Unveiling the multifaceted role of adropin in various diseases (Review)

LING CHEN[1], JIANRAO LU[1], JING HU[1] and XUEZHONG GONG[2]

[1]Department of Nephrology, Seventh People's Hospital of Shanghai University of Traditional Chinese Medicine, Shanghai 200137, P.R. China; [2]Department of Nephrology, Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai 200071, P.R. China

Received May 10, 2024; Accepted July 31, 2024

DOI: 10.3892/ijmm.2024.5414

Abstract. Adropin is a secreted peptide encoded by the energy homeostasis-associated gene, which also functions as a membrane-bound protein facilitating intercellular communication. This peptide has been detected in various tissues and body fluids, including the brain, liver, kidney, heart, pancreas, small intestine, endothelial cells and colostrum. Notably, the amino acid sequences of adropin are identical in humans, mice and rats. Previous studies have demonstrated that adropin levels fluctuate under different physiological and pathological conditions. Adropin plays a role in regulating carbohydrate metabolism, lipid metabolism and intercellular molecular signaling pathways, implicating its involvement in the progression of numerous diseases, such as acute myocardial infarction, lung injury, non-alcoholic fatty liver disease/non-alcoholic steatohepatitis, kidney disease, polycystic ovary syndrome, obesity, and diabetes, atherosclerosis, systemic sclerosis and cancer. Despite its significance, the precise role and mechanism of this protein remain inadequately understood and studied. To elucidate the function of adropin and its clinical research status, a systematic review of recent studies on adropin across various diseases was conducted. Additionally, several challenges and limitations associated with adropin research in both animal and clinical contexts were identified, aiming to offer valuable insights for future investigation.

Contents

1. Introduction
2. Structure of adropin
3. Regulation of adropin expression
4. Association of adropin with the development of multiple diseases
5. Conclusions and future prospectives

1. Introduction

Adropin, a novel 76-amino acid polypeptide, is detected in various organs and tissues, including the liver, endothelial cells, heart, small intestine, pancreas, serum, kidney and brain (1-3). Initially discovered by Kumar *et al* in 2008 (1) during an

Correspondence to: Professor Jing Hu, Department of Nephrology, Seventh People's Hospital of Shanghai University of Traditional Chinese Medicine, 358 Datong Road, Shanghai 200137, P.R. China
E-mail: 6264570@qq.com

Professor Xuezhong Gong, Department of Nephrology, Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, 274 Zhijiang Middle Road, Shanghai 200071, P.R. China
E-mail: shnanshan@yeah.net

Abbreviations: ACR, albumin/urine creatinine ratio; ADRP, adipocyte differentiation-related protein; AMPK, AMP-activated protein kinase; AKT, protein kinase B; BMI, body mass index; CD36, cluster of differentiation 36; CKD, chronic kidney disease; CRC, colorectal cancer; DIO, diet-induced obesity; eNOS, endothelial nitric oxide synthase; ENHO, energy homeostasis-associated gene; ERα, estrogen receptor α; ERK1/2, extracellular regulated kinase 1/2; ESRD, end-stage renal disease; FF, follicular fluid; GCN5L1, general control of amino acid synthesis 5 like-1; GPR19, G-protein coupled receptor 19; GLP-1, glucagon-like peptide-1; HDL, high-density lipoprotein; HFD, high-fat diet; HD, hemodialysis; IR, insulin resistance; LDL, low-density lipoprotein; LXRα, liver X receptor α; MIP-1/2, macrophage inflammatory protein 1/2; MAFLD, dysfunction-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NLRP3, NLR family pyrin domain containing 3; PI3K, phosphatidylinositol-3 kinase; PDH, pyruvate dehydrogenase; PD, peritoneal dialysis; PDK4, pyruvate dehydrogenase kinase 4; PPARγ, peroxisome proliferator-activated receptor γ; PDA, pancreatic ductal adenocarcinoma; PP2A, protein phosphatase 2A; Rock, Rho-associated coiled-coil containing protein kinase; ROR, retinoic acid receptor-related orphan receptor; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; SREBP-1, sterol regulatory element-binding protein 1; TGF-β, transforming growth factor β; TC, total cholesterol; TG, triglycerides; T2DM, type 2 diabetes mellitus; VEGFR2, vascular endothelial growth factor receptor-2; VSMC, vascular smooth muscle cell

Key words: adropin, glucose metabolism, lipid metabolism, molecular signaling pathway, disease

investigation into the hypothalamic regulation of liver metabolism, adropin was identified in the livers of C57BL/6J mice lacking melanocortin-3 receptors through a microarray analysis of total gene expression. This encoding gene is associated with energy homeostasis and lipid metabolism, earning it the designation of the energy homeostasis-related (ENHO) gene (1).

Adropin functions as a secreted peptide that is bound to and secreted by cell membranes and as a membrane-bound protein that facilitates intercellular communication. Extensive research has demonstrated the significant impact of adropin on mechanisms related to increased obesity, glucose and lipid metabolism, as well as insulin resistance (IR) (4-6). In glucose metabolism, adropin enhances glucose utilization in mice, regulating the insulin signaling pathway (6,7). Additionally, adropin treatment mitigates non-alcoholic fatty liver disease (NAFLD) progression by inhibiting protein phosphatase 2A (PP2A), activating the AMP-activated protein kinase (AMPK) pathway and reducing hepatic glucose production in the context of IR (4). Regarding lipid metabolism, adropin reduces serum triglycerides (TGs), total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol levels in hypertensive rats (6). Adropin downregulates the expression of lipogenic proteins, sterol regulatory element-binding protein (SREBP) 1 and adipocyte differentiation-related protein (ADRP), in diabetic kidney disease (DKD) mice, improving lipid deposition in renal tissue (8). Additionally, adropin influences disease development by modulating molecular signaling pathways. Specifically, it activates the phosphatidylinositol-3 kinase (PI3K)/protein kinase B (AKT) and extracellular regulated kinase (ERK)1/2 pathways through vascular endothelial growth factor receptor 2 (VEGFR2), protecting endothelial cells (9). Moreover, adropin inhibits the osteogenic differentiation of vascular smooth muscle cells (VSMCs) and reduces vascular calcification by activating the Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signaling pathway (10).

These findings indicate that adropin participates in disease development through multiple pathways, including glucose metabolism, lipid metabolism and molecular signaling pathways. However, the effects of each pathway are interconnected, making the impact of adropin on disease mechanisms complex. In previous reviews, the role of adropin in energy and metabolic disorders has been described (11-14). Compared with previous reviews, the present review not only includes a section regarding the regulation of adropin, but also a summary of some of the associated molecular signaling pathways. To elucidate the function and clinical research status of adropin, research on adropin in various diseases, including acute myocardial infarction (AMI), lung injury, NAFLD/non-alcoholic steatohepatitis (NASH), kidney disease, obesity, diabetes, atherosclerosis, polycystic ovary syndrome (PCOS), multiple sclerosis (MS) and cancer, from the past decade was systematically reviewed. Compared with previous reviews, the present review identified several challenges and limitations associated with adropin research in both animal and clinical contexts, aiming to offer valuable insights for future investigations.

2. Structure of adropin

The ENHO gene encodes adropin, a polypeptide consisting of 76 amino acids (MGAAISQGALIAIVCNGLVGFLLLLWVILCWACHSRSADVDSLSESSPNSSPGPCPEKAPPPQKPSHEGSYLLQP). The ENHO gene, located on chromosome 9p13.3, comprises one intron and two exons (1). The first 33 amino acids serve as a secretory signal peptide (1), while amino acids 34-76 possess biological activity (7) (Fig. 1). Adropin has a molecular weight of 4.499 Da (1). Structurally, the N-terminal amino acids 1-9 are cytoplasmic, amino acids 9-30 span the membrane, and amino acids 30-76 are extracellular (15,16). The amino acid sequence of adropin is 100% identical across rats, mice and humans (1,17).

3. Regulation of adropin expression

Kumar *et al* (1) demonstrated that adropin is nutritionally regulated in mice. In C57BL/6J mice, adropin expression increased rapidly with a high-fat diet (HFD) but decreased in fasted mice, compared with the control group (1). Additionally, mice on a diet high in fat and low in carbohydrates exhibit higher adropin expression, whereas those on a diet low in fat and high in carbohydrates show reduced adropin levels (18). The rapid upregulation of hepatic ENHO mRNA in response to macronutrient changes suggests the involvement of intracellular lipid sensors (18). This evidence indicates that adropin expression is linked to dietary fat intake.

Adropin expression is regulated by several factors, including liver X receptor α (LXRα), retinoic acid receptor-related orphan receptor (ROR), estrogen receptor α (ERα), STAT3 and glucagon-like peptide-1 (GLP-1) (16-21) (Fig. 2). LXRα is a nuclear receptor and a sensor for blood lipids and glucose and plays a notable role in the regulation of lipid metabolism (19). In HepG2 cells, the LXRα agonist, GW3965, reduces ENHO expression, an effect that can be blocked by LXRα-targeting antisense RNA (20). Reduced hepatic ENHO mRNA levels were observed in diet-induced obese mice treated with the LXRα agonist, indicating that LXRα regulated liver ENHO expression (1). Furthermore, another study found that ENHO expression is rhythmic in the liver of male mice, peaking during maximum food consumption in the dark phase, which is related to the transcriptional activation of the circadian clock genes, RORα/γ (21).

Recent research on female mice with NAFLD under HFD conditions revealed a negative correlation between adropin levels and both lipogenic gene expression and a fatty liver, which was an ERα-dependent effect (22). Additionally, hepatic ERα induced adropin-inhibited hepatic lipogenesis and lipid deposition in women with high dietary lipid intake (22). A concurrent study indicated that liver adropin regulation involves estrogen. Ovariectomized mice treated with estrogen exhibited elevated hepatic ENHO expression, in which estrogen-dependent ERα bound to the ENHO gene. Adropin treatment also improved metabolic disorders in the mice (23).

In HepG2 cells treated with a high-glucose medium, Kuo *et al* (24) observed a clear upregulation of the phosphorylated (p-)STAT3/STAT3 ratio, reactive oxygen species (ROS) expression and ENHO mRNA levels as the glucose levels increased. This effect was mitigated by pretreatment with Stattic or STAT3-specific small interfering RNAs. Similar outcomes were noted in animal models, suggesting

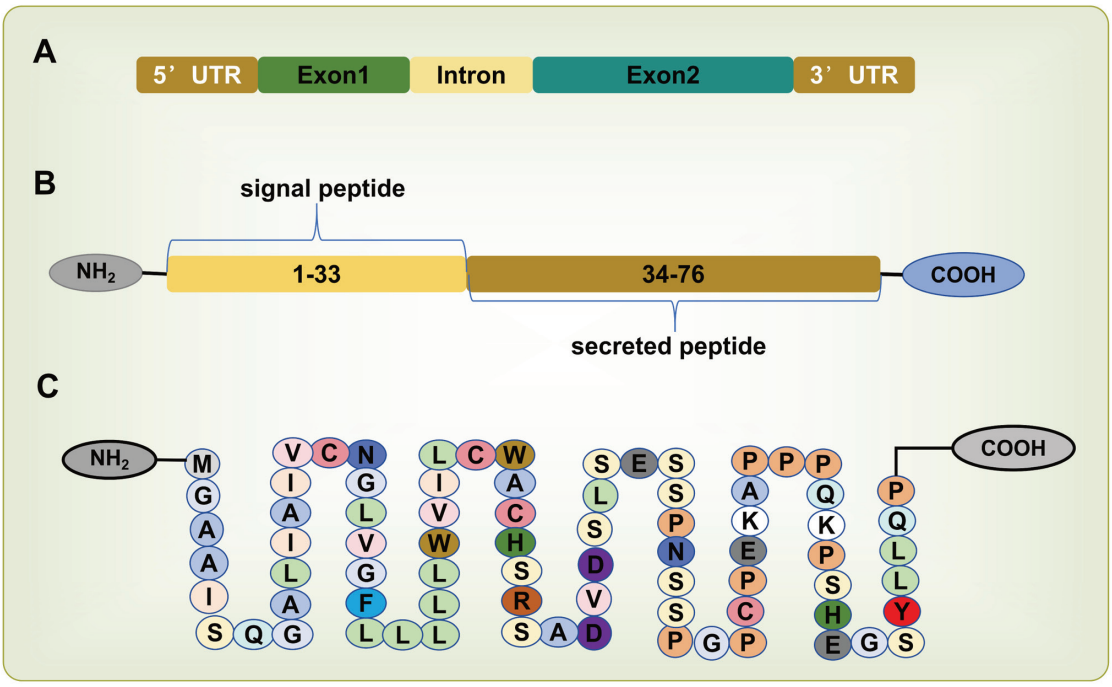

Figure 1. Structure of adropin. (A) The energy homeostasis-associated gene encoding adropin consists of 2 exons and 1 intron. (B) Adropin is a polypeptide consisting of 76 amino acids. Amino acids 1-33 are a secretory signal peptide and amino acids 34-76 are biologically active. (C) The 76 amino acids that make up adropin. UTR, untranslated region.

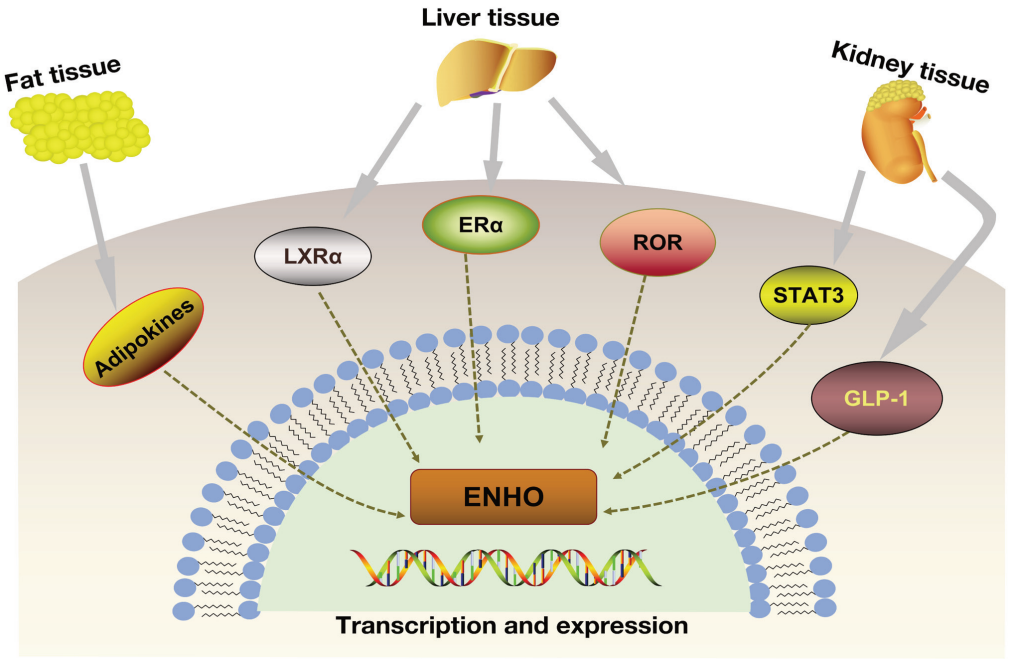

Figure 2. Expression of adropin is affected by LXRα, ROR, ERα, STAT3 and GLP-1. Dietary fat can affect adropin levels. In the liver, adropin levels are affected by the LXRα, ROR and Erα genes. STAT3 and GLP-1 have been found to affect adropin levels in diabetic nephropathy. The dotted line indicates that it is uncertain whether it is a direct target modulation. ENHO, energy homeostasis-associated gene; ERα, estrogen receptor α; LXRα, liver X receptor α; GLP-1, glucagon-like peptide-1; ROR, retinoic acid receptor-related orphan receptor; STAT3, signal transducer and activator of transcription 3.

that STAT3 is integral to ENHO gene regulation and promotes hepatic adropin expression in diabetic rats (24).

Li *et al* (25) found that myricetin dose-dependently increased plasma β-endorphin and adropin levels, effects that were inhibited by a GLP-1 receptor antagonist. Further mechanistic experiments using the HepG2 cell line showed that myricetin-induced GLP-1 receptor activation modulated adropin expression. In diabetic rats, the effect of myricetin on plasma adropin was primarily mediated through endogenous β-endorphin following GLP-1 receptor activation *via* acute bolus injection. Chronic myricetin treatment also enhanced adropin secretion in diabetic rats, suggesting a link between

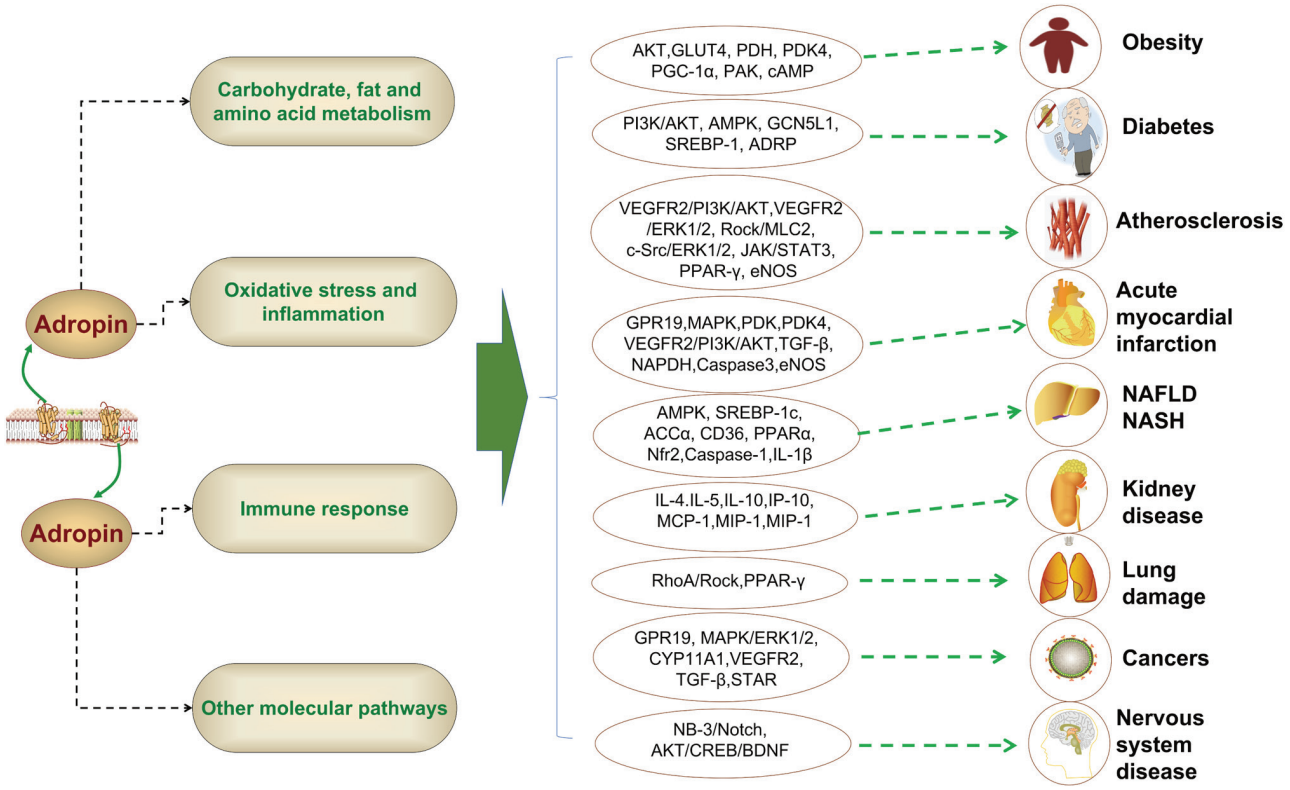

Figure 3. Adropin is involved in the occurrence of various diseases through multiple mechanisms. Adropin can participate in the development of metabolic diseases by affecting carbohydrate, lipid and amino acid metabolism, and can also participate in the development of non-metabolic diseases by affecting inflammation, immune response and signaling molecules or pathways. ADRP, adipocyte differentiation-related protein; ACCα, acetyl-CoA carboxylase α; AMPK, AMP-activated protein kinase; AKT, protein kinase B; BDNF, brain-derived neurotrophic factor; CD36, cluster of differentiation 36; CREB, cyclic AMP response element-binding protein; cAMP, cyclic adenosine monophosphate; CYP11A1, cholesterol side-chain cleavage enzyme, cytochrome P450scc; eNOS, endothelial nitric oxide synthase; ERK1/2, extracellular regulated kinase 1/2; GLUT4, glucose transporters type 4; GCN5L1, general control of amino acid synthesis 5 like-1; GPR19, G-protein coupled receptor 19; MLC2, myosin light chain; MCP-1, monocyte chemoattractant protein-1; MIP-1, macrophage inflammatory protein 1; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NAPDH, nicotinamide adenine dinucleotide phosphate; Nrf2, nuclear factor erythroid 2-related factor 2; PI3K, phosphatidylinositol-3 kinase; PDH, pyruvate dehydrogenase; PDK4, pyruvate dehydrogenase kinase 4; PGC-1, peroxisome proliferator-activated receptor gamma coactivator-1; PAK, protein kinase A; PPARγ, peroxisome proliferator-activated receptor γ; Rock, Rho-associated coiled-coil containing protein kinase; RhoA, ras homolog gene family member A; STAT3, signal transducer and activator of transcription 3; STAR, steroidogenesis, the steroidogenic acute regulatory; SREBP-1, sterol regulatory element-binding protein 1; TGF-β, transforming growth factor β; VEGFR2, vascular endothelial growth factor receptor-2.

adropin expression and GLP-1 (25). However, as with LXRα, ROR, ERα and STAT3, current studies only demonstrate that adropin expression is regulated by these upstream molecules. It remains unclear whether these molecules directly target and regulate adropin, necessitating further detailed research.

4. Association of adropin with the development of multiple diseases

Adropin significantly influences energy balance regulation and the metabolism of fatty acids and glucose (26,27). Acting as a membrane-bound protein, adropin facilitates intercellular communication, and its involvement spans various diseases, including AMI (28), lung injury (29), NAFLD/NASH (30), kidney disease (31), PCOS (32), obesity (33), diabetes (34), atherosclerosis (35), MS (36) and cancer (37,38) (Fig. 3). The molecular mechanisms through which adropin contributes to these diseases are detailed in Table I.

AMI. Globally, AMI ranks among the leading causes of both morbidity and mortality (39). A report has indicated that adropin enhances cardiac energy metabolism and improves cardiac efficiency by promoting glucose oxidation and suppressing fatty acid oxidation in the heart (40). In cardiomyocytes, adropin activates G-protein coupled receptor 19 (GPR19), which leads to MAPK-mediated phosphorylation. This process downregulates the phosphorylation of pyruvate dehydrogenase kinase 4 (PDK4) and promotes the phosphorylation of pyruvate dehydrogenase (PDH) (11). Aydin *et al* (41) observed that serum adropin levels gradually increased as myocardial damage from infarction worsened within the first 1-24 h in myocardial infarction rats. Another study demonstrated that adropin treatment effectively improved cardiac function in mice with radiation-induced myocardial injury, inhibited oxidative stress and myocardial fibrosis, reduced cardiomyocyte apoptosis and promoted microangiogenesis (42). The primary mechanism involves adropin activating the VEGFR2/PI3K/AKT pathway. Additionally, adropin treatment decreased the expression of transforming growth factor β1 (TGF-β1), NOX4 and caspase 3 in cardiomyocytes while promoting endothelial nitric oxide synthase (eNOS) expression (42).

Yu *et al* (28) found that patients who had experienced AMI had significantly lower serum adropin levels compared

Table I. Mechanism of action of adropin in the development of various diseases.

Disease	Mechanism	Impact	(Refs.)
AMI	Adropin→GPR19↑→MAPK↑→PDK-4↓→PDH↑→Glucose oxidation↑; adropin→VEGFR2↑→PI3K↑→AKT↑→ROS, fibrosis, apoptosis↓; adropin→eNOS, TGF-β, NADPH, caspase3↓	Improve	(11,42)
Lung damage	Adropin→RhoA↓→ROCK↓→ROS, inflammation, fibrosis↓; adropin→PPARγ↓→Macrophage M2 polarization↑→inflammation↓	Improve	(29,48)
NAFLD/NASH	Adropin→PP2A↓→AMPK↑→Glucose production↓; adropin→Nrf2↑ →ROS↓; adropin→Caspase-1, IL-1β↓→ROS and inflammation↓; adropin→SREBP-1c, ACCα, CD36↓; PPARα↑	Improve	(4,38,52,54)
Kidney-related diseases	Adropin→IFN-γ, IL-4, IL-5, IL-10, IL-12, IL-17A, CXCL2↓; IP-10, MCP-1, MIP-1α, MIP-2↑	Improve	(61)
PCOS	Still not clear	Improve	
Obesity	Adropin→AKT, GLUT4↑→insulin sensitivity↑; adropin→PGC-1α↓→ PDK-4 ↓→PDH ↑→Glucose oxidation↑; adropin→PAK↓→cAMP↓ →blood sugar improvement↑	Improve	(7,77)
Diabetes	Adropin→PI3K↑→AKT↑, AMPK↑→insulin regulation↑; adropin→TG, TC, ALT, AST, GGT, ALP, LDL↓	Improve	(86,92)
DKD	Adropin→SREBP-1, ADRP↓→Mitochondrial damage and lipogenesis↓	Improve	(8)
Diabetic cardiomyopathy	Adropin→GCN5L1↑→Glucose oxidation↑; adropin→Drp1, collagen I, and collagen III↓; Mitofusin-1 and Mitofusin-2↑	Improve	(91,103)
Diabetic retinopathy	Still not clear	Improve	
Atherosclerosis	Adropin→VEGFR2↑→PI3K↑→AKT↑VEGFR2↑→ERK1/2↑→eNOS↑ →NO↑→endothelial function↑; adropin→Rock↓→MLC2↓ →endothelial permeability↓; adropin→c-Src↓→erk1/2↓→endothelial cell proliferation↓; adropin→JAK2↑→STAT3↑→Vascular calcification↓; adropin→TGF-β↓→Smad2/3↓→EMT↓	Improve	(9,10,107,109,110)
MS	TGFβ → Adropin↓→GPR19↓→fibrosis↑		(36)
Breast cancer	Adropin→GPR19↑→MAPK↑→ERK1/2↑→EMT↑→pr oliferation and metastasis↑	Promote	(118)
Adrenocortical carcinoma	Adropin→TGF-β↑→STAR, CYP11A1↓→cortisol and aldosterone↓		(119)
PDA	Adropin→VEGFR2, Ki67, cyclin D1, MMP2↓→cell proliferation and angiogenesis↑	Promote	(121)
Others (nervous system)	Adropin→NB-3↑→Notch↑→physical coordination ability↑; adropin→AKT↑→CREB↑→BDNF↑→Memory capacity↑	Improve	(16,124)

ADRP, adipocyte differentiation-related protein; ACCα, acetyl-CoA carboxylase α; AMPK, AMP-activated protein kinase; AMI, acute myocardial infarction; AKT, protein kinase B; BDNF, brain-derived neurotrophic factor; CD36, cluster of differentiation 36; CREB, cyclic AMP response element-binding protein; cAMP, cyclic adenosine monophosphate; CYP11A1, cholesterol side-chain cleavage enzyme, cytochrome P450scc; Drp1, dynamin-related protein 1DKD, diabetic kidney disease; EMT, endothelial-to-mesenchymal transition; eNOS, endothelial nitric oxide synthase; ERK1/2, extracellular regulated kinase 1/2; GLUT4, glucose transporters type 4; GCN5L1, general control of amino acid synthesis 5 like-1; GPR19, G-protein coupled receptor 19; JAK2, Janus kinase 2; MLC2, myosin light chain; MCP-1, monocyte chemoattractant protein-1; MIP-1, macrophage inflammatory protein 1; MS, multiple sclerosis; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NAPDH, nicotinamide adenine dinucleotide phosphate; Nrf2, nuclear factor erythroid 2-related factor 2; PI3K, phosphatidylinositol-3 kinase; PDA, pancreatic ductal adenocarcinoma; PDH, pyruvate dehydrogenase; PDK4, pyruvate dehydrogenase kinase 4; PGC-1, glucagon-like peptide-1; PAK, protein kinase A; PPARγ, peroxisome proliferator-activated receptor γ; PCOS, polycystic ovary syndrome; Rock, Rho-associated coiled-coil containing protein kinase; RhoA, ras homolog gene family member A; STAT3, signal transducer and activator of transcription 3; STAR, steroidogenesis, the steroidogenic acute regulatory; SREBP-1, sterol regulatory element-binding protein 1; TGF-β, transforming growth factor β; VEGFR2, vascular endothelial growth factor receptor-2; →, promote; ↑, upregulate; ↓, down-regulate.

with those with stable angina pectoris and normal controls. In a study from 2022, Adıyaman *et al* (43) evaluated serum adropin levels and their link to folic acid and cobalamin in 70 patients with ST-segment elevation myocardial infarction

(STEMI) and 70 controls. Within the first 24 h, the STEMI group exhibited notably elevated levels of adropin, troponin and C-reactive protein, while the amine and folate levels were considerably lower than in the control group (43). Therefore, patients with early-stage myocardial infarction may benefit from screening adropin as a cardiac biomarker. However, the underlying mechanism behind the negative relationship between adropin, cobalamin and folic acid levels in patients with myocardial infarction remains under investigation. Another study by Chang *et al* (44) divided 163 patients with AMI into low (n=82) and high (n=80) adropin groups based on serum adropin levels. The clinical follow-up revealed that the low adropin group exhibited a higher rate of recurrent myocardial infarction compared with the high adropin group (44), indicating that adropin levels are crucial for the long-term prognosis of patients with AMI.

Lung damage. Myeloperoxidase (MPO)-antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis frequently leads to potentially fatal alveolar hemorrhage or fibrosis (45,46). Gao *et al* (47) utilized adropin gene knockout (AdrKO) C57BL/6J mice to explore the pathogenesis of lung injury linked to MPO-ANCA. The results indicated that AdrKO mice exhibited reduced phosphorylation of AKT1 (Ser473) and eNOS (Ser1177) and a loss of regulatory T cells, with the adropin allele mutation increasing susceptibility to MPO-ANCA-related alveolar hemorrhage. These results suggest that initial events in MPO-ANCA-associated lung injury may be mediated at the molecular level by adropin mutations or deficiency (47). Additionally, Rizk *et al* (48) demonstrated that adropin mitigated diabetic lung injury by inhibiting the ras homolog gene family member A/Rho-associated coiled-coil containing protein kinase (Rock) pathway, apoptosis, inflammatory response, oxidative stress and lung tissue fibrosis. Concurrently, an animal study revealed that adropin promoted M2 macrophage polarization in the lungs and reduced the severity of acute pancreatitis-related lung injury by modulating peroxisome proliferator-activated receptor (PPAR)γ phosphorylation in lung macrophages (29).

A prospective study involving 57 participants [28 controls and 29 patients with acute pulmonary embolism (PE)] reported a notably lower level of adropin in the PE group compared with the control group (49). At an optimal cut-off value of 213.78 pg/ml, the sensitivity of adropin was 82% and its specificity was 75%. These results suggest that adropin could serve as a potential marker to rule out PE, which warrants further investigation (49).

NAFLD/NASH. NAFLD is a chronic hepatic disorder characterized by excessive fat accumulation and metabolic disturbances of carbohydrates and lipids (50,51). Adropin plays a protective role against disorder in sugar and lipid metabolism (11). A study by Zhang *et al* (52) demonstrated that adropin suppressed TC accumulation in tilapia liver cells and reduced the expression of SREBP-1c, acetyl-CoA carboxylase α and cluster of differentiation 36 (CD36), while increasing PPARα expression. Notably, adropin inhibits liver glucose output and TC accumulation in tilapia through AMPK activation. Chen *et al* (4) showed that AdrKO mice exhibited an unbalanced increase in hepatic glucose production before the onset of HFD-induced systemic IR. Further research indicated that adropin treatment might active the AMPK pathway by inhibiting PP2A, thereby reducing hepatic glucose synthesis under IR conditions (4). Additionally, adropin overexpression or treatment was found to ameliorate palmitic acid-induced oxidative stress in hepatocytes (53). In NASH mice, adropin activates the nuclear factor erythroid 2-related factor 2 signaling pathway and reduces ROS production by hepatocyte mitochondria, thereby protecting against liver damage (38). Another notable study revealed that exercise inhibited HFD-induced or methionine- and choline-deficient diet-induced NLR family pyrin domain containing 3 (NLRP3) inflammasome (NLRP3, Caspase-1 and IL-1β) in NASH mice, with serum adropin levels negatively correlated with serum IL-1β levels (54). Further findings showed that adropin treatment reduced the expression of Caspase-1 and IL-1β in hepatic cells and palmitic acid-treated Kupffer cells, as well as decreased ROS levels in PA-stimulated hepatic cells and Kupffer cells (54). A recent study confirmed that hepatic adropin levels were inversely related to lipogenic gene expression and fatty liver in female mice under HFD conditions, an effect dependent on hepatic ERα (22). Consequently, adropin could be a therapeutic target for metabolic diseases such as NAFLD/NASH.

Patients with NAFLD/NASH exhibit decreased serum adropin levels. A study by Kutlu *et al* (30) including 51 patients with hepatic steatosis and 30 healthy controls, observed significantly reduced serum adropin levels in the NAFLD group compared with the healthy controls and patients with IR. Moreover, adropin levels were negatively correlated with serum insulin, homeostasis model assessment of IR (HOMA-IR), urea, γ-glutamyl transferase, TC and TG levels (30). A subsequent case-control study (15 normal participants, 26 with NAFLD and 21 with NASH) revealed significantly lower serum adropin levels in patients with NASH compared with the normal controls and patients with NAFLD, including an inverse relationship between the histological severity of NAFLD and serum adropin levels (53). In a study of 62 participants [30 patients with metabolic dysfunction-associated fatty liver disease (MAFLD) and 32 healthy controls] Li *et al* (55) showed that patients with MAFLD had significantly lower circulating adropin levels than healthy controls, with serum adropin levels that were negatively correlated with NAFLD activity score, intrahepatic TG and TC (55). Furthermore, liraglutide treatment for type 2 diabetes mellitus (T2DM) combined with MAFLD resulted in increased serum adropin levels, which were closely associated with decreased liver fat content and improved glucose and lipid metabolism (56). Therefore, adropin may serve as a potential marker for the positive effects of liraglutide in treating T2DM and MAFLD.

Kidney-related diseases. Chronic kidney disease (CKD) is a chronic disease with a high incidence rate that is a general term for most kidney diseases (57). CKD poses a serious threat to the health of individuals; therefore, it is of great significance to study the pathogenesis and treatment targets of CKD (58-60). Most studies indicate that adropin is involved in the onset and progression of kidney-related diseases. In a study on the regulatory effects of adropin and spexin on systemic inflammation,

rats with adenine-induced chronic kidney failure (CKF) were divided into CKF, CKF + saline, CKF + adropin, CKF + spexin and CKF + adropin + spexin groups. The results showed that concurrent treatment with adropin and spexin reduced urinary protein and 24-h urine output (61). Furthermore, treatment with adropin alone significantly reduced the levels of granulocyte colony stimulating factor, IFN-γ, IL-4, IL-5, IL-10, IL-12, IL-17A and C-X-C motif chemokine ligand 1, while increasing levels of monocyte chemoattractant protein-1, IFN-γ-induced protein 10, macrophage inflammatory protein (MIP)-1 and MIP-2 (61). This suggests that adropin exerts a regulatory impact on both the inflammatory response and renal function, potentially offering protection against systemic inflammation and the progression of renal failure.

In clinical studies, Grzegorzewska *et al* (62) found that among 50 patients undergoing hemodialysis (HD; 27 males and 23 females) and 26 healthy participants, those undergoing HD exhibited reduced levels of circulating adropin compared with the controls. A concurrent study assessing circulating adropin and irisin levels in 48 patients with end-stage renal disease (ESRD) undergoing chronic hemodialysis (HD) or peritoneal dialysis (PD) and 36 healthy participants revealed that the adropin levels in patients with ESRD were negatively related to body weight, extra- and intra-cellular water and albumin concentration (63). Thus, adropin could serve as a novel indicator of nutritional status in patients with ESRD (63), although further research is needed to elucidate its mechanism of action. Kałużna *et al* (64) explored the relationship between adropin, irisin and cardiac status in 79 patients with ESRD (under HD, PD or kidney transplantation) and 40 healthy controls. The findings indicated a significant positive correlation between adropin concentration and both cardiac troponin T and plasma N-terminal probrain natriuretic peptide. Adropin was also correlated with the left ventricular systolic internal diameter and relative wall thickness, suggesting that adropin may become a candidate marker for cardiac dysfunction in patients undergoing HD (64). Comparative analysis of adropin concentration changes post-kidney transplantation revealed that levels were higher in patients before and after transplantation compared with the controls (65), remaining elevated for 1 year and significantly dropping 5-7 days post-transplantation (66). The plasma adropin levels peaked 12 months after transplantation (65). Further studies are required to understand the mechanisms underlying these changes in kidney transplant recipients. A 2023 cross-sectional study classified participants into four groups: Control (n=50), CKD stages 1-2 (n=50), CKD stages 3-4 (n=50) and CKD stage 5 (n=50) (67). The results showed that the fourth group (CKD stage 5) exhibited significantly reduced serum adropin levels compared with the other three groups (67). Adropin levels are inversely associated with cardiovascular risk biomarkers, suggesting that low serum adropin levels may be a predictor of CKD, HD and their complications (68,69).

PCOS. Multiple clinical studies have demonstrated that adropin influences the occurrence of PCOS (32,70,71). In a cross-sectional study involving 152 women with PCOS and 152 non-PCOS controls, serum adropin levels were significantly reduced in patients with PCOS and inversely linked to TNF-α levels (70). Another study comparing 60 women with PCOS to 60 non-PCOS participants found notably lower levels of adropin in both the serum and follicular fluid (FF) of the PCOS group. Furthermore, the adropin levels were negatively correlated with the LDL levels but positively correlated with body mass index (BMI) and high-density lipoprotein (HDL) levels (71). This suggests that adropin may impact the pathophysiological processes of PCOS through its role in human metabolism.

A study investigating the effect of PCOS on adropin levels observed reduced serum adropin levels in both the lean and overweight PCOS groups compared with the control group, with no significant difference between the lean and overweight PCOS groups (72). Therefore, it is suggested that BMI is not the cause of the changes in serum adropin levels. In a larger study involving 67 control participants and 220 patients with PCOS, a significant decrease in adropin levels was found in both the plasma and FF of patients with PCOS (73). Adropin concentration was negatively correlated with BMI, free androgen index, HOMA-IR, androstenedione and TC, and positively correlated with sex hormone binding globulin and HDL. Additionally, the FF adropin concentration in the PCOS group was negatively related to HOMA-IR, isoleucine and valine levels (73). This indicates that reduced adropin levels in women with PCOS may contribute to IR and abnormal branched-chain amino acid metabolism. Recent meta-analyses confirmed that the plasma adropin levels in women with PCOS were significantly lower than those in non-PCOS individuals, and these reduced levels were significantly correlated with BMI, dyslipidemia and IR (74,75). However, further research is required to elucidate the mechanism by which adropin-related glucose, lipid and amino acid metabolism affect PCOS.

Obesity. Obesity poses a serious health hazard globally, leading to metabolic system disorders and worsening health conditions (76). In HFD-induced obese mice, adropin has been shown to reduce obesity and improve blood lipid and sugar homeostasis (6). An early study by Kumar *et al* (1) demonstrated that adropin prevents obesity-related hyperinsulinemia and hepatic steatosis by regulating glucose and lipids metabolism. In diet-induced obesity (DIO) mice, Gao *et al* (7) found that adropin treatment improved glucose tolerance, insulin action and metabolic flexibility in utilizing glucose. Adropin treatment enhanced the phosphorylation of AKT in muscle cells in response to insulin and increased the expression of glucose transporter type 4 on cell surfaces, indicating sensitization of the insulin signaling pathway. Additionally, adropin activated PDH and downregulated PDK-4, which inhibits PDH. Furthermore, adropin treatment downregulated peroxisome proliferator-activated receptor γ coactivator 1-α, which regulates carnitine palmitoyltransferase 1B, CD36 and PDK4 expression (7). Gao *et al* (77) also investigated the molecular mechanism underpinning the effect of adropin on liver glucose metabolism in DIO mice. The results indicated that adropin reduced the endoplasmic reticulum stress response and c-Jun N-terminal kinase activity in the liver, thereby enhancing the liver insulin signaling pathway. Additionally, adropin treatment inhibited protein kinase A activity, leading to decreased phosphorylation of the inositol trisphosphate receptor, which mediates calcium efflux in the endoplasmic reticulum, and cyclic adenosine monophosphate

response element-binding protein, a key transcription factor that regulates glucose metabolism in the liver. Consequently, blood glucose regulation in DIO mice improved upon adropin administration (77). Obesity-related metabolic dysregulation has been reported to lead to mild cognitive impairment and increase the risk of dementia (78,79). Ghoshal *et al* (80) found that overexpression of the adropin gene improved recognition memory in LDL receptor-deficient C57BL/6J obese mice. The authors proposed that adropin may enhance cognitive function in patients with severe metabolic disorders through pathways related to intercellular communication and neuronal processes. However, the specific mechanisms remain to be explored.

Research indicates that serum adropin levels are significantly decreased in obese children (81-83). Yin *et al* (84) propose that adropin levels could serve as a biomarker for predicting metabolic syndrome in obese children. Another study found that obese prepubertal children had significantly higher adropin levels compared with their normal-weight counterparts. Notably, the adropin concentration in prepubertal girls was higher than in prepubertal boys, whereas adolescent girls had lower levels than adolescent boys (33). This suggests that adropin levels are associated with sex hormones that regulate pubertal development, although further research is needed to confirm this.

A systematic review and meta-analysis of adults with obesity revealed that overweight and obese participants had significantly lower circulating adropin levels than normal-weight participants, indicating a potential role of adropin in obesity development (85). A study by Erman *et al* (5), which included 50 obese patients and 22 controls, examined the relationship between serum adropin and IR. The findings showed that the serum adropin level was inversely related to BMI, waist circumference, diastolic blood pressure, fasting blood glucose and insulin levels. The researchers suggested that serum adropin may help regulate glucose and lipid metabolism and IR in obese patients. However, further research is necessary to fully understand the potential of adropin in regulating metabolic disorders and its precise mechanisms of action in obese populations.

Diabetes and its complications. Multiple reports have shown that adropin levels are associated with the occurrence of diabetes and its complications, including DKD, diabetic cardiomyopathy and diabetic retinopathy (DR) (86-88). Adropin levels are closely related to IR independent of obesity. Moreover, glycemic stability can be improved through the overexpression or exogenous administration of adropin (5). Adropin reduces hepatic glucose synthesis, thereby lowering blood glucose levels in mice (26).

Diabetes. The metabolic characteristics of patients with diabetes include typical disorders of glucose and lipid metabolism (89). Glucose metabolism disorders are primarily characterized by significantly high blood sugar, often accompanied by IR and insulin deficiency. In patients with diabetes, fat synthesis decreases while decomposition accelerates, leading to lipid metabolism disorders. These disorders manifest as hypertriglyceridemia, hypercholesterolemia or elevated LDL levels (89,90). A study found that adropin can restore glucose oxidation in prediabetic obese mice by regulating mitochondrial acetyltransferase general control of amino acid synthesis 5 like-1 (GCN5L1) expression. Adropin regulated mitochondrial acetyltransferase GCN5L1 expression, altering the acetylation status and activity of fuel metabolism enzymes to facilitate glucose utilization (91). He *et al* (86) discovered that adropin significantly activated key regulatory molecules of the AMPK, PI3K/AKT and insulin signaling pathways, including p-AKT, PI3K, insulin receptor, insulin receptor substrate 1 and AKT. The authors concluded that adropin exerts anti-diabetic effects in diabetic rats by modulating the PI3K/AKT and insulin signaling pathways. Furthermore, adropin was found to regulate lipid metabolism in diabetic rats, significantly reducing the LDL, very LDL, TG and cholesterol levels, while increasing HDL in a dose-dependent manner (86). Similarly, Skrzypski *et al* (92) reported that adropin treatment in T2DM mice reduced liver mass, aspartate aminotransferase, alanine aminotransferase, serum γ-glutamyl transferase and alkaline phosphatase, cholesterol and hepatic triacylglycerol levels.

A study involving 116 patients with T2DM and 60 normal controls in China indicated that serum adropin levels were downregulated in patients with T2DM, particularly in overweight and obese individuals (93). Choi and Yim (94) suggested that plasma adropin could be a predictive marker for obesity and obesity-related cancer in Korean patients with T2DM. A 2023 meta-analysis on circulating adropin expression and diabetes also found reduced adropin levels in patients with diabetes compared with healthy individuals (95). These studies suggest that adropin is related to glucose and lipid homeostasis and insulin sensitivity and serves a role in diabetes pathogenesis. Additionally, Palizban *et al* (96) analyzed the rs7903146 allele frequency in 93 patients with T2DM and 53 healthy individuals, finding that patients with T2DM carrying rs7903146T/T and rs7903146C/T had higher adropin levels and had an increased risk of developing T2DM (96). Another study found that high-intensity interval training increased plasma adropin and nitrate/nitrite levels, improving blood pressure and flow-mediated dilation in patients with T2DM. Increased plasma adropin levels may lower blood pressure partly by enhancing NO production (97). Tičinović Kurir *et al* (98) reported that liraglutide treatment in obese male patients with T2DM significantly increased plasma adropin concentration, reduced weight and improved IR indicators. Similarly, sitagliptin treatment significantly enhanced serum adropin expression in patients with T2DM (99). These reports suggest that adropin concentration holds considerable promise as a biomarker for therapeutic improvement in patients with diabetes following drug treatment.

DKD. DKD is a common clinical complication of diabetes and the main cause of ESRD (100,101). To explore the correlation between serum adropin concentration and DKD, Hu and Chen (87) analyzed 245 individuals with T2DM and 81 healthy controls. The patients with T2DM were divided into three groups (normoalbuminuria, microalbuminuria and macroalbuminuria) based on the urinary albumin/creatinine ratio (ACR). The results demonstrated that the serum adropin concentration in patients with T2DM was significantly lower than that in the control group. Furthermore, patients with T2DM accompanied by microalbuminuria and macroalbuminuria exhibited lower serum adropin levels than those with normoalbuminuria. Serum adropin was positively correlated with glomerular filtration rate and negatively correlated with

BMI, blood urea nitrogen, creatinine and ACR. The study concluded that elevated serum adropin was associated with improved renal function and serum adropin was inversely associated with DKD development (87). Another study evaluated serum adropin levels in patients with T2DM with and without renal disease. This study included 135 participants (45 patients with DKD, 45 non-renal diabetic patients and 45 healthy controls), and adropin levels in fasting venous serum were measured. The results indicated that patients with DKD exhibited lower serum adropin levels compared with both the controls and non-renal diabetic patients (102). Additionally, serum adropin was negatively correlated with BMI, fasting blood glucose, glycated hemoglobin, blood urea, creatinine, LDL and ACR, and positively correlated with HDL and albumin. Therefore, serum adropin levels could serve as a biomarker for detecting DKD (102). A recent study showed that adropin can improve renal lipotoxicity in mice with DKD. The primary mechanism involves adropin treatment inhibiting ROS production and protecting mitochondria from damage. Adropin also reduces ADRP and SREBP-1 lipogenic protein expression in DKD mice, thereby improving lipid deposition in renal tissue (8). However, further research is needed to elucidate the precise mechanisms.

Diabetic cardiomyopathy. Adropin has been shown to regulate the expression of GCN5L1, altering the acetylation activity and status of enzymes involved in fuel metabolism, thereby facilitating glucose utilization (91). Under high-fat conditions, adropin exposure increases myocardial glucose oxidation (91), potentially opening novel avenues for treating diabetic cardiomyopathy in the future. Another study demonstrated that adropin treatment reduced the perivascular collagen area, collagen volume fraction and the relative protein expression levels of dynamin-related protein 1, collagen I and collagen III in diabetic cardiomyopathy rats (103). Additionally, cardiac diastolic function and the expression of Mitofusin-1 and Mitofusin-2 were upregulated in the adropin-treated group (103). Currently, no clinical studies have reported on the relationship between adropin and diabetic cardiomyopathy.

DR. To investigate the correlation between serum and vitreous adropin concentrations and the presence of DR, Li *et al* (104) conducted a study involving 165 patients with T2DM (52 without DR, 69 with non-proliferative DR and 44 with proliferative DR). The control group included 68 healthy participants who had undergone vitrectomy for retinal detachment. The results showed that control participants had significantly higher serum and vitreous adropin concentrations compared with patients with diabetes. Patients with proliferative DR exhibited significantly lower serum and vitreous adropin concentrations compared with patients with non-proliferative DR and those with T2DM without DR. Additionally, patients with non-proliferative DR exhibited lower serum and vitreous adropin concentrations compared with patients with T2DM without DR. Logistic regression analysis revealed that serum and vitreous adropin were associated with a decreased risk of T2DM and DR, leading to the conclusion that serum and vitreous adropin concentrations are inversely related to the presence of DR (104).

In a subsequent study, Li *et al* (88) measured the concentrations of plasma cytokines (adropin, copeptin, neprilysin and chitotriosidase) in 392 patients with TD2M (with or without retinopathy) and 120 healthy volunteers to predict the risk of DR in patients with diabetes. It was found that the patients with concurrent diabetes and retinopathy had reduced levels of adropin and increased levels of copeptin, neprilysin and chitotriosidase compared with both the normal controls and patients with diabetes without retinopathy (88). However, further *in vivo* and *in vitro* studies are needed to explore the underlying mechanisms.

Atherosclerosis. Low levels of adropin are closely associated with the occurrence of coronary atherosclerosis (105,106). In the pathophysiology of atherosclerosis, adropin impacts three critical vascular cells: VSMCs, macrophages and endothelial cells. Adropin treatment may reduce atherosclerotic lesion development, irrespective of metabolic abnormalities or blood pressure (107). Lovren *et al* (9) demonstrated that adropin protects endothelial cells by activating the ERK1/2 and PI3K/AKT pathways via VEGFR2, enhancing the expression of eNOS, increasing NO release and improving endothelial cell function (9,108). Adropin consistently promotes capillary formation, proliferation, migration and vascular permeability and reduces TNF-α-induced apoptosis in endothelial cells (9). Additionally, adropin treatment has been shown to reduce endothelial cell permeability by inhibiting the Rock/myosin light chain 2 pathway (107). In ApoE$^{-/-}$ mice, adropin treatment reduced the development of atherosclerotic lesions by regulating plaque stability and vascular elasticity. This was achieved by suppressing VSMC proliferation by downregulating the c-Src/ERK1/2 pathway and upregulating the PI3K/AKT pathway, thereby increasing fibronectin and elastin expression in VSMCs (109). Furthermore, adropin enhances the anti-inflammatory activity of endothelial cells by increasing the expression of PPAR-γ, decreasing monocyte-endothelial cell adhesion and promoting monocyte differentiation into anti-inflammatory phenotypes, thus reducing the inflammatory development of atherosclerosis (109). Li and Xie (110) found that histone deacetylases 11-atherosclerosis (HDAC11-AS1) improved blood lipid levels and atherosclerosis in ApoE$^{-/-}$ mice on an HFD by negatively regulating HDAC11. This mechanism involves HDAC11-AS1 enhancing LPL expression through adropin histone deacetylation. A recent study has also indicated that adropin restrains the differentiation of VSMCs into osteogenic cells and reduces vascular calcification via the JAK2/STAT3 pathway (10). Moreover, adropin treatment may alleviate atherosclerosis in ApoE$^{-/-}$/ENHO$^{-/-}$ mice by inhibiting endothelial-to-mesenchymal transition through the TGF-β/Smad2/3 signaling pathway (111).

Human studies have also linked decreased serum adropin levels to coronary atherosclerosis (35). Elevated adropin levels in overweight participants after high-intensity interval training may indicate improved endothelial function by enhancing NO-related signaling pathways (112). Wei *et al* (34) examined 503 patients with T2DM and found that increased serum adropin levels were correlated with a decreased risk of carotid atherosclerosis. Low circulating adropin levels may thus promote carotid atherosclerosis (34). These outcomes suggest that adropin could be a novel target for treating atherosclerosis.

MS. MS is a chronic autoimmune disease characterized by progressive neuronal loss, demyelination and central

nervous system inflammation (113,114). Clinical studies have consistently shown significantly diminished adropin levels in patients with MS compared with control groups (115,116). However, the molecular mechanisms linking MS and adropin remain unclear. A study by Demirdöğen *et al* (117) recruited 80 participants (40 patients with MS and 40 healthy volunteers) to investigate the serum adropin levels in patients with MS and their correlation with hypothalamic atrophy. The study found that patients with MS exhibited significantly reduced adropin levels compared with healthy controls, although no significant correlation was observed between serum adropin levels and pituitary diameter or third ventricular diameter. While adropin shows high potential as a diagnostic marker for MS, comprehensive validation studies are needed (117). A 2024 report highlighted the critical role of adropin in remodeling fibrotic tissue in systemic sclerosis. Consistent downregulation of adropin was observed in the skin of patients with systemic sclerosis (36). *In vivo* and *in vitro* experiments demonstrated that the profibrotic cytokine, TGF-β, suppressed adropin expression via a JNK-dependent pathway. Adropin treatment restored adropin signaling, inhibiting TGF-β-induced activation of fibroblasts and primary human dermal fibroblasts, thereby reducing fibrotic tissue remodeling (36). Notably, knocking down the adropin receptor, GPR19, abolished the anti-fibrotic effects of adropin in fibroblasts. These insights suggest that TGF-β-induced downregulation of adropin expression may be a potential pathological mechanism in systemic sclerosis (36).

Cancer. Research has demonstrated the involvement of adropin in the biological effects of cancer cells. The pathological processes involved are not only related to carbohydrate and sterol metabolism but also the regulation of intercellular pathways. A previous clinical study including 74 patients (47 patients with endometrial cancer and 27 healthy participants) demonstrated that patients with endometrial cancer had significantly reduced serum adropin levels compared with the control patients (38). However, the specific pathological mechanism remains unclear.

It is reported that adropin could promote MCF-7 cells to enter the early apoptosis stage and have a protective effect on breast cancer (37). Another study showed that adropin-mediated GPR19 activation could promote mesenchymal-epithelial transition through the MAPK/ERK1/2 pathway, thereby promoting the proliferation and metastasis of breast tumor cells (118). However, more research is needed to explore the mechanism of action in breast cancer.

Stelcer *et al* (119) found that adropin can activate TGF-β signaling and reduce the expression levels of steroidogenic genes (such as steroidogenesis, the steroidogenic acute regulatory and cholesterol side-chain cleavage enzyme and cytochrome P450scc) in human adrenal cancer (HAC15) cells, thereby inhibiting cortisol and aldosterone biosynthesis and secretion. In addition, the proliferation of adropin-treated HAC15 cells was significantly enhanced compared with untreated cells. The specific mechanism involves the regulation of adropin via the ERK1/2 and AKT-dependent signaling pathways. It was also found that GPR19 expression was increased in adrenocortical carcinoma compared with normal adrenal glands (119).

It has also been demonstrated that adropin expression is likewise diminished in advanced colorectal cancer (CRC) tumor nest cells (120). The expression of adropin by cancer cells is negatively related to the infiltration of macrophages into the CRC tissue matrix. Nonetheless, promoting adropin expression in tumor macrophages can enhance tumor invasion and metastasis (120). An investigation into the effects of adropin treatment on macrophages revealed that low-dose adropin promoted glucose utilization, while high-dose adropin increased carnitine palmitoyltransferase 1α expression in macrophages. As a result, it was hypothesized that fluctuations in adropin levels within malignant cells or macrophages within tumor tissues contributed to the progression of CRC to varying degrees. Therefore, tumor progression in various stages of CRC can be slowed by elevating or lowering adropin levels (120).

In a recent study in 2023 it was found that adropin expression was increased in pancreatic ductal adenocarcinoma (PDA) tissue compared with adjacent tissue (121). The proliferative and migratory capabilities of PDA cells are significantly enhanced by adropin, which also increases the expression of cyclin D1, Ki67, p-VEGFR2 and MMP-2. However, these effects were significantly reversed after knocking down adropin expression or blocking VEGFR2. In addition, in PDA, adropin upregulation enhances angiogenesis and cancer cell proliferation in the tumor microenvironment through persistent activation of the VEGFR2 signaling pathway, thus establishing an environment conducive to tumor progression (121). These findings suggest that PDA could potentially be effectively treated by targeting adropin.

It is well known that the functional expression of genes is affected by the microenvironment. In different cancer types, adropin is affected by different molecules and pathways or acts on different downstream molecules to play anticancer or cancer-promoting effects. Since there are few relevant research reports, the specific mechanism cannot be elucidated. More research should be conducted in the future to explore more potential functions of adropin.

5. Conclusions and future prospectives

Adropin, a key peptide hormone, is integral to maintaining energy homeostasis and regulating glucose and fatty acid metabolism. There is a strong association between low adropin levels and IR that is independent of obesity (122). Conversely, upregulation or exogenous administration of adropin can improve glucose homeostasis (11). In HFD-induced obese mice, adropin reduces obesity and enhances blood lipid and glucose homeostasis (6). Additionally, adropin promotes cardiac glucose oxidation and inhibits cardiac fatty acid oxidation, thereby improving cardiac energy metabolism and efficiency (40). Adropin also influences lipid metabolism by regulating the expression of genes associated with liver disease and the PPARα receptor, a key regulator of lipogenesis (123). Moreover, adropin interacts with the NB-3/Notch signaling pathway to regulate physical activity and movement coordination (16). Adropin enhances spatial memory in rats by modulating the AKT/cyclic AMP response element-binding protein/brain-derived neurotrophic factor signaling pathway (124). These studies over the past decade indicate

that adropin is involved in both metabolic and non-metabolic regulation in various diseases. Adropin-based therapies may emerge as novel treatments for diseases related to glucose and lipid metabolism.

Adropin, a novel regulatory peptide, presents numerous challenges for preclinical research. First, its pharmacokinetics in circulation remain largely unknown, as protein degradation may limit the efficacy of peptide hormone administration. Numerous questions about adropin physiology necessitate further investigation. For instance, the origin of circulating adropin and whether liver-produced adropin regulates other tissues require elucidation in both animal models and patients. Second, adropin expression is influenced by fat and various molecules, yet the specific regulatory mechanisms remain unclear. Additionally, lifestyle, diet, weight and body composition across different races and nationalities may affect adropin levels. Third, current animal studies suggest the involvement of adropin in glucose oxidation, lipid metabolism, metabolic diseases, endothelial function and cardiovascular diseases. However, research on the function of adropin is still preliminary, with most studies focusing on mRNA-level gene expression. Notable questions persist, such as the association between reduced plasma adropin levels and disease progression, contrasted with high levels observed in kidney transplant candidates. Changes in adropin levels also appear to influence CRC progression, though the mechanisms remain undefined. Given the identical amino acid sequences in humans and mice, animal study conclusions are likely applicable to humans. A comprehensive understanding of the function of adropin could lead to its therapeutic use in various metabolic disorders, warranting continued exploration. Fourth, mounting evidence links adropin to inflammatory diseases, where it not only promotes the secretion of inflammatory cytokines but also indirectly regulates immune cell phenotypes and behaviors. Additionally, animal studies suggest a connection between adropin and the circadian clock, although this area requires further research to clarify its potential impacts.

Several issues warrant attention in the clinical research of adropin. First, most published clinical studies on adropin are limited to observational studies that demonstrate correlations between plasma adropin levels and diet, various diseases and metabolic parameters (such as obesity and coronary heart disease risk). The growing body of evidence from preclinical studies may inspire future clinical trials to explore the potential benefits of adropin or its analogs in treating obesity, diabetes, fatty liver disease and diabetic cardiovascular disease. Second, reduced plasma levels of adropin appear to be associated with various pathologies and often correlate with accelerated disease progression. A number of researchers suggest that adropin could serve as a serum marker for diseases such as diabetes, atherosclerosis and AMI. However, each new biomarker must be thoroughly evaluated for its clinical relevance such as determining the appropriate patient groups, optimal measurement time points and whether the biomarker provides additional information beyond the existing ones. Thus, to establish adropin as a disease biomarker in various pathologies, prospective large-scale studies in well-defined populations are necessary. In conclusion, while future research on adropin faces numerous challenges, exploring its potential functions and those of its analogs remains highly valuable for the treatment of obesity, diabetes, cardiovascular diseases and more.

Acknowledgements

Not applicable.

Funding

This work was supported by grants from Pudong New Area Traditional Chinese Medicine Brand Multiplication Plan-Chronic Nephropathy (grant no. PDZY-2021-0302), Construction of He Liqun's famous TCM studio (grant no. PDZY-2022-0703), Clinical Observation on the Efficacy of Guben Tongluo Formula in Treating Chronic Kidney Disease Phase 1-3 (grant no. PW2022D-12) and Pilot Project of Inheritance, Innovation and Development of Traditional Chinese Medicine in Pudong New Area (grant no. YC-2023-0602).

Availability of data and materials

Not applicable.

Authors' contributions

LC contributed to acquisition, analysis, interpretation and drafted the manuscript. JL participated in revising the manuscript. JH and XG contributed to conception and design and critically revised the manuscript. All authors read and approve the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Kumar KG, Trevaskis JL, Lam DD, Sutton GM, Koza RA, Chouljenko VN, Kousoulas KG, Rogers PM, Kesterson RA, Thearle M, *et al*: Identification of adropin as a secreted factor linking dietary macronutrient intake with energy homeostasis and lipid metabolism. Cell Metab 8: 468-481, 2008.
2. Marczuk N, Cecerska-Heryć E, Jesionowska A and Dołęgowska B: Adropin-physiological and pathophysiological role. Postepy Hig Med Dosw (Online) 70: 981-988, 2016.
3. Aydin S, Kuloglu T, Aydin S, Eren MN, Yilmaz M, Kalayci M, Sahin I, Kocaman N, Citil C and Kendir Y: Expression of adropin in rat brain, cerebellum, kidneys, heart, liver, and pancreas in streptozotocin-induced diabetes. Mol Cell Biochem 380: 73-81, 2013.
4. Chen X, Chen S, Shen T, Yang W, Chen Q, Zhang P, You Y, Sun X, Xu H, Tang Y, *et al*: Adropin regulates hepatic glucose production via PP2A/AMPK pathway in insulin-resistant hepatocytes. FASEB J 34: 10056-10072, 2020.

5. Erman H, Ozdemir A, Sitar ME, Cetin SI and Boyuk B: Role of serum adropin measurement in the assessment of insulin resistance in obesity. J Investig Med 69: 1318-1323, 2021.
6. Akcılar R, Emel Koçak F, Şimşek H, Akcılar A, Bayat Z, Ece E and Kökdaşgil H: The effect of adropin on lipid and glucose metabolism in rats with hyperlipidemia. Iran J Basic Med Sci 19: 245-251, 2016.
7. Gao S, McMillan RP, Zhu Q, Lopaschuk GD, Hulver MW and Butler AA: Therapeutic effects of adropin on glucose tolerance and substrate utilization in diet-induced obese mice with insulin resistance. Mol Metab 4: 310-324, 2015.
8. Yu M, Wang D, Zhong D, Xie W and Luo J: adropin carried by reactive oxygen species-responsive nanocapsules ameliorates renal lipid toxicity in diabetic mice. ACS Appl Mater Interfaces 14: 37330-37344, 2022.
9. Lovren F, Pan Y, Quan A, Singh KK, Shukla PC, Gupta M, Al-Omran M, Teoh H and Verma S: Adropin is a novel regulator of endothelial function. Circulation 122 (11 Suppl): S185-S192, 2010.
10. Wang L, Jin F, Wang P, Hou S, Jin T, Chang X and Zhao L: Adropin inhibits vascular smooth muscle cell osteogenic differentiation to alleviate vascular calcification via the JAK2/STAT3 signaling pathway. Biomed Res Int 2022: 9122264, 2022.
11. Ali II, D'Souza C, Singh J and Adeghate E: Adropin's role in energy homeostasis and metabolic disorders. Int J Mol Sci 23: 8318, 2022.
12. Jasaszwili M, Billert M, Strowski MZ, Nowak KW and Skrzypski M: Adropin as A Fat-Burning hormone with multiple functions-review of a decade of research. Molecules 25: 549, 2020.
13. Li L, Xie W, Zheng XL, Yin WD and Tang CK: A novel peptide adropin in cardiovascular diseases. Clin Chim Acta 453: 107-113, 2016.
14. Niepolski L and Grzegorzewska AE: Salusins and adropin: New peptides potentially involved in lipid metabolism and atherosclerosis. Adv Med Sci 61: 282-287, 2016.
15. Petersen TN, Brunak S, von Heijne G and Nielsen H: SignalP 4.0: discriminating signal peptides from transmembrane regions. Nat Methods 8: 785-786, 2011.
16. Wong CM, Wang Y, Lee JT, Huang Z, Wu D, Xu A and Lam KS: Adropin is a brain membrane-bound protein regulating physical activity via the NB-3/Notch signaling pathway in mice. J Biol Chem 289: 25976-25986, 2014.
17. Zhang C, Yan Y, Zhang Q and Jiang Q: Molecular cloning and characterization of the novel adropin from tilapia (Oreochromis niloticus): Involvement in the control of food intake. Neuropeptides 88: 102165, 2021.
18. Ganesh Kumar K, Zhang J, Gao S, Rossi J, McGuinness OP, Halem HH, Culler MD, Mynatt RL and Butler AA: Adropin deficiency is associated with increased adiposity and insulin resistance. Obesity (Silver Spring) 20: 1394-1402, 2012.
19. Bindesbøll C, Fan Q, Nørgaard RC, MacPherson L, Ruan HB, Wu J, Pedersen TA, Steffensen KR, Yang X, Matthews J, *et al*: Liver X receptor regulates hepatic nuclear O-GlcNAc signaling and carbohydrate responsive element-binding protein activity. J Lipid Res 56: 771-785, 2015.
20. Stayrook KR, Rogers PM, Savkur RS, Wang Y, Su C, Varga G, Bu X, Wei T, Nagpal S, Liu XS and Burris TP: Regulation of human 3 alpha-hydroxysteroid dehydrogenase (AKR1C4) expression by the liver X receptor alpha. Mol Pharmacol 73: 607-612, 2008.
21. Ghoshal S, Stevens JR, Billon C, Girardet C, Sitaula S, Leon AS, Rao DC, Skinner JS, Rankinen T, Bouchard C, *et al*: Adropin: An endocrine link between the biological clock and cholesterol homeostasis. Mol Metab 8: 51-64, 2018.
22. Meda C, Dolce A, Vegeto E, Maggi A and Della Torre S: ERα-Dependent regulation of adropin predicts sex differences in liver homeostasis during high-fat diet. Nutrients 14: 3262, 2022.
23. Stokar J, Gurt I, Cohen-Kfir E, Yakubovsky O, Hallak N, Benyamini H, Lishinsky N, Offir N, Tam J and Dresner-Pollak R: Hepatic adropin is regulated by estrogen and contributes to adverse metabolic phenotypes in ovariectomized mice. Mol Metab 60: 101482, 2022.
24. Kuo FY, Cheng KC, Li Y, Cheng JT and Tsai CC: Promotion of adropin expression by hyperglycemia is associated with STAT3 activation in diabetic rats. Diabetes Metab Syndr Obes 13: 2269-2277, 2020.
25. Li YX, Cheng KC, Liu IM and Niu HS: Myricetin Increases circulating adropin level after activation of glucagon-like peptide 1 (GLP-1) receptor in type-1 diabetic rats. Pharmaceuticals (Basel) 15: 173, 2022.
26. Thapa D, Xie B, Manning JR, Zhang M, Stoner MW, Huckestein BR, Edmunds LR, Zhang X, Dedousis NL, O'Doherty RM, *et al*: Adropin reduces blood glucose levels in mice by limiting hepatic glucose production. Physiol Rep 7: e14043, 2019.
27. Jasaszwili M, Pruszyńska-Oszmałek E, Wojciechowicz T, Strowski MZ, Nowak KW and Skrzypski M: Adropin slightly modulates lipolysis, lipogenesis and expression of adipokines but not glucose uptake in rodent adipocytes. Genes (Basel) 12: 914, 2021.
28. Yu HY, Zhao P, Wu MC, Liu J and Yin W: Serum adropin levels are decreased in patients with acute myocardial infarction. Regul Pept 190-191: 46-49, 2014.
29. Ding F, Liu G, Gao F, Zheng Z, Hong Y, Chen Y and Weng S: Adropin attenuates pancreatitis-associated lung injury through PPARγ phosphorylation-related macrophage polarization. Int J Mol Med 52: 95, 2023.
30. Kutlu O, Altun Ö, Dikker O, Aktaş Ş, Özsoy N, Arman Y, Özgün Çil E, Özcan M, Aydın Yoldemir Ş, Akarsu M, *et al*: Serum adropin levels are reduced in adult patients with nonalcoholic fatty liver disease. Med Princ Pract 28: 463-469, 2019.
31. Berezina TA, Obradovic Z, Boxhammer E, Berezin AA, Lichtenauer M and Berezin AE: Adropin predicts chronic kidney disease in type 2 diabetes mellitus patients with chronic heart failure. J Clin Med 12: 2231, 2023.
32. Kuliczkowska-Płaksej J, Mierzwicka A, Jończyk M, Stachowska B, Urbanovych A and Bolanowski M: Adropin in women with polycystic ovary syndrome. Endokrynol Pol 70: 151-156, 2019.
33. Herrero L, de Dios O, Gavela-Pérez T, Riestra P, Jois A, Soriano-Guillén L and Garcés C: Opposite association of adropin concentrations with obesity in prepubertal children compared with adolescents. Obesity (Silver Spring) 28: 1736-1741, 2020.
34. Wei W, Liu H, Qiu X, Zhang J, Huang J, Chen H, Qiu S, Lin R, Li S and Tu M: The association between serum adropin and carotid atherosclerosis in patients with type 2 diabetes mellitus: A cross-sectional study. Diabetol Metab Syndr 14: 27, 2022.
35. Zhao LP, You T, Chan SP, Chen JC and Xu WT: Adropin is associated with hyperhomocysteine and coronary atherosclerosis. Exp Ther Med 11: 1065-1070, 2016.
36. Liang M, Dickel N, Györfi AH, SafakTümerdem B, Li YN, Rigau AR, Liang C, Hong X, Shen L, Matei AE, *et al*: Attenuation of fibroblast activation and fibrosis by adropin in systemic sclerosis. Sci Transl Med 16: eadd6570, 2024.
37. Tuna BG, Atalay PB, Altunbek M, Kalkan BM and Dogan S: Effects of chronic and intermittent calorie restriction on adropin levels in breast cancer. Nutr Cancer 69: 1003-1010, 2017.
38. Nergiz S, Altinkaya SO, Kurt Ömürlü İ, Yuksel H, Küçük M and Demircan Sezer S: Circulating adropin levels in patients with endometrium cancer. Gynecol Endocrinol 31: 730-735, 2015.
39. Reed GW, Rossi JE and Cannon CP: Acute myocardial infarction. Lancet 389: 197-210, 2017.
40. Altamimi TR, Gao S, Karwi QG, Fukushima A, Rawat S, Wagg CS, Zhang L and Lopaschuk GD: Adropin regulates cardiac energy metabolism and improves cardiac function and efficiency. Metabolism 98: 37-48, 2019.
41. Aydin S, Kuloglu T, Aydin S, Kalayci M, Yilmaz M, Çakmak T and Eren MN: Elevated adropin: A candidate diagnostic marker for myocardial infarction in conjunction with troponin-I. Peptides 58: 91-97, 2014.
42. Li B, Wang Z, He Y, Chen T, Zhang Y, Yuan X and Li P: Adropin improves radiation-induced myocardial injury via VEGFR2/PI3K/Akt pathway. Oxid Med Cell Longev 2022: 8230214, 2022.
43. Adıyaman M, Canpolat Erkan RE, Kaya İ and Aba Adıyaman Ö: Serum adropin level in the early period of ST-Elevation myocardial infarction and its relationship with cobalamin and folic acid. Cureus 14: e32748, 2022.
44. Chang X, Jin F, Wang L, Jiang Y, Wang P, Liu J and Zhao L: Adropin-A new player in energy regulation predicts long-term prognosis of patients with acute myocardial infarction. Heliyon 9: e17803, 2023.
45. Foucher P, Heeringa P, Petersen AH, Huitema MG, Brouwer E, Tervaert JW, Prop J, Camus P, Weening JJ and Kallenberg CG: Antimyeloperoxidase-associated lung disease. An experimental model. Am J Respir Crit Care Med 160: 987-994, 1999.
46. Saeki T, Fujita N, Kourakata H, Yamazaki H and Miyamura S: Two cases of hypertrophic pachymeningitis associated with myeloperoxidase antineutrophil cytoplasmic autoantibody (MPO-ANCA)-positive pulmonary silicosis in tunnel workers. Clin Rheumatol 23: 76-80, 2004.

47. Gao F, Fang J, Chen F, Wang C, Chen S, Zhang S, Lv X, Zhang J, He Q, Weng S, *et al*: Enho mutations causing low adropin: A possible pathomechanism of MPO-ANCA Associated lung injury. EBioMedicine 9: 324-335, 2016.
48. Rizk FH, El-Saka MH, Ibrahim RR, El-Deeb OS, Ibrahim HA, El Saadany AA, Mashal SS, Ammar L, Abdelsattar AM and Barhoma RA: Possible mitigating effect of adropin on lung injury in diabetic rats: Targeting the role of Rho A/Rho-associated kinase pathway. Biofactors 49: 928-939, 2023.
49. Orun S, Celikkol A, Basol BI and Yeniay E: Diagnostic accuracy of adropin as a preliminary test to exclude acute pulmonary embolism: a prospective study. BMC Pulm Med 22: 351, 2022.
50. Byrne CD and Targher G: NAFLD: A multisystem disease. J Hepatol 62 (1 Suppl): S47-S64, 2015.
51. Younossi Z, Tacke F, Arrese M, Chander Sharma B, Mostafa I, Bugianesi E, Wai-Sun Wong V, Yilmaz Y, George J, Fan J and Vos MB: Global perspectives on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Hepatology 69: 2672-2682, 2019.
52. Zhang C, Zhang Q, Huang Z and Jiang Q: Adropin inhibited tilapia hepatic glucose output and triglyceride accumulation via AMPK activation. J Endocrinol 246: 109-122, 2020.
53. Chen X, Sun X, Shen T, Chen Q, Chen S, Pang J, Mi J, Tang Y, You Y, Xu H and Ling W: Lower adropin expression is associated with oxidative stress and severity of nonalcoholic fatty liver disease. Free Radic Biol Med 160: 191-198, 2020.
54. Yang W, Liu L, Wei Y, Fang C, Liu S, Zhou F, Li Y, Zhao G, Guo Z, Luo Y and Li L: Exercise suppresses NLRP3 inflammasome activation in mice with diet-induced NASH: A plausible role of adropin. Lab Invest 101: 369-380, 2021.
55. Li N, Xie G, Zhou B, Qu A, Meng H, Liu J and Wang G: Serum adropin as a potential biomarker for predicting the development of type 2 diabetes mellitus in individuals with metabolic dysfunction-associated fatty liver disease. Front Physiol 12: 696163, 2021.
56. Zhang L, Wu X, Li X, Chang X, Ding X, Wang Q, Jiang T, Wang G and Liu J: Longitudinal changes in serum adropin levels and liver fat content during liraglutide treatment in newly diagnosed patients with type 2 diabetes mellitus and metabolic dysfunction-associated fatty liver disease. Acta Diabetol 60: 971-979, 2023.
57. Zhu T, Du Y, Xuan M, Guo C and Rao X: Clinical characteristics and Chinese Medicine therapy of chronic kidney disease combined with cardiovascular disease. Integr Med Nephrol Androl 10: e00023, 2023.
58. Song Z and Gong X: research progress on the potential mechanisms of acute kidney injury and chronic kidney disease induced by proton pump inhibitors. Integr Med Nephrol Androl 10: e00027, 2023.
59. Tao P, Huo J and Chen L: Bibliometric analysis of the relationship between gut microbiota and chronic kidney disease from 2001-2022. Integr Med Nephrol Androl 11: e00017, 2024.
60. Zhang HQ, Wu S, Chen X, Fang YX, Lan QM, Zhou ZJ, Qiao YH, Li J, Zhao YR, Pei M and Yang B: Potential efficacy and mechanism of medicinal plants on chronic kidney disease-associated vascular calcification: A review. Tradit Med Res 9: 51, 2024.
61. Memi G and Yazgan B: Adropin and spexin hormones regulate the systemic inflammation in adenine-induced chronic kidney failure in rat. Chin J Physiol 64: 194-201, 2021.
62. Grzegorzewska AE, Niepolski L, Mostowska A, Warchoł W and Jagodziński PP: Involvement of adropin and adropin-associated genes in metabolic abnormalities of hemodialysis patients. Life Sci 160: 41-46, 2016.
63. Kałużna M, Hoppe K, Schwermer K, Ibrahim AY, Pawlaczyk K and Ziemnicka K: Adropin and irisin levels in relation to nutrition, body composition, and insulin resistance in patients with end-stage renal disease on chronic hemodialysis and peritoneal dialysis. Pol Arch Med Wewn 126: 474-482, 2016.
64. Kałużna M, Pawlaczyk K, Schwermer K, Hoppe K, Człapka-Matyasik M, Ibrahim AY, Sawicka-Gutaj N, Minczykowski A, Ziemnicka K, Oko A and Ruchała M: Adropin and irisin: New biomarkers of cardiac status in patients with end-stage renal disease? A preliminary study. Adv Clin Exp Med 28: 347-353, 2019.
65. Cecerska-Heryć E, Adamiak D, Serwin N, Grygorcewicz B and Dołęgowska B: Comparative analysis of adropin concentration changes in response to kidney transplantation. Eur J Intern Med 84: 112-114, 2021.
66. Maciorkowska M, Musiałowska D and Małyszko J: Adropin and irisin in arterial hypertension, diabetes mellitus and chronic kidney disease. Adv Clin Exp Med 28: 1571-1575, 2019.
67. Kaur R, Krishan P, Kumari P, Singh T, Singh V, Singh R and Ahmad SF: Clinical significance of adropin and afamin in evaluating renal function and cardiovascular health in the presence of CKD-MBD biomarkers in chronic kidney disease. Diagnostics (Basel) 13: 3158, 2023.
68. Liu F, Cui B, Zhao X, Wu Y, Qin H, Guo Y, Wang H, Lu M, Zhang S, Shen J, *et al*: Correlation of serum adropin levels with risk factors of cardiovascular disease in hemodialysis patients. Metab Syndr Relat Disord 19: 401-408, 2021.
69. Boric-Skaro D, Mizdrak M, Luketin M, Martinovic D, Tokic D, Vilovic M, Supe-Domic D, Kurir TT and Bozic J: Serum adropin levels in patients on hemodialysis. Life (Basel) 11: 337, 2021.
70. Kume T, Calan M, Yilmaz O, Kocabas GU, Yesil P, Temur M, Bicer M and Calan OG: A possible connection between tumor necrosis factor alpha and adropin levels in polycystic ovary syndrome. J Endocrinol Invest 39: 747-754, 2016.
71. Bousmpoula A, Kouskouni E, Benidis E, Demeridou S, Kapeta-Kourkouli R, Chasiakou A and Baka S: Adropin levels in women with polycystic ovaries undergoing ovarian stimulation: Correlation with lipoprotein lipid profiles. Gynecol Endocrinol 34: 153-156, 2018.
72. Inal ZO, Erdem S, Gederet Y, Duran C, Kucukaydin Z, Kurku H and Sakarya DK: The impact of serum adropin and ischemia modified albumin levels based on BMI in PCOS. Endokrynol Pol 69: 135-141, 2018.
73. Ye Z, Zhang C and Zhao Y: Potential effects of adropin on systemic metabolic and hormonal abnormalities in polycystic ovary syndrome. Reprod Biomed Online 42: 1007-1014, 2021.
74. Varikasuvu SR, Reddy EP, Thangappazham B, Varshney S, Das VL and Munikumar M: Adropin levels and its associations as a fat-burning hormone in patients with polycystic ovary syndrome: A correlational meta-analysis. Gynecol Endocrinol 37: 879-884, 2021.
75. Ke Y, Hu J, Zhu Y, Wang Y, Chen S and Liu S: Correlation between circulating adropin levels and patients with PCOS: An updated systematic review and meta-analysis. Reprod Sci 29: 3295-3310, 2022.
76. Engin A: The definition and prevalence of obesity and metabolic syndrome. Adv Exp Med Biol 960: 1-17, 2017.
77. Gao S, Ghoshal S, Zhang L, Stevens JR, McCommis KS, Finck BN, Lopaschuk GD and Butler AA: The peptide hormone adropin regulates signal transduction pathways controlling hepatic glucose metabolism in a mouse model of diet-induced obesity. J Biol Chem 294: 13366-13377, 2019.
78. Dye L, Boyle NB, Champ C and Lawton C: The relationship between obesity and cognitive health and decline. Proc Nutr Soc 76: 443-454, 2017.
79. Miller AA and Spencer SJ: Obesity and neuroinflammation: A pathway to cognitive impairment. Brain Behav Immun 42: 10-21, 2014.
80. Ghoshal S, Banerjee S, Zhang J, Niehoff ML, Farr SA and Butler AA: Adropin transgenesis improves recognition memory in diet-induced obese LDLR-deficient C57BL/6J mice. Peptides 146: 170678, 2021.
81. Altincik A and Sayin O: Evaluation of the relationship between serum adropin levels and blood pressure in obese children. J Pediatr Endocrinol Metab 28: 1095-1100, 2015.
82. Chen RM, Yuan X, Ouyang Q, Lin XQ, Ai ZZ, Zhang Y and Yang XH: Adropin and glucagon-like peptide-2 are associated with glucose metabolism in obese children. World J Pediatr 15: 565-571, 2019.
83. Yuan X, Chen R, Ouyang Q, Lin X, Ai Z, Zhang Y and Yang X: Novel associations of serum adropin and lipopolysaccharide-binding protein versus lipid profiles in childhood obesity. J Pediatr Endocrinol Metab 33: 265-270, 2020.
84. Yin C, Zhang H, Zhang M and Xiao Y: Adropin and apelin-12 efficiently predict metabolic syndrome in obese children. Pediatr Diabetes 21: 1132-1139, 2020.
85. Soltani S, Kolahdouz-Mohammadi R, Aydin S, Yosaee S, Clark CCT and Abdollahi S: Circulating levels of adropin and overweight/obesity: A systematic review and meta-analysis of observational studies. Hormones (Athens) 21: 15-22, 2022.
86. He L, Zhang FJ, Li HY, Li L, Song LG, Mao Y, Li J, Liu HM, Li FL, Xu LY, *et al*: Anti-diabetic role of adropin in streptozotocin induced diabetic rats via alteration of PI3K/Akt and insulin signaling pathway. J Oleo Sci 70: 657-664, 2021.
87. Hu W and Chen L: Association of serum adropin concentrations with diabetic nephropathy. Mediators Inflamm 2016: 6038261, 2016.

88. Li B, Li N, Guo S, Zhang M, Li J, Zhai N, Wang H and Zhang Y: The changing features of serum adropin, copeptin, neprilysin and chitotriosidase which are associated with vascular endothelial function in type 2 diabetic retinopathy patients. J Diabetes Complications 34: 107686, 2020.
89. Jiang S, Young JL, Wang K, Qian Y and Cai L: Diabetic-induced alterations in hepatic glucose and lipid metabolism: The role of type 1 and type 2 diabetes mellitus (Review). Mol Med Rep 22: 603-611, 2020.
90. Jones JG: Hepatic glucose and lipid metabolism. Diabetologia 59: 1098-1103, 2016.
91. Thapa D, Xie B, Zhang M, Stoner MW, Manning JR, Huckestein BR, Edmunds LR, Mullett SJ, McTiernan CF, Wendell SG, *et al*: Adropin treatment restores cardiac glucose oxidation in pre-diabetic obese mice. J Mol Cell Cardiol 129: 174-178, 2019.
92. Skrzypski M, Kołodziejski PA, Pruszyńska-Oszmałek E, Wojciechowicz T, Janicka P, Krążek M, Małek E, Strowski MZ and Nowak KW: Daily treatment of mice with type 2 diabetes with adropin for four weeks improves glucolipid profile, reduces hepatic lipid content and restores elevated hepatic enzymes in serum. Int J Mol Sci 23: 9807, 2022.
93. Zang H, Jiang F, Cheng X, Xu H and Hu X: Serum adropin levels are decreased in Chinese type 2 diabetic patients and negatively correlated with body mass index. Endocr J 65: 685-691, 2018.
94. Choi HN and Yim JE: Plasma adropin as a potential marker predicting obesity and obesity-associated cancer in korean patients with type 2 diabetes mellitus. J Cancer Prev 23: 191-196, 2018.
95. Soltani S, Beigrezaei S, Malekahmadi M, Clark CCT and Abdollahi S: Circulating levels of adropin and diabetes: A systematic review and meta-analysis of observational studies. BMC Endocr Disord 23: 73, 2023.
96. Palizban AA, Yazdani AH and Jahanbani-Ardakani H: Role of rs7903146 polymorphism and adropin serum level in patients with diabetes mellitus; a case-control study from Isfahan, Iran. Arch Physiol Biochem 128: 378-381, 2022.
97. Davoodi M, Hesamabadi BK, Ariabood E, Izadi MR, Ghardashi-Afousi A, Bigi MAB, Asvadi-Fard M and Gaeini AA: Improved blood pressure and flow-mediated dilatation via increased plasma adropin and nitrate/nitrite induced by high-intensity interval training in patients with type 2 diabetes. Exp Physiol 107: 813-824, 2022.
98. Tičinović Kurir T, Miličević T, Novak A, Vilović M and Božić J: Adropin-potential link in cardiovascular protection for obese male type 2 diabetes mellitus patients treated with liraglutide. Acta Clin Croat 59: 344-350, 2020.
99. Wang Q, An Y, Zhang L, Zhang Y, Wang G and Liu J: Regulation of Adropin by Sitagliptin monotherapy in participants with newly diagnosed type 2 diabetes. BMC Endocr Disord 22: 306, 2022.
100. Wang X, Liu C, Jiang H, Chen BC, Yang X, Xiao M, Xie YQ and Li K: Network pharmacology and verification experiment-based prediction of active components and potential targets of Alpiniae Oxyphyllae Fructus-Saposhnikoviae Radix (Yizhiren-Fangfeng) for treatment of diabetic kidney disease. Tradit Med Res 8: 26, 2023.
101. Liu SM, Yan ZJ, Xiao M and Xie YQ: Mechanistic study of lipid metabolism disorders in diabetic kidney disease treated with GLQMP based on network pharmacology, molecular docking and in vitro experiments. Tradit Med Res 9: 11, 2024.
102. Es-Haghi A, Al-Abyadh T and Mehrad-Majd H: The clinical value of serum adropin level in early detection of diabetic nephropathy. kidney Blood Press Res 46: 734-740, 2021.
103. Liu M, Ai J, Shuai Z, Tang K, Li Z and Huang Y: Adropin alleviates myocardial fibrosis in diabetic cardiomyopathy rats: A preliminary study. Front Cardiovasc Med 8: 688586, 2021.
104. Li S, Sun J, Hu W, Liu Y, Lin D, Duan H and Liu F: The association of serum and vitreous adropin concentrations with diabetic retinopathy. Ann Clin Biochem 56: 253-258, 2019.
105. Yang C, DeMars KM and Candelario-Jalil E: Age-Dependent decrease in adropin is associated with reduced levels of endothelial nitric oxide synthase and increased oxidative stress in the rat brain. Aging Dis 9: 322-330, 2018.
106. Shahdadian F, Saneei P, Lotfi K, Feizi A, Askari G and Safavi SM: Association of plant-based diets with adropin, atherogenic index of plasma, and metabolic syndrome and its components: A cross-sectional study on adults. Front Nutr 10: 1077709, 2023.
107. Yang C, DeMars KM, Hawkins KE and Candelario-Jalil E: Adropin reduces paracellular permeability of rat brain endothelial cells exposed to ischemia-like conditions. Peptides 81: 29-37, 2016.
108. Jurrissen TJ, Ramirez-Perez FI, Cabral-Amador FJ, Soares RN, Pettit-Mee RJ, Betancourt-Cortes EE, McMillan NJ, Sharma N, Rocha HNM, Fujie S, *et al*: Role of adropin in arterial stiffening associated with obesity and type 2 diabetes. Am J Physiol Heart Circ Physiol 323: H879-H891, 2022.
109. Sato K, Yamashita T, Shirai R, Shibata K, Okano T, Yamaguchi M, Mori Y, Hirano T and Watanabe T: Adropin contributes to anti-atherosclerosis by suppressing monocyte-endothelial cell adhesion and smooth muscle cell proliferation. Int J Mol Sci 19: 1293, 2018.
110. Li L and Xie W: LncRNA HDAC11-AS1 suppresses atherosclerosis by inhibiting HDAC11-Mediated adropin histone deacetylation. J Cardiovasc Transl Res 15: 1256-1269, 2022.
111. Ying T, Wu L, Lan T, Wei Z, Hu D, Ke Y, Jiang Q and Fang J: Adropin inhibits the progression of atherosclerosis in ApoE(-/-)/Enho(-/-) mice by regulating endothelial-to-mesenchymal transition. Cell Death Discov 9: 402, 2023.
112. Abbasian S, Ravasi AA, Soori R, Aydin S, Choobineh S and Aydin S: High-intensity interval training ameliorates endothelial dysfunction through adropin, nitric oxide, MR-proADM, and copeptin changes in overweight subjects. Hormones (Athens) 21: 707-717, 2022.
113. Kamma E, Lasisi W, Libner C, Ng HS and Plemel JR: Central nervous system macrophages in progressive multiple sclerosis: Relationship to neurodegeneration and therapeutics. J Neuroinflammation 19: 45, 2022.
114. McGinley MP, Goldschmidt CH and Rae-Grant AD: Diagnosis and treatment of multiple sclerosis: A review. JAMA 325: 765-779, 2021.
115. Cinkir U, Bir LS, Topsakal S, Avci Cicek E and Tekin S: Investigation of blood leptin and adropin levels in patients with multiple sclerosis: A CONSORT-clinical study. Medicine (Baltimore) 100: e27247, 2021.
116. Algul S and Ozcelik O: Evaluating the energy regulatory hormones of nesfatin-1, irisin, adropin and preptin in multiple sclerosis. Mult Scler Relat Disord 68: 104221, 2022.
117. Demirdöğen F, Akdağ T, Gündüz ZB and Odabaş FO: Investigation of serum adropin levels and its relationship with hypothalamic atrophy in patients with multiple sclerosis. Mult Scler Relat Disord 67: 103999, 2022.
118. Rao A and Herr DR: G protein-coupled receptor GPR19 regulates E-cadherin expression and invasion of breast cancer cells. Biochim Biophys Acta Mol Cell Res 1864: 1318-1327, 2017.
119. Stelcer E, Milecka P, Komarowska H, Jopek K, Tyczewska M, Szyszka M, Lesniczak M, Suchorska W, Bekova K, Szczepaniak B, *et al*: Adropin stimulates proliferation and inhibits adrenocortical steroidogenesis in the human adrenal carcinoma (HAC15) cell line. Front Endocrinol (Lausanne) 11: 561370, 2020.
120. Jia L, Liao L, Jiang Y, Hu X, Lu G, Xiao W, Gong W and Jia X: Low-dose adropin stimulates inflammasome activation of macrophage via mitochondrial ROS involved in colorectal cancer progression. BMC Cancer 23: 1042, 2023.
121. Hu J, Wu Q, Ding Q, Wu W, Li Q and Zheng Z: High level of adropin promotes the progression of pancreatic ductal adenocarcinoma. Curr Cancer Drug Targets 24: 629-641, 2024.
122. Butler AA and Havel PJ: Adropin and insulin resistance: Integration of endocrine, circadian, and stress signals regulating glucose metabolism. Obesity (Silver Spring) 29: 1799-1801, 2021.
123. Smati S, Régnier M, Fougeray T, Polizzi A, Fougerat A, Lasserre F, Lukowicz C, Tramunt B, Guillaume M, Burnol AF, *et al*: Regulation of hepatokine gene expression in response to fasting and feeding: Influence of PPAR-α and insulin-dependent signalling in hepatocytes. Diabetes Metab 46: 129-136, 2020.
124. Ozkan A, Aslan MA, Sinen O, Munzuroglu M, Derin N, Parlak H, Bulbul M and Agar A: Effects of adropin on learning and memory in rats tested in the Morris water maze. Hippocampus 32: 253-263, 2022.

Copyright © 2024 Chen et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.