in a different region; in addition, data transformation was carried out in this study for systematic analysis since most studies reported in median and percentiles; (ii) there are inevitable differences in the level of experimental conditions in different places, which has a certain impact on the effect of the experiment.

5. Conclusion

Based on current fundamental research and the results of this study, we have reason to believe that the local synthesis of leptin can enlarge the aortic diameter and increase the dilation of the aortic wall. Although it is still impossible to ascertain the fact that it can promote the formation of dissection due to the lack of evidence, it can be concluded that the increase in dilation of the aortic wall can, to a certain extent, promote the formation of dissection, especially in AD patients with underlying diseases, such as atherosclerosis, and that any event that results in vascular wall instability will eventually lead to the occurrence of AD. In conclusion, this study provides evidence that leptin is a risk factor for AD.

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Conflict of interest

The paper has no financial interest in any individual or organization; it does not infringe on the intellectual property rights of others. The manuscript and images are original and have not been published before. All authors have no conflicts of interest or financial ties to disclose.

Author contributions

Conceptualization: Ling Chen and Liangwan Chen

Methodology: Ling Chen and Liangwan Chen

Writing – original draft: Ling Chen and YangXi

Writing – review & editing: Ling Chen, YangXi, and Fan Xu

All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

All data generated or analyzed during this study are included in this published article.

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