

Context-dependent duality of the apelin/elabela-APJ system in diabetes and its complications (Review)

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Abstract. The apelin/elabela-apelin receptor (APJ) signaling system is a key regulator of metabolic homeostasis and cardiovascular function in diabetes mellitus. However, its therapeutic application is complicated by its functional divergence: the system exerts protective effects in some tissues while driving pathology in others. The present review examined these distinct roles, focusing on how the biological outcome depends on the specific ligand, disease stage and tissue microenvironment. It discussed the molecular mechanisms underlying this divergence, as well as the varying roles of the same receptor at different stages of the same disease. Finally, it evaluated emerging therapeutic strategies, such as stabilized analogs and biased agonists, proposing that precise targeting of the APJ

conformational landscape offers a pathway to move beyond glycemic control toward multi-organ protection in diabetes.

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1. Introduction

Diabetes mellitus (DM), a chronic metabolic disorder characterized by hyperglycemia, poses a severe global health burden and leads to multi-organ complications (1,2). Despite advances in glucose-lowering therapies, the progressive nature of diabetic complications underscores an unmet need for strategies that move beyond glycemic control to directly protect target organs (3,4).

The apelin/elabela-apelin receptor (APJ) signaling system, composed of the G protein-coupled receptor APJ and its two endogenous ligands, apelin and elabela (ELA), plays a fundamental role in maintaining metabolic homeostasis (5,6). While it modulates crucial processes such as insulin secretion, vascular tone, and cell survival, its net effect is notoriously context-dependent, shifting from protective to pathogenic across different disease stages, tissue types and even between its two ligands (7-11). Currently, it remains unclear how the APJ system integrates signals from apelin and ELA to produce divergent outcomes in complications such as retinopathy and nephropathy. These knowledge gaps, particularly regarding ligand-specific biased signaling and tissue-specific receptor behavior, represent major obstacles to clinical application.

Through a systematic review of the literature, the present review first provided a concise overview of the Apelin/ELA-APJ system. Its complex and often contradictory,

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Abbreviations: ACE2, angiotensin-converting enzyme 2; AMPK, AMP-activated protein kinase; BKCa, large conductance calcium-activated potassium; DM, diabetes mellitus; ELA, elabela; EMT, epithelial-mesenchymal transition; Foxo3a, forkhead box O3a; GLUT4, glucose transporter 4; GPCR, G protein-coupled receptor; KLF15, krüppel-like factor 15; mTOR, mammalian target of rapamycin; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor-k-gene binding; NLRP3, NOD-like receptor family pyrin domain containing 3; NO, nitric oxide; NOX2, NADPH oxidase 2/gp91phox; PI3K, phosphatidylinositol 3-kinase; RAS, renin-angiotensin system; ROS, reactive oxygen species; SIRT3, sirtuin 3; TGF-β, transforming growth factor β; VEGFR2, vascular endothelial growth factor receptor 2

Key words: apelin, elabela, apelin receptor, diabetes mellitus, diabetic complications

roles in systemic glucose metabolism and in the pathogenesis of diabetic kidney disease, cardiomyopathy and retinopathy were then dissected. Finally, these insights were synthesized to evaluate critically emerging therapeutic strategies, arguing that the future of targeting this system lies in context-guided precision intervention.

2. A brief description of the apelin/ELA system

Understanding the multifaceted Apelin/ELA-APJ system is important for deciphering its context-dependent roles in diabetes. This section outlined its core components, expression and key signaling mechanisms that form the basis for its complex physiological and pathological functions. For a comprehensive treatise on the biochemistry and broad physiology of this system, readers are referred to excellent dedicated reviews (12-15).

Molecular components of the system

APJ. APJ is a class of G protein-coupled receptor (GPCR), initially identified as an orphan receptor with high sequence homology to the angiotensin II type 1 receptor (AT1R) (16-18). Despite this structural similarity, APJ does not bind angiotensin II. Instead, it forms a critical counter-regulatory axis against AT1R signaling, antagonizing a number of angiotensin II's deleterious effects in cardiovascular and renal tissues (19,20). APJ is found to be widely expressed in heart, blood vessels, kidney, ovary and human early embryonic tissues (13,21). This broad distribution, coupled with its evolutionary kinship to the AT1R, positions the APJ system as a key counter-regulatory module to the renin-angiotensin system (RAS), a relationship with profound implications for vascular and metabolic homeostasis in diabetes.

Apelin. Apelin was isolated through reverse pharmacology approaches as its first cognate ligand in 1998 (15). It is derived from a preproprotein and enzymatically processed into multiple active isoforms, including apelin-36, -17, and -13 (Fig. 1A) (22). Among these, apelin-36 is the most widely distributed subtype, with high expression levels particularly observed in the lungs, testes and uterus (23). Apelin-13, though less abundant in a number of tissues, is a highly potent isoform (24,25). (Pyr¹) apelin-13, which contains an N-terminal pyroglutamate modification, exhibits increased stability against aminopeptidase degradation and represents the most abundant Apelin isoform in human plasma and the cardiovascular system (24,26). Apelin-17 has been identified as a potential biomarker for idiopathic pulmonary arterial hypertension (27). It also contributes to diuresis by modulating the arginine-vasopressin system, thereby aiding in the correction of hyponatremia (28,29). All apelin isoforms bind to the APJ, albeit with varying affinities, leading to distinct downstream biological effects (30,31). The interaction between apelin and APJ depends critically on specific structural motifs within the peptide. The RPRL sequence, in particular, facilitates the formation of a stable beta-sheet structure that is essential for receptor binding (32). The existence of multiple bioactive isoforms with distinct pharmacokinetic profiles and tissue distributions forms a molecular basis for the nuanced and context-dependent regulation exerted by the apelin arm of the system.

ELA. ELA or Toddler, is a distinct peptide encoded by the *APELA* gene, discovered as a second endogenous ligand for APJ in 2013 (33). It is cleaved to produce the mature ELA-32 peptide, which is cleaved by furin to produce ELA-21 and ELA-11 (Fig. 1A) (33,34). Its identification resolved the phenotypic disparity between APJ and apelin gene knockout models, with APJ deficiency causing more severe developmental defects, underscoring ELA's non-redundant role (35,36). Unlike apelin, ELA is critically expressed during embryogenesis and maintains prominent expression in adult vascular endothelium and kidney (37,38). Despite minimal sequence homology with apelin, ELA binds APJ with high affinity but is proposed to engage distinct downstream signaling profiles (39,40). The differential spatiotemporal expression and signaling bias of these two ligands form the molecular basis for their potentially divergent, and occasionally opposing, roles in diabetic pathophysiology.

Expression patterns and physiological roles. The evolutionarily conserved expression profile of APJ across mammalian species reflects its pan-tissue regulatory functions in homeostatic maintenance and pathological mechanisms (16). Spatiotemporal expression profiling reveals conserved receptor distribution patterns, being expressed in key metabolic tissues such as adipose, skeletal muscle, liver and pancreatic islets; in the cardiovascular-renal system, spanning the heart, vasculature and kidney; and throughout the central nervous system (16,18,41,42). This ubiquitous tissue distribution phylogenetically correlates with APJ's pleiotropic regulatory capacities, spanning neurohumoral modulation, angiogenesis, and energy metabolism.

Functionally, this ligand-receptor system engages in pleiotropic regulation. It is a key determinant of cardiovascular homeostasis, modulating vascular tone, cardiac contractility and angiogenesis (6,26,43). In metabolic regulation, it enhances insulin sensitivity, promotes glucose uptake and regulates lipid handling, with apelin itself being an insulin-responsive adipokine (7,44). APJ activation could enhance mitochondrial biogenesis and autophagy, highlighting its potential role in metabolic diseases such as DM (45,46). It also contributes to fluid balance and hormonal secretion, including in the hypothalamus and pituitary (47). The system promotes vasodilation, reduces cardiac afterload, inhibits angiotensin II-induced hypertrophy and protects endothelial cells from apoptosis. In the kidney, it modulates glomerular hemodynamics and tubular function (38,48-51). The very pervasiveness of this system means that its dysregulation in diabetes has the potential to disrupt multiple organ systems simultaneously. Conversely, its protective functions position it as an endogenous compensatory mechanism against hyperglycemic injury (Fig. 1B). The ensuing sections will explore how this delicate balance tips toward protection or pathology in specific diabetic complications.

Signaling mechanisms and functional diversity. The APJ functions as a sophisticated molecular switch, where the physiological outcome is determined not by a single pathway, but by the type of the receptor activation. APJ predominantly couples with $G_{\alpha_{i/6}}$ and $G_{\alpha_{q/11}}$ subfamilies, with distinct

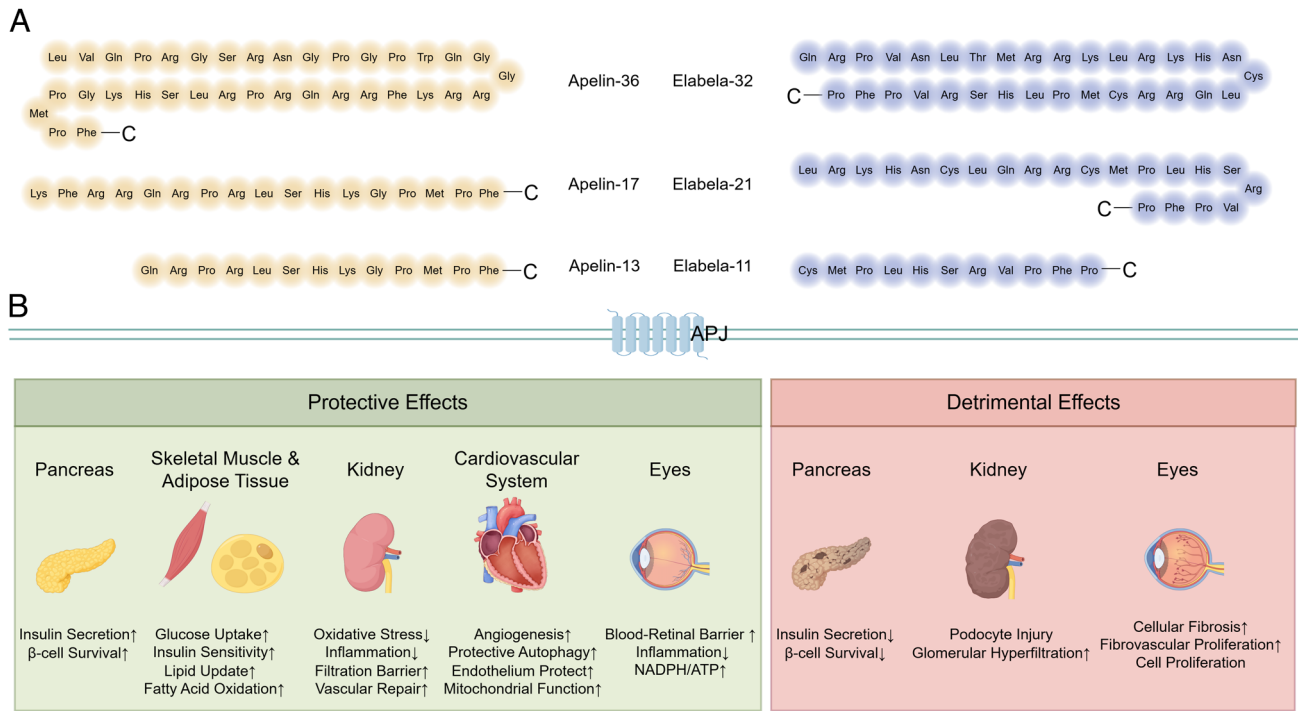


Figure 1. Biosynthesis and duality role of the apelin/ELA-APJ axis. (A) The APLN gene encodes a 77-amino acid preproapelin, which undergoes sequential proteolytic cleavage to generate bioactive isoforms, primarily apelin-36, apelin-17 and apelin-13. Similarly, ELA is processed from its 54-amino-acid precursor into active fragments, such as ELA-32, ELA-21, and ELA-11. (B) The APJ system exhibits functional divergence across organ microenvironments. ELA-APJ. ELA, elabela; APJ, apelin receptor; NADPH, nicotinamide adenine dinucleotide phosphate.

activation mechanisms (52). Real-time bioluminescence resonance energy transfer/Förster resonance energy transfer imaging has revealed that $G\alpha_{12}$ and $G\alpha_{13}$ undergo molecular rearrangement without subunit dissociation, whereas $G\alpha_o$ and $G\alpha_q$ follow the classical dissociation model (53). This diversity in G-protein engagement enables APJ to simultaneously modulate cyclic adenosine monophosphate inhibition, intracellular Ca^{2+} release and phosphatidylinositol 3-kinase (PI3K)/Akt activation, depending on the cellular context (52). The termination and diversification of these signals depend on the phosphorylation barcode at the APJ C-terminus. Research has revealed a specific phosphorylation barcode on APJ, where residues such as Ser339 are important for β -arrestin recruitment and sustained ERK signaling, while Ser335 phosphorylation specifically mediates ELA-induced β -arrestin interactions (54). This ligand-influenced phosphorylation pattern underlies the emerging concept of ligand-specific signaling bias. Apelin and ELA stabilize different APJ conformations, leading to biased engagement of downstream G proteins and β -arrestin (34,55,56).

While GPCRs function as monomers, they also dynamically form homodimers, heterodimers and higher-order oligomers with unique functions. APJ constitutively heterodimerizes with AT1R, as well as with other GPCRs, including the κ -opioid receptor, neurotensin receptor-1 and bradykinin receptors (55,57). Within the APJ-AT1R heterodimer, APJ engagement selectively attenuates AT1R-mediated β -arrestin recruitment while preserving G_q -dependent calcium mobilization, a pattern of biased antagonism that cannot be explained by simple pathway crosstalk. Apelin-13 increases APJ-AT1R heterodimer abundance, thereby potentiating

cardioprotective signaling outputs, whereas angiotensin II itself does not affect dimer stability (55). APJ signaling antagonizes angiotensin II/AT1R actions and may upregulate angiotensin-converting enzyme 2 (ACE2), thereby shifting the RAS balance toward the protective angiotensin-(1-7) axis (50,51). This physical interaction explains how the apelin system counteracts the pathological pressure of the RAS even when AT1R expression is high (58).

These signaling events converge on PI3K/Akt and AMP-activated protein kinase (AMPK) activation, promoting glucose transporter 4 (GLUT4) translocation, nitric oxide (NO) production and cell survival (44,59,60). Under physiological conditions, the MAPK and STAT3 pathways contribute to adaptive cellular growth and repair. However, in sustained chronic hyperglycemia or hypoxia, these same signals can drive excessive cell proliferation, migration and extracellular matrix deposition, linking the system to fibrosis and pathological remodeling observed in advanced complications (61,62). Therefore, the net biological effect is not intrinsic to the receptor, but an emergent property of ligand identity, phosphorylation state, oligomeric configuration and metabolic milieu. This principle shapes the context-dependent duality of the system in diabetic complications.

3. Apelin/ELA-APJ system in diabetes

The apelin/ELA-APJ system plays a multifaceted role in glucose metabolism. Its effect is not universally beneficial or detrimental but is dictated by specific physiological and pathological contexts. Understanding this ligand-specific functional duality is key to appreciating the system's role in diabetes.

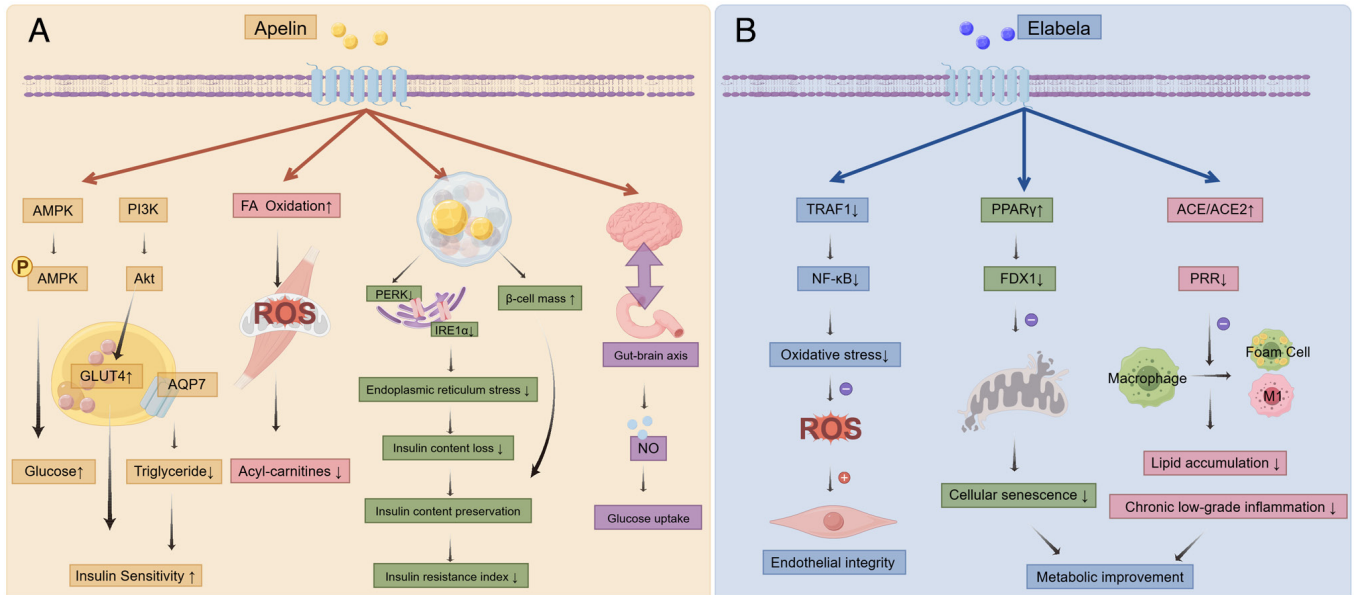


Figure 2. Role of the apelin/ELA-APJ axis in diabetic homeostasis. (A) The Apelin system affects glucose absorption and the survival of pancreatic islet cells by regulating fat, β -cell endoplasmic reticulum, skeletal muscle, brain-gut axis, etc. (B) The ELA system maintains homeostasis by preserving the integrity of endothelial cells, regulating oxidative stress, and controlling lipid deposition. ELA, elabela; APJ, apelin receptor; AMPK, AMP-activated protein kinase; FAA, free fatty acid; NO, nitric oxide; TRAF-1, tumor necrosis factor receptor-associated factor 1; PPAR, peroxisome proliferator-activated receptor; ACE, angiotensin-converting enzyme; FDX1, ferredoxin 1; PPR, (Pro)renin receptor; ROS, Reactive oxygen species.

Apelin: A multipotent and context-dependent metabolic regulator. Apelin transcends the simplistic definition of an insulin secretion modulator, emerging instead as a sophisticated systemic regulator of glucose metabolism whose actions are finely tuned by concentration, metabolic status and tissue environment. Its role in diabetes is best understood not as uniformly beneficial or detrimental, but as a series of adaptive and maladaptive responses to specific metabolic stresses across different organs (7,44,63,64).

Biphasic guardian of pancreatic β -cells. Initial investigation has positioned apelin as an inhibitory modulator of insulin secretion *in vivo* and in isolated islets (65). This acute suppression appears to be mediated through a PI3K-dependent phosphodiesterase 3B pathway, a mechanism potentiated by co-administration with glucagon-like peptide-1 (63). However, higher concentrations or chronic exposure improve overall glucose metabolism and normalize insulin levels (66). Genetic ablation of apelin results in fasting hyperinsulinemia and systemic insulin resistance, whereas chronic apelin-13 improves overall glucose metabolism and normalizes insulin levels (67). This long-term benefit is linked to enhanced insulin sensitivity and direct β -cell protection, including mitigation of endoplasmic reticulum stress in type 1 diabetes (T1D) and promotion of β -cell mass expansion in type 2 diabetes (T2D) models (45,68). Conditional knockout of APJ in islets impairs compensatory β -cell hyperplasia, confirming the essential role of the receptor in adaptation to metabolic demand (69). These findings reposition the long-term benefit of apelin as stemming more from its ability to enhance insulin sensitivity and preserve functional β -cell mass, rather than from its direct and variable effects on acute insulin secretion.

Insulin-sensitizing hormone in peripheral tissues. The primary benefit of apelin in diabetes appears to be its potent

insulin-sensitizing effect in key metabolic tissues. In adipocytes, apelin-13 enhances glucose uptake via the PI3K/Akt pathway, promoting GLUT4 translocation and membrane expression, and upregulates aquaporin 7 to ameliorate lipid accumulation (60,70). Enhancement of glucose uptake mediated by apelin occurs through dose-dependent activation of AMPK phosphorylation; however, no significant effect on lipolysis has been observed (71). In skeletal muscle, chronic apelin-13 treatment promotes complete fatty acid oxidation, enhances mitochondrial oxidative capacity and biogenesis and reduces the accumulation of toxic lipid intermediates, thereby ameliorating insulin resistance at the muscular level (72). Differing from findings in mouse models, the baseline expression levels of apelin and its receptor APJ in adipose tissue and skeletal muscle do not differ markedly between patients with T2D and healthy controls (73). This highlights the tissue-specific and species-specific regulation of the apelin system, which may vary with the degree of insulin resistance (Fig. 2A).

These pre-clinical findings are supported by clinical evidence. Serum apelin levels are elevated in patients with both T1D and T2D compared with healthy controls, with the highest levels found in patients with T1D (74). Critically, a proof-of-concept clinical trial has provided the direct evidence in humans, demonstrating that apelin infusion acutely improved glucose tolerance and insulin sensitivity in patients with T2D (75). This collective evidence solidifies the hypothesis that increased circulating apelin levels are a counter-regulatory response to insulin resistance and hyperglycemia, primarily acting to enhance insulin sensitivity in the periphery.

Central-peripheral dichotomy. Central administration of low-dose apelin lowers blood glucose levels, while higher

doses induce insulin resistance (59). However, in obese mice, apelin promotes hypothalamic inflammation, suppresses brown adipose tissue thermogenesis and contributes to the pathogenesis of T2D (59,76). An additional layer of complexity involves the gut-brain axis. Apelin can modulate duodenal contraction rhythms, which in turn influence hypothalamic NO levels to fine-tune skeletal muscle glucose uptake (47). This central-peripheral conflict necessitates therapeutic strategies that can selectively engage the beneficial peripheral actions while avoiding potential central adverse effects.

ELA in diabetes: A promising but still unexplored guardian peptide. Within the apelinergic system, structural divergence dictates functional specialization. Apelin isoforms share a conserved C-terminal receptor, while ELA possesses a distinct N-terminal architecture, promoting a unique active conformation of APJ (53,55). Coupled with its persistent expression in adult vascular endothelium and kidneys, this structural and signaling distinction positions ELA as a separate, developmentally-rooted guardian within glucose homeostasis and diabetic complication pathways, diverging from the primary roles of apelin in metabolic adaptation (10,52).

Clinical and mechanistic foundations. Consistently reduced plasma ELA levels have been observed in individuals with T2D (77,78). This is not an isolated phenomenon. Our previous findings further underscored the clinical relevance of ELA, demonstrating a close relationship between serum ELA levels and the development and progression of diabetic nephropathy (77,79). Consequently, it is hypothesized that insufficient ELA expression might be a critical factor underlying systemic glycemic dysregulation and insulin resistance.

To elucidate the pathophysiological consequences of diminished ELA levels, researchers have employed various models to investigate their protective mechanisms from multiple perspectives (Fig. 2B). Regarding vascular endothelial protection, under high-glucose conditions, ELA specifically inhibits the tumor necrosis factor receptor-associated factor 1/NF- κ B axis, mitigating oxidative DNA damage and preserving vascular integrity (80). In terms of ameliorating cellular metabolic status, synergistic effects have been uncovered. ELA acts synergistically with the classic insulin sensitizer rosiglitazone by specifically activating peroxisome proliferator-activated receptor γ and suppressing the expression of its downstream target ferredoxin 1, ultimately alleviating mitochondrial damage and delaying cellular senescence (81). Tang *et al* (82) offer a novel perspective on the regulation of lipid metabolism and inflammation. ELA enhanced the expression levels of ACE and ACE2 in macrophages, while inhibiting the (pro) renin receptor system, modulating macrophage polarization to suppress inflammation.

Discrepant therapeutic outcomes in preclinical research. Despite promising mechanisms, the therapeutic translation of ELA has yielded contradictory results across models (10,83). In streptozotocin-induced T1D, prolonged exogenous administration of ELA-32 reduced peripheral glucose levels and restored insulin concentrations (83). By contrast, our research using db/db mice yielded divergent outcomes: Extended ELA-21 treatment failed to improve fasting blood glucose and

glycated hemoglobin levels (10). It was hypothesized that the efficacy of ELA is contingent upon the underlying metabolic milieu. In the insulinopenic environment of T1D, the actions of ELA may directly counter serious glucose-induced damage. Conversely, in the db/db model, which is characterized by profound leptin receptor deficiency, rampant obesity and systemic insulin resistance, this dominant metabolic dysregulation may create a signaling environment that overwhelms or fundamentally alters ELA-APJ signaling. This hypothesis predicts that the therapeutic window of ELA is narrower than initially assumed, favoring earlier or less metabolically chaotic disease stages.

4. Apelin/ELA-APJ system and diabetic kidney disease

Diabetic kidney disease (DKD) progression is driven by a confluence of metabolic, hemodynamic and inflammatory injuries (84). Hemodynamic imbalance, tubule-glomerular feedback changes, renal hypoxia, lipotoxicity, podocyte injury, inflammation, mitochondrial dysfunction, impaired autophagy and increased sodium and hydrogen exchanger activity are involved in the occurrence and development of diabetic nephropathy (84,85). Within this milieu, the apelin/ELA-APJ system plays a decisive yet divergent role. Apelin exhibits a stark functional duality, swinging from renoprotection to injury, while ELA consistently signals toward protection, though the underlying metabolic environment may modulate its efficacy.

The dual faces of apelin in diabetic kidney disease. The role of Apelin in DKD remains controversial and inadequately defined by large-scale clinical studies. Current evidence reveals a system whose function pivots markedly based on the pathological context, particularly the diabetes type and the stage of renal involvement.

Circulating apelin as a marker of disease. In the human kidney, the apelin system is widely expressed across renal vasculature, glomeruli and tubules (86). Plasma apelin concentrations in patients with DKD increased with declining renal function and correlated positively with albuminuria severity. This elevation may represent compensatory upregulation, reduced renal clearance, or both, creating ambiguity for biomarker interpretation. Apelin levels were independently associated with a decline in eGFR, positioning it as both a disease monitor and a potential intervention point (86,87).

Evidence from experimental models. Substantial evidence from animal models supports the renoprotective role of apelin, particularly under specific conditions (Fig. 3A). In insulin-deficient mice, apelin-13 treatment prevents pathological renal hypertrophy and reduces albuminuria through antioxidant enzyme upregulation and histone deacetylation-mediated inflammation suppression (88,89). Even in T2D models, where its role is more controversial, apelin exhibits protective effects. Apelin inhibits epithelial-mesenchymal transition (EMT) in podocytes by suppressing the immunoproteasome subunit β 5i, and attenuates glomerular endothelial fibrosis through a sirtuin 3 (SIRT3)-Krüppel-like factor 15 (KLF15)-dependent pathway (90,91). One report suggested that apelin increased

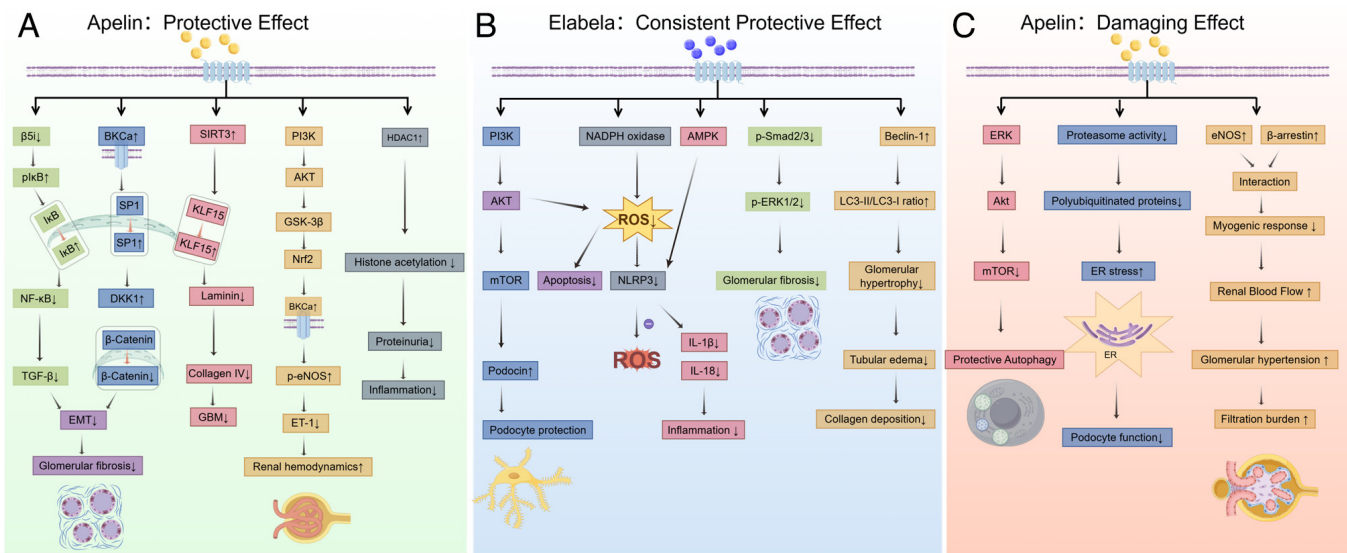


Figure 3. Dual role of apelin and the protective role of ELA in diabetic kidney disease. (A) Protective effects of apelin. Apelin can exert both protective effects by upregulating antioxidant defenses, inhibiting podocyte injury and fibrosis and improving endothelial function. (B) ELA consistently demonstrates renoprotective properties by preserving podocytes, reactivating autophagy in renal tubules, and mitigating inflammation and oxidative stress. (C) Detrimental effects of apelin in the diabetic kidney. In certain contexts, apelin exerts damaging effects by impairing proteasome activity and autophagic flux, leading to endoplasmic reticulum stress, podocyte dysfunction and accumulation of polyubiquitinated proteins. Apelin also disrupts vascular homeostasis through eNOS/ β -arrestin interaction, reducing myogenic response while increasing renal blood flow, glomerular hypertension and filtration burden. (p)I κ B, (phosphorylated) inhibitor of NF- κ B; NF- κ B, nuclear factor κ B; TGF- β , transforming growth factor- β ; EMT, epithelial-mesenchymal transition; BKC α , large-conductance calcium-activated potassium channel; SP1, specificity protein 1; DKK1, dickkopf-related protein 1; SIRT3, sirtuin 3; KLF15, krüppel-like factor 15; GBM, glomerular basement membrane; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; GSK-3 β , glycogen synthase kinase-3 β ; Nrf2, nuclear factor erythroid 2-related factor 2; p-eNOS, phosphorylated endothelial nitric oxide synthase; ET-1, endothelin-1; HDAC1, histone deacetylase 1; mTOR, mammalian target of rapamycin; NADPH, nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species; AMPK, AMP-activated protein kinase; NLRP3, NOD-like receptor family pyrin domain containing 3; IL-1 β , interleukin-1 β ; IL-18, interleukin-18; p-Smad2/3, phosphorylated Smad2/3; p-ERK1/2, phosphorylated extracellular-regulated kinase 1/2; LC3-II/LC3-I, microtubule-associated protein 1 light chain 3-II/I.

the activity of large-conductance calcium-activated potassium (BKC α) channels, promoting the nuclear translocation of the SP1 transcription factor. This enhanced the expression of Dickkopf-related protein 1, which inhibited β -catenin nuclear translocation and subsequent EMT (92). Huang *et al* (93) proposed that apelin upregulated the α and β 4 subunits of the BKC α channel via the PI3K/AKT axis, leading to increased NO bioavailability and reduced endothelin-1 expression, thereby mitigating glomerular hypertension. Conditioned medium from human Wharton's jelly-derived mesenchymal stem cells improves renal function by upregulating apelin mRNA levels while downregulating transforming growth factor beta (TGF- β) mRNA levels (94), whereas quercetin treatment achieves similar benefits by reducing the expression of both molecules (95). These findings collectively established the renoprotective potential of apelin under hyperglycemic conditions.

By contrast, evidence from models of advanced T2D has revealed the pathogenic potential of apelin (Fig. 3C). In these settings, characterized by profound insulin resistance and metabolic dysregulation, apelin signaling appears to become maladaptive. It impairs podocyte function by inhibiting proteasome activity, leading to toxic accumulation of polyubiquitinated proteins and endoplasmic reticulum stress (96). Liu *et al* (8) further demonstrated that apelin suppressed protective autophagy in glomeruli via activation of the Akt and mammalian target of rapamycin (mTOR) pathways, exacerbating cellular injury. Apelin could disrupt the intrinsic myogenic response of renal resistance vessels, causing inappropriate vasodilation

that may exacerbate glomerular hyperfiltration and capillary pressure, and driving DKD progression (97). Paradoxically, in cultured podocytes, apelin was observed to reduce mTOR phosphorylation and enhance autophagic activity (8).

The role of Elabela in diabetic kidney disease. In contrast to the context-dependent duality of Apelin, accumulating evidence positions ELA as a more uniformly protective agent in DKD. Its role extends beyond that of a passive biomarker to an active guardian peptide, with deficiency contributing to disease progression.

A marker of renal health. Clinical observations consistently associate ELA with renal protection. Our previous study demonstrated a progressive decline in serum ELA concentrations throughout DKD progression, suggesting the potential utility of ELA as a prognostic biomarker for disease monitoring (77). This relationship has been independently validated in a Turkish observational study (79). In a previous study, across different stages of chronic kidney disease, a gradual reduction in ELA concentrations paralleling eGFR decline was observed, with multivariate linear regression confirming eGFR as an independent predictor of serum ELA levels (98). These findings indicate that reduced ELA levels are not merely a consequence of renal impairment but may signify a loss of an endogenous protective mechanism.

Mechanistic foundation of renoprotection. Mechanistic studies have elucidated multiple protective pathways through

which ELA exerts its beneficial effects (Fig. 3B). In T1D models, exogenous ELA administration restored the expression of podocyte-specific proteins, including synaptopodin and podocin, via activation of the PI3K/Akt/mTOR pathway, thereby stabilizing the glomerular filtration barrier (83). Tubular injury is now recognized as a crucial factor in the development of DKD. ELA treatment reactivates high glucose-inhibited renal tubular autophagy, promoting survival in diabetic tubules (10). Its anti-fibrotic potential is linked to predominant renal tubular expression, with specific knockout of tubular ELA exacerbating renal injury and fibrosis (99), mediated by the suppression of Smad2/3 phosphorylation (100). Regarding oxidative stress regulation, ELA reduces renal reactive oxygen species (ROS) generation by blocking the NADPH oxidase (NOX2)/ROS/NOD-like receptor family pyrin domain containing 3 (NLRP3) pathway and through PI3K/Akt-mediated survival signaling, thereby alleviating oxidative damage (101,102). Additionally, ELA modulates the AMPK/NLRP3 signaling axis to inhibit inflammasome activation and the subsequent release of pro-inflammatory cytokines (103).

Current evidence is predominantly derived from animal studies, with limited human data available. Existing clinical investigations are constrained by small sample sizes and insufficient long-term follow-up. While ELA exhibits clear efficacy in T1D, in db/db mice has yielded divergent outcomes, with no statistically significant improvements in core metabolic parameters (10,83). This discrepancy underscores a contingency: The efficacy of ELA may be constrained in profoundly insulin-resistant and dysmetabolic environments, suggesting its therapeutic window may be favorable in earlier or less metabolically chaotic stages of disease.

Comparative implications: Ligand selection based on disease stage. Due to the context-dependent role of apelin, patients with early disease may be more likely to benefit from apelin treatment than patients with advanced T2D with severe insulin resistance (90,94,97). Its signaling flexibility, rooted in multiple phosphorylation sites and G protein coupling options, creates opportunity but also the risk of unintended pathway activation (53,54). By contrast, the protective action of ELA likely traces back to the receptor level. As aforementioned, ELA induces distinct phosphorylation patterns on the receptor's C-terminus (54). ELA may exert its effects mainly via transient PI3K/Akt-driven survival signaling and preserve autophagy (10,83,102). Rather than examining whether the APJ system is protective or harmful, it could be explored under what conditions, and through which ligand, it assumes one role or the other. The convergence of both ligands on shared downstream effectors, such as SIRT3, also suggests that the most durable strategy may lie not in choosing one ligand over the other, but in identifying nodes common to both protective pathways (11,90).

5. Apelin/ELA-APJ system and diabetic cardiomyopathy

Diabetic cardiomyopathy (DCM) is characterized by myocardial dysfunction independent of coronary artery disease or hypertension, driven by metabolic disturbances, oxidative stress, inflammation, and microvascular impairment (104).

Within this pathological framework, the Apelin/ELA-APJ system, widely expressed in cardiomyocytes, vascular endothelium, and smooth muscle, emerges as a critical endogenous regulator (11,14,49,64). In contrast to its more paradoxical roles in renal and retinal complications, evidence in DCM predominantly points toward a protective adaptation, though nuanced by clinical context and therapeutic modulation.

The role of Apelin in diabetic cardiomyopathy. Apelin orchestrates a multifaceted defense against DCM through coordinated modulation of metabolism, redox balance, and microvascular function. Its clinical relevance, however, is shaped by a complex interplay of disease subtype, comorbidities, and pharmacologic interventions.

Fundamental protective mechanisms. The mitochondrial deacetylase SIRT3 emerges as a pivotal mediator of the antioxidant and anti-inflammatory effects of apelin (Fig. 4A). Apelin treatment elevates myocardial SIRT3 expression in DCM models, concurrently promoting the expression of angiogenesis-related factors (105,106). In diabetic myocardial infarction models, apelin activates protective autophagy through SIRT3-dependent mechanisms, which in turn inhibits NADPH oxidase-driven ROS generation and blocks the inflammatory pathway (106,107). Genetic ablation of SIRT3 completely abolishes these effects, unequivocally establishing its indispensable role (105-107).

Beyond the SIRT3 pathway, apelin protects vascular function in diabetes by counteracting angiotensin II-induced vasoconstriction and enhancing endothelium-dependent vasodilation via the PI3K/Akt-endothelial nitric oxide synthase pathway (108). Apelin also attenuates cardiac microvascular inflammation and adhesion molecule expression in T2D mice via suppression of the NF- κ B pathway (64). At the cellular level, it upregulates connexin 43 in cardiomyocytes under high glucose conditions, thereby improving gap junctional communication and electrical stability (109). Apelin also mediates pro-angiogenic signals from regulatory T cells, promoting microvascular density and perfusion in DCM (110).

From a metabolic perspective, chronic apelin-13 treatment reduces myocardial free fatty acid and glycogen content in T2D rats, suppressing excessive fatty acid oxidation (45). Complementing these findings, apelin-12 restores the phosphocreatine/ATP ratio, indicating improved energy reserve (111). Furthermore, apelin restores erythrocyte deformability and enhances the myocardial antioxidant defense capacity (9,112,113). These preclinical findings paint a compelling picture of comprehensive cardioprotection. However, the transition to human disease reveals complexities that temper enthusiasm for uncomplicated therapeutic translation.

Clinical complexities and translational insights. Population studies have produced more nuanced and notably inconsistent results. While reduced apelin levels are associated with cardiac remodeling severity in hypertensive patients with diabetes, differences between diabetic patients with and without complications frequently fail to reach statistical significance (114,115). Associations have been observed in children with T1D and Egyptian diabetic patients, while apelin levels exhibit no association with carotid intima-media

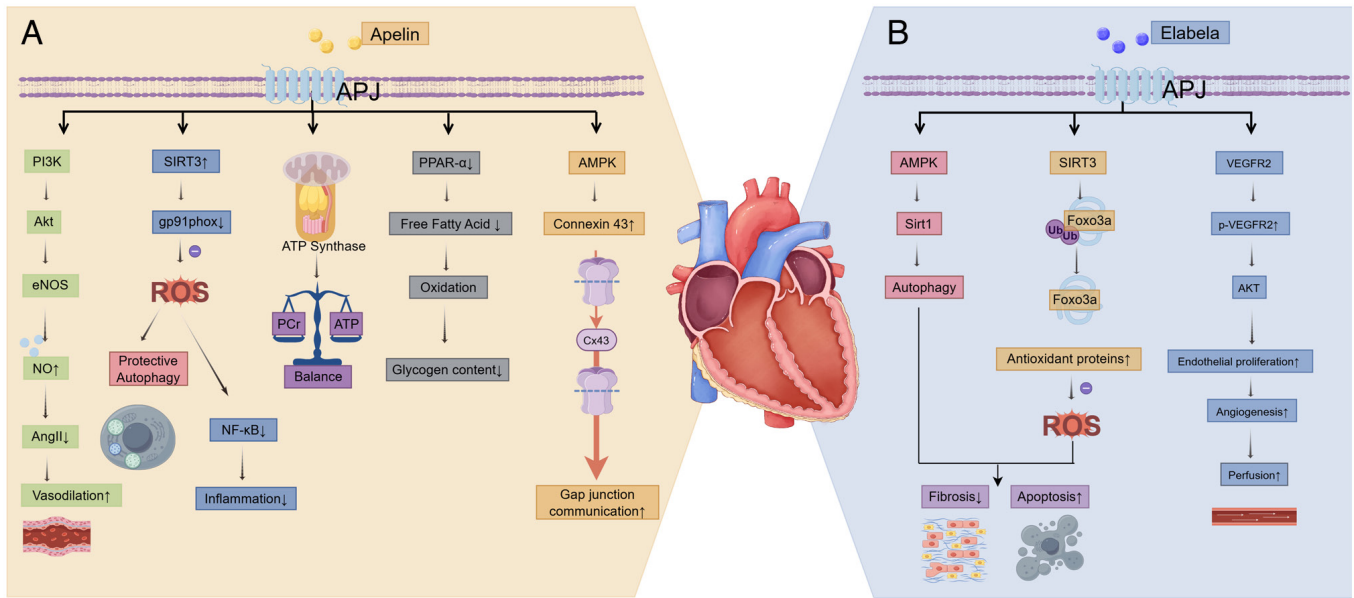


Figure 4. Protective mechanisms of the apelin/ELA-APJ system against diabetic cardiomyopathy. In the diabetic heart, both (A) apelin and (B) ELA mitigate key pathological processes, including metabolic derangement, oxidative stress, inflammation, fibrosis and microvascular rarefaction. APJ, apelin receptor; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; eNOS, endothelial nitric oxide synthase; AngII, angiotensin II; SIRT3, sirtuin 3; gp91phox, glycoprotein 91 phagocyte oxidase; ATP, adenosine triphosphate; PCr, phosphocreatine; PPAR- α , peroxisome proliferator-activated receptor α ; AMPK, AMP-activated protein kinase; Cx43, connexin 43; SIRT1/3, sirtuin 1/3; Foxo3a, forkhead box O3a; Ub, ubiquitin; VEGFR2, vascular endothelial growth factor receptor 2.

thickness in populations predisposed to T2D (116,117). These discrepancies likely reflect differences in diabetes duration, the metabolic profile of T1D vs. T2D and the confounding effects of concurrent medications.

Therapeutic interventions further complicate this narrative. Pioglitazone suppresses apelin transcriptional activity by inducing KLF4 expression (118), while dapagliflozin increases serum apelin levels (119). Non-pharmacologic interventions such as physical exercise could elevate apelin levels, as well as improve cardiovascular risk markers (120). These diametrically opposed drug effects not only reveal differential regulation of the apelin system by various glucose-lowering agents but may partially explain their distinct cardiovascular protective profiles. The association between increased apelin levels following dapagliflozin treatment and improved left ventricular function offers novel insights into the cardiovascular benefits of this drug class.

In biomarker development, the apelin/N-terminal pro-brain natriuretic peptide ratio has demonstrated superior predictive value for heart failure with preserved ejection fraction in diabetic patients compared with either biomarker alone, suggesting that single biomarkers may be insufficient to reflect complex cardiovascular pathological states (121). The lack of significant apelin level differences between patients with tight compared with poor glycemic control suggests system regulation relating more fundamentally to the presence of diabetes itself rather than glycemic management specifically (122).

Role of ELA in DCM. Direct research on ELA in the specific context of DCM is nascent, but a compelling protective role may be inferred from its well-established actions in related cardiovascular pathologies and is supported by emerging direct evidence. These findings collectively position ELA as a promising endogenous guardian against diabetic heart injury.

Mechanistic insights from broad cardiovascular protection. The core pathological processes of DCM, including severe oxidative stress, inflammatory responses, endothelial dysfunction and cellular apoptosis, are also central to other cardiovascular conditions (85,104). In non-diabetic models, ELA has been demonstrated to intervene in these processes effectively (14,18). In myocardial ischemia-reperfusion injury, ELA exerts cardioprotective effects by activating PI3K/AKT signaling to enhance cell survival and mitochondrial function (123), while suppressing TGF β 1-Smad2/3 and ERK/hypoxia-inducible factor-1 signaling to inhibit fibroblast migration (124,125). ELA also modulates the AMPK-Sirt1 axis to regulate apoptosis and autophagy (124). Regarding atherosclerosis, clinical observations have indicated reduced circulating levels of ELA in patients with the condition, and ELA itself possessed functions that stabilized the endothelium and inhibited smooth muscle cell proliferation (14,126). The related peptide apelin-13 has also been shown to inhibit macrophage foam cell formation and promote cholesterol efflux via the APJ receptor (127). Given the exacerbation of these same pathways in diabetes, dysregulation of the ELA-APJ axis likely contributes to accelerated cardiovascular damage in DCM, while ELA supplementation represents a rational therapeutic strategy.

Emerging direct evidence in diabetic contexts. Preliminary research directly investigating ELA in diabetic heart disease have begun to illuminate its protective mechanisms (Fig. 4B). In the diabetic heart, ELA activates SIRT3, promoting the deacetylation of the transcription factor Forkhead Box O3a (Foxo3a) and subsequent upregulation of antioxidant defenses. This pathway mitigates oxidative stress, thereby attenuating cardiomyocyte fibrosis and apoptosis (11). ELA expression is upregulated in diabetic ischemic tissues, where it promotes endothelial cell proliferation by upregulating vascular

endothelial growth factor receptor 2 (VEGFR2) and its phosphorylation levels, activating the downstream AKT signaling pathway (128). Functional experiments have confirmed that specific knockout of ELA in endothelial cells impaired blood flow recovery and capillary density in ischemic tissues, highlighting its essential role in vascular repair (129). This inducibility contrasts with the relatively constitutive expression of ELA in healthy endothelium and may represent an attempt to activate protective signaling pathways that becomes inadequate in sustained diabetes.

Complementary rather than redundant. The cardiac APJ narrative, while less dichotomous than renal or retinal presentations, reveals equally important principles for therapeutic development. The two ligands engage SIRT3 as a common protective node, yet arrive through distinct signaling architectures with different context sensitivities (11,107,130). Circulating apelin levels rise in advanced disease, but whether this represents exhausted compensation or active pathogenesis remains unclear (114). Divergent effects of glucose-lowering approaches on apelin levels also caution against inferring causality from cross-sectional associations (119,120). For ELA, the protective signal is consistent and the evidence base remains thin; whether its efficacy becomes contextually constrained in the severely insulin-resistant or chronically remodeled heart has not been systematically tested (11,128). The challenge in DCM is therefore not whether to activate or inhibit, but how to engage the right pathways with precision. Whether through apelin analogs in metabolically normalized patients, ELA supplementation for vascular protection or synergistic pairing, represents a unifying therapeutic goal.

6. Apelin/ELA-APJ system and diabetic retinal disease

Diabetic retinopathy (DR), a leading cause of vision loss, evolves from early neurovascular dysfunction to advanced proliferative stages characterized by pathological angiogenesis and fibrosis (131,132). Expanding beyond the traditional focus on vascular endothelial cells, recent studies reveal that diabetes affects neurons, glial cells and other retinal cell types (133,134), prompting the term 'diabetic retinal disease' (DRD) to describe these broader structural and functional alterations (135). Research on the apelin/ELA-APJ system in this context reveals a paradigm of context-dependency. Its role is not static but undergoes a dramatic reversal contingent upon disease stage, offering a unique lens through which to understand how a single signaling axis can be both a protector and a perpetrator within the same organ.

The role of apelin in diabetic retinal disease. Apelin's function in DRD is not merely dualistic but dynamically inverted across the disease continuum. It acts as a protective guardian in early stages, yet transforms into a pathological driver in proliferative diabetic retinopathy (PDR). This switch represents one of the striking examples of context-dependent signaling in diabetic complications.

Pathological driver in proliferative DRD. In PDR, apelin and its receptor are consistently upregulated in vitreous, fibrovascular and epiretinal membranes (136-138). Immunohistochemistry

has localized apelin to endothelial, glial and epithelial components of these pathological tissues, implicating it directly in neovascularization and fibrosis (138).

At the molecular and cellular level, high glucose conditions upregulate apelin expression in human retinal pigment epithelial (RPE) cells and apelin subsequently promotes RPE cell proliferation, migration and collagen I expression through activation of the PI3K/Akt and MEK/Erk signaling pathways (62). Similarly, in diabetic models, apelin activates the Janus kinase 2/STAT3 pathway in Müller glial cells to drive fibrosis (61,139). These findings establish apelin as an active participant in the fibrovascular proliferation that characterizes advanced disease.

A protective guardian in early-stage DRD. In contrast to its apparently detrimental role in advanced PDR, apelin exhibits protective effects in early DRD stages or specific contexts. In T2D mouse models, apelin enhances blood-retinal barrier integrity by upregulating tight junction proteins via the PI3K/Akt pathway, thereby reducing vascular leakage. Apelin concurrently mitigates retinal inflammation by downregulating adhesion molecules and suppressing NF- κ B activation (140). Additionally, apelin-13 exhibits protective effects on retinal ganglion cells by activating the PI3K/Akt pathway to inhibit apoptosis, enhancing the pentose phosphate pathway enzyme activity to increase NADPH and ATP production while reducing oxidative stress, and inhibiting mitochondrial cytochrome *c* release (141). These actions collectively preserve the neurovascular unit in the face of early diabetic insult.

The Role of ELA in DRD. In contrast to the stage-dependent functional reversal of Apelin, emerging research on ELA in DRD suggests a profile that is more uniformly associated with vascular protection, particularly against oxidative injury. While direct evidence in diabetic models remains less extensive, convergent findings from clinical observations and related disease models position ELA as a compelling candidate for stabilizing the retinal vasculature.

Evidence supporting the vascular protective role. Clinical studies indicated that serum ELA levels were elevated in patients with PDR compared to those without retinopathy, a finding that coincided with longer diabetes duration in the PDR group (142). This correlation invites investigation into whether elevated ELA represents a compensatory protective response to severe vascular stress.

Mechanistic insights were primarily derived from the oxygen-induced retinopathy model, which replicates the obliterative and ischemic phases relevant to DRD. During the obliterative phase, exogenous ELA reduced avascular area and promoted physiological retinal vessel regrowth by inhibiting ferroptosis through modulation of the xCT/GPX4 axis, thereby preserving mitochondrial function and endothelial cell survival under ischemic stress (143). Given that oxidative stress is a cornerstone of DRD pathophysiology, these findings provide a strong rationale for ELA's potential to protect retinal microvessels from hyperglycemia-induced degeneration.

Reasons why ligands diverge. The functional shift of apelin from a guardian to a driver likely reflects changes in the

retinal cellular environment and signaling landscape as DRD progresses. In early stages, characterized by metabolic stress and oxidative damage, apelin signaling through pro-survival pathways in endothelial cells and neurons may predominate (140). In the hypoxic, inflammatory milieu of PDR, its signaling may be shunted toward fibrotic pathways (61). ELA does not undergo a similar inversion and instead appears to be consistently protective. ELA induces a distinct APJ phosphorylation barcode and transient signal kinetics, whereas apelin favors sustained β -arrestin signaling (54).

This bias may render ELA less susceptible to pathological rerouting, even in a hostile microenvironment. Whether the protective capacity of ELA is also overwhelmed in late stages, or whether its elevation in patient vitreous remains functionally protective, has not been directly tested. This staged, personalized approach to APJ modulation, informed by mechanistic understanding of ligand-specific signaling, offers a path toward therapeutic utility in a disease where previous attempts at pathway manipulation have often failed due to oversimplification.

7. Current challenges and future perspectives

While the present review focused on the classic triad of diabetic complications (cardiomyopathy, nephropathy and retinopathy), emerging evidence suggests that the APJ axis also influences diabetic neuropathy and wound healing (80,144). Preliminary studies have indicated that apelin may promote neuron survival and vascular regeneration, potentially mitigating diabetic neuropathy (145,146). Apelin may alleviate diabetes-associated hearing loss by reducing cochlear endoplasmic reticulum stress and mitochondrial dysfunction (147). However, compared with the robust data in the heart and kidneys, the mechanisms in these tissues remain under-characterized. Future research should determine whether the protective efficacy observed in cardiovascular tissues translates to the nervous system or if the pro-angiogenic risks, as seen in the retina, outweigh the benefits (61,137,140,141).

Apelin epitomizes this duality, acting as an insulin sensitizer yet a potential central disruptor, a guardian in early diabetic complications but a driver in advanced proliferative states (65,76,90,97). By contrast, ELA exhibits a more consistent protective profile in diabetic kidney, heart and retinal models, although its efficacy may be attenuated in profound insulin-resistant states, highlighting its own context-dependency (90,93,97). The divergent roles of apelin and ELA likely arise from ligand-specific signaling bias, differential cellular expression and distinct interactions with the phosphorylation of the receptor.

Despite therapeutic promise, several hurdles remain for clinical translation. To overcome the rapid degradation of native apelin peptides, researchers have developed stabilized analogues with extended half-lives and enhanced *in vivo* efficacy (148-150). More advanced strategies include gene and cell-based therapies, such as engineering mesenchymal stem cells to serve as sustained Apelin delivery platforms, which have shown promise in rodent models (7,151). However, validation has largely been confined to rodent models, and a loss of therapeutic efficacy may be observed during chronic exposure. Given the heterodimerization between APJ and AT1R,

therapeutic strategies must account for the patient's concurrent use of ACE inhibitors or angiotensin receptor blockers, which are standard-of-care in diabetes (55,58).

In summary, the apelin/ELA-APJ system represents a double-edged sword in diabetes management. The complexity of the apelin/ELA-APJ system constitutes its great strength as a multifaceted modulator. Embracing this complexity and guiding research with a principle of precision intervention will be essential to fully unlock its potential and offer a novel, integrative strategy to combat the multifaceted diabetic syndrome.

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Authors' contributions

ZH and JZ were responsible for writing the text and completing the figures. MS, JC, AL and YY were responsible for researching the data, discussing the content. HZ was responsible for reviewing and editing the manuscript prior to submission. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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