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ANGPTL3 as a target for treating lipid disorders in type 2 diabetes patients

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Abstract

Type 2 diabetes mellitus (T2DM) is a globally prevalent metabolic disorder, and cardiovascular disease (CVD) is a significant cause of mortality and morbidity in diabetic individuals. In addition to hyperglycemia, lipid abnormalities associated with T2DM play a crucial role in the development of CVD complications. Diabetic dyslipidemia is characterized by elevated levels of triglyceride (TG)-rich lipoproteins and small dense low-density lipoprotein (LDL) particles, reduced high-density lipoprotein (HDL) cholesterol, and impaired HDL function. Angiopoietin protein-like 3 (ANGPTL3) is a liver-derived protein that plays a crucial role in regulating plasma lipoprotein metabolism by inhibiting lipoprotein lipase and influencing lipid levels. Inhibiting ANGPTL3 has shown promising effects in promoting HDL-mediated cholesterol reverse transport and reducing the levels of TG-rich lipoproteins and LDL cholesterol. Here, we explore the potential of ANGPTL3 as a therapeutic target for lipid management in T2DM patients.

Keywords Type 2 diabetes mellitus, Diabetic dyslipidemia, Insulin resistance, Cardiovascular disease, Angiopoietin-like protein 3

Introduction

Type 2 diabetes mellitus (T2DM) is a prevalent metabolic disorder characterized not only by hyperglycemia but also by lipid abnormalities, which significantly contribute to the elevated cardiovascular risk observed in these patients [1, 2]. Dyslipidemia in T2DM typically manifests as decreased levels of high-density lipoprotein (HDL) cholesterol and elevated levels of atherosclerosis-inducing lipids or lipoproteins, including very-low-density lipoprotein (VLDL), chylomicrons (CM), and small dense low-density lipoprotein (sdLDL) [3]. Addressing this lipid abnormality is crucial for reducing the burden of cardiovascular diseases commonly associated with T2DM.

In the pursuit of novel therapeutic targets for dyslipidemia, angiopoietin-like protein 3 (ANGPTL3) has emerged as a promising candidate [4]. ANGPTL3 is a secreted protein that plays a crucial role in lipid metabolism by inhibiting lipoprotein lipase (LPL) and endothelial lipase, leading to increased circulating levels of triglycerides, LDL cholesterol, and HDL cholesterol [5]. Genetic studies have demonstrated that individuals with loss-of-function mutations in the *ANGPTL3* gene have significantly lower levels of all three lipids and a reduced risk of atherosclerotic cardiovascular disease [6], providing a strong rationale for targeting ANGPTL3 in lipid management.

With the development of monoclonal antibodies and other biologic therapies designed to inhibit ANGPTL3

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[4], there is potential to address the lipid disturbances found in T2DM patients more effectively. Recent pharmacological strategies aimed at inhibiting ANGPTL3, including monoclonal antibodies and gene silencing techniques, have demonstrated significant lipid-lowering effects in clinical trials, positioning ANGPTL3 as a promising candidate for managing residual cardiovascular risk [7]. By summarizing the characteristics of dyslipidemia in patients with T2DM and the potential therapeutic applications of ANGPTL3 inhibitors, this study seeks to contribute to ongoing efforts to improve the cardiovascular health and overall well-being of individuals living with T2DM.

ANGPTL3 Biology and Function

ANGPTL3, encoded by the *ANGPTL3* gene on chromosome 1, is a liver-exclusive protein crucial for systemic lipid homeostasis. This 53-kDa glycoprotein is characterized by an N-terminal coiled-coil domain and a C-terminal domain that shares homology with the angiopoietin family of proteins [8]. It has been reported that the gene expression of ANGPTL3 in the liver is regulated by the oxysterol-responsive liver-X receptor (LXR), and it seems that in the mouse liver, this expression is not influenced by fasting or refeeding [9, 10]. The expression of ANGPTL3 is suppressed by PPAR, statins, insulin, leptin, thyroid hormones, and lipopolysaccharides [10–16]. The ANGPTL family includes several proteins, with ANGPTL3, ANGPTL4, and ANGPTL8 being particularly important in triglyceride metabolism [17]. ANGPTL3 inhibits LPL, which reduces the breakdown of triglycerides into free fatty acids and glycerol, thereby leading to an increased presence of triglycerides in the bloodstream [7]. ANGPTL4 is predominantly expressed in adipose tissue and is also regulated by insulin [18]. ANGPTL4 acts as a potent inhibitor of LPL, particularly in the context of fasting and exercise, when its expression is upregulated [17, 19]. Insulin suppresses ANGPTL4 expression in adipose tissue, which allows for increased LPL activity and enhanced triglyceride uptake in this tissue during the fed state [19]. ANGPTL8 is expressed in both the liver and adipose tissue and is significantly induced by feeding [20]. The interplay between ANGPTL3, ANGPTL4, and ANGPTL8, along with their insulin-dependent regulation, is essential for maintaining lipid homeostasis [17]. ANGPTL8 acts as a regulator of both ANGPTL3 and ANGPTL4 [17]. It enhances the LPL-inhibiting activity of ANGPTL3 by forming a complex with it [20, 21]. Conversely, ANGPTL8 can form a complex with ANGPTL4 that reduces its LPL-inhibiting activity, thereby allowing for increased LPL function in white adipose tissue [20]. Apolipoprotein C-III (ApoC-III) is another key protein involved in regulating triglyceride levels by inhibiting LPL [22]. ApoC-III is primarily found in triglyceride-rich lipoproteins such as VLDL and chylomicrons. It plays a crucial role by influencing LPL-mediated hydrolysis of triglycerides, thereby reducing their clearance from the bloodstream [22]. Inhibition of ApoC-III has been shown to significantly lower triglyceride levels and improve lipid profiles, highlighting its importance in cardiovascular risk management [23]. ANGPTL3 and apoC-III represent innovative targets for reducing lipid levels [22]. In addition to its effects on triglycerides, ANGPTL3 also regulates LDL cholesterol and HDL cholesterol levels [4]. Loss-of-function mutations in *ANGPTL3* have been associated with familial combined hypolipidemia, a condition characterized by significantly reduced levels of all major lipids in the blood, including triglycerides, LDL cholesterol, and HDL cholesterol [24]. Furthermore, ANGPTL3 inhibition has been found to enhance HDL-mediated reverse cholesterol transport in mice, which is considered an antiatherosclerotic property [25–27]. ANGPTL3 regulates HDL function through two key mechanisms: 1) inhibiting EL to preserve HDL composition [28] and 2) directly modulating HDL composition and metabolism as a component of HDL particles [29]. These dual actions of ANGPTL3 highlight its pivotal role in the regulation of HDL function, which has important implications for managing cardiometabolic disorders, especially diabetic dyslipidemia. ANGPTL3 inhibitors can increase the activity of EL, thereby increasing its phospholipid lipase activity and allowing it to hydrolyze HDL phospholipids, resulting in the formation of small HDLs (Fig. 1).

Potential role of ANGPTL3 in diabetic dyslipidemia

1) Diabetic dyslipidemia

In diabetic patients, dyslipidemia is characterized by elevated plasma triglyceride-rich lipoprotein (TRL) levels, reduced HDL cholesterol levels, and increased concentrations of small dense LDL (sdLDL) cholesterol particles, collectively known as diabetic dyslipidemia [3]. The main mechanisms underlying these lipid abnormalities in individuals with diabetes involve both hepatic overproduction and delayed clearance of TRLs [30]. Insulin resistance plays a crucial role by impairing the normal regulation of LPL activity, which is essential for the hydrolysis of triglycerides and the clearance of TRL remnants. Additionally, insulin resistance leads to increased lipolysis, resulting in elevated free fatty acids that the liver converts into VLDL, further contributing to hypertriglyceridemia [30]. These disturbances collectively contribute to the atherogenic lipid profile observed in diabetic patients, increasing their cardiovascular dis-

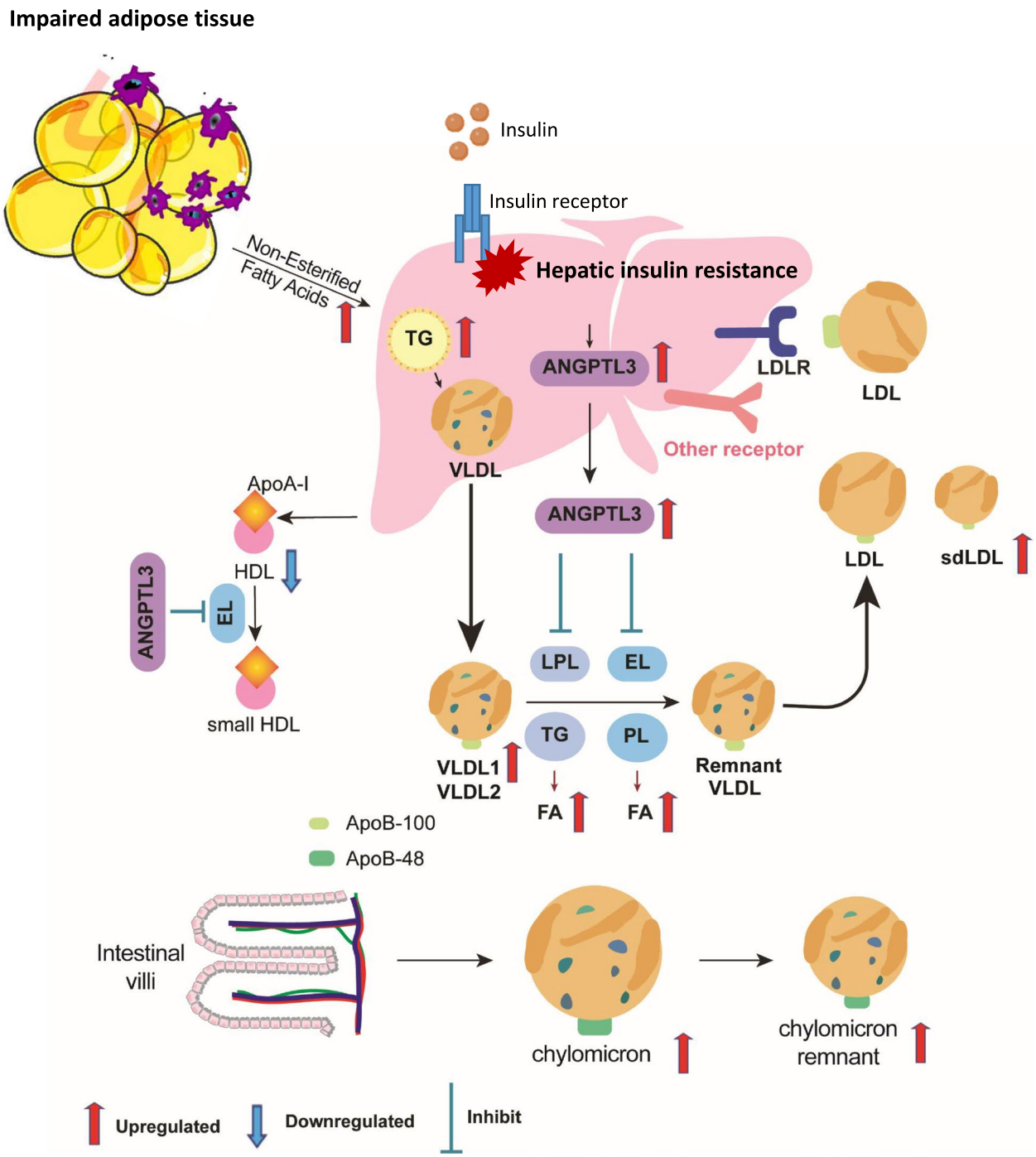

Fig. 1 Mechanisms leading to diabetic dyslipidemia. Type 2 diabetes mellitus (T2DM) is associated with decreased levels of high-density lipoprotein-cholesterol (HDL-C) and elevated levels of atherosclerosis-inducing lipids or lipoproteins, namely, very-low-density lipoprotein (VLDL), chylomicron (CM), and small dense low-density lipoprotein (sdLDL). Under insulin-resistant conditions, insulin is insufficient to suppress the lipolysis of stored triglycerides (TGs) in adipose tissues, leading to increased levels of circulatory FFAs, which can serve as substrates for hepatic VLDL assembly. In addition, insulin in the liver fails to suppress gluconeogenesis but activates lipogenesis and increases the secretion of hepatic VLDLs, especially VLDL1. The levels of ANGPTL3 are increased under insulin-resistant conditions, which inhibits the activity of LPL and delays the clearance of VLDL. In individuals with T2DM, HDL-C levels tend to decrease, whereas ANGPTL3 inhibitors can regulate HDL function by increasing the activity of EL to preserve HDL composition, resulting in the production of small HDL. Moreover, T2DM not only leads to an increased presence of chylomicrons but also reduces their catabolism, resulting in the accumulation of chylomicron remnants in the plasma. ANGPTL3: angiopoietin-like protein 3; LPL, lipoprotein lipase; EL, endothelial lipase

ease risk. Notably, individuals with insulin resistance, even in the prediabetic stage, can exhibit significant signs of diabetic dyslipidemia, highlighting the crucial role of insulin resistance in the development of this lipid disorder, independent of hyperglycemia [25, 26].

2) ANGPTL3 and insulin resistance
Insulin resistance is a condition in which the response of peripheral tissues to insulin is diminished, leading to hyperglycemia. It is fundamental in the pathogenesis of T2DM and often coexists with other metabolic disturbances, including dyslipidemia. The relationship between ANGPTL3 and insulin resistance is an emerging area of research. There are varying results regarding the impact of ANGPTL3 inhibition on insulin sensitivity. Some studies indicate that inhibiting ANGPTL3 can improve insulin sensitivity [31]; however, other studies have not consistently demonstrated significant improvements in insulin sensitivity with ANGPTL3 inhibition [32]. Elevated levels of ANGPTL3 have been observed in insulin-resistant states, such as obesity [33], suggesting that ANGPTL3 may exacerbate insulin resistance. ANGPTL3 deficiency has been associated with improved insulin sensitivity, highlighting its potential as a therapeutic target for managing insulin resistance and related metabolic disorders. Human genetics studies have shown that a complete lack of *ANGPTL3* in humans is associated with improved insulin sensitivity and decreased levels of free fatty acids in the serum [31, 34]. Compared with noncarriers, individuals with homozygous loss-of-function variants in ANGPTL3 had significantly lower plasma insulin levels and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) scores [31]. However, the study's limitations include a relatively small sample size, particularly among homozygous carriers, which may affect the generalizability of the findings. The cohort consisted of only 6–8 homozygotes and 5–8 noncarriers [31], which may not fully represent the broader population. This limited sample size could impact the statistical power and the ability to detect more subtle effects of *ANGPTL3* deficiency. T2DM was also absent among homozygotes with loss of function of *ANGPTL3* [34]. Preclinical data have shown that the inhibition of ANGPTL3 improves insulin resistance in diet-induced obese mice [35]. The increased insulin sensitivity with inactivation of ANGPTL3 may be explained by increased glucose uptake by white adipose tissues [36]. As discussed above, the leading cause of diabetic dyslipidemia is believed to be insulin resistance. Since the inhibition of ANGPTL3 may ameliorate insulin resistance, ANGPTL3 may be a promising target for treating dyslipidemia and hyperglycemia. However, in recent clinical trials, no improvement in glucose metabolism was observed with ANGPTL3 inhibition. An RCT revealed that patients with fasting triglycerides > 150 mg/dL (> 1.7 mmol/L), type 2 diabetes, and hepatic steatosis who were treated with vupanorsen, an antisense oligonucleotide targeting ANGPTL3, for 6 months did not show improvement in glucose metabolism. In addition, zodasiran, an RNAi therapeutic targeting ANGPTL3, caused a transient elevation in HbA1c levels in patients with preexisting diabetes who received the highest dose of zodasiran [32]. Although ANGPTL3 is associated with metabolic disorders, including T2DM [37, 38], no significant correlation was found between the levels of ANGPTL3 and glycated hemoglobin (HbA1c) [39, 40]. The inconsistent findings regarding the effects of ANGPTL3 inhibition on insulin resistance and glucose metabolism may arise from several factors. These include differences in sample size and population diversity, where small or nonrepresentative samples can lead to variability in results. Methodological variations, such as differences in study design, intervention types, and patient populations, can also contribute to differing outcomes. Additionally, the biological complexity of the role of ANGPTL3 in various tissues and metabolic conditions, along with compensatory mechanisms in the body, may result in diverse effects. The translational differences between preclinical animal studies and human studies further complicate the interpretation of the results. To address these discrepancies, researchers could implement several strategies. Conducting large-scale clinical trials with diverse populations would help validate the effects of ANGPTL3 inhibition. Longitudinal studies could provide insights into the long-term impacts on glucose metabolism. Mechanistic studies exploring the pathways influenced by ANGPTL3 in different tissues via omics approaches could elucidate differential effects. Biomarker analysis beyond traditional measures such as HbA1c could offer a more nuanced understanding of metabolic changes. Additionally, investigating combination therapies that include ANGPTL3 inhibition alongside other metabolic interventions might reveal synergistic or opposing effects. These comprehensive strategies can increase our understanding of the complex role of ANGPTL3 in metabolic processes and help resolve current inconsistencies in research findings.

3) ANGPTL3- and T2DM-related hypertriglyceridemia
In individuals with diabetes, key insulin-resistant organs include the liver, muscle, and adipose tissue.

The liver in diabetic patients often displays selective hepatic insulin resistance, where insulin fails to inhibit gluconeogenesis but instead promotes lipogenesis and enhances the production of hepatic VLDL. This dysregulation leads to a combination of hyperglycemia and hypertriglyceridemia [27]. In contrast, under healthy conditions, insulin was reported to induce a 66% reduction in the secretion of VLDL-TG and a 53% decrease in VLDL-apolipoprotein B (ApoB) production [28]. In insulin-resistant adipose tissues, insulin is insufficient to suppress the lipolysis of stored TG, especially during the postprandial period, thus leading to high free fatty acid flux. High levels of circulating free fatty acids released from fat cells can serve as substrates for hepatic VLDL assembly and subsequently increase VLDL secretion. VLDL can be classified into two forms: smaller cholesterol-rich VLDL2 and larger TAG-enriched VLDL1, which can be isolated by cumulative flotation gradient ultracentrifugation [41]. The latter is the precursor for the production of sdLDL in circulation. Insulin can suppress the secretion of VLDL1 without affecting the secretion of VLDL2; however, VLDL1 is elevated during insulin resistance [42, 43], which in turn increases the level of sdLDL [43]. It is believed that the elevated secretion of large VLDL1 particles in T2DM initiates a sequence of events that generate atherosclerotic remnants [43]. Inactivation of ANGPTL3 has been shown to significantly reduce the production of VLDL in cells, animal models, and humans [42, 44–46]. Research has revealed that inactivation of ANGPTL3 via the monoclonal antibody REGN1500 consistently reduces the secretion of the VLDL-triglyceride (VLDL-TG) in mice [45]. This reduction may be attributed to the decreased availability of free fatty acids, which are essential for VLDL-TG synthesis in the liver. Inactivation of ANGPTL3 in human hepatocytes decreased the secretion of TG-enriched VLDL1 upon insulin stimulation [42], indicating that inhibition of ANGPTL3 may also reduce all VLDL1-related atherosclerotic remnants in individuals with T2DM. A short-term clinical study revealed that treatment with an antisense oligonucleotide targeting hepatic ANGPTL3 mRNA for six months resulted in significant reductions in TG and remnant cholesterol in patients with T2DM [47].

In addition to the excessive production of VLDL by the liver, the reduced clearance of VLDL and CM also plays a significant role in diabetic dyslipidemia. VLDL originates from the liver, whereas CM is secreted by the intestine. The key process in clearing VLDL/CM involves the hydrolysis of triglycerides by LPL, which is anchored to the endothelial cell surface. Studies have indicated a decrease in LPL activity in individuals with T2DM [29, 30], potentially leading to impaired VLDL/CM clearance. The interplay of insulin resistance, elevated FFAs, and altered lipoprotein metabolism plays a crucial role in the development of dyslipidemia in diabetic patients (Fig. 1). In individuals with diabetes or diabetic animal models, elevated levels of ANGPTL3 have been observed [11, 48], indicating a potential role for ANGPTL3 in diabetic dyslipidemia. Inhibition of ANGPTL3 can increase LPL activity, thereby increasing the hydrolysis of triglycerides in VLDL [49]. This process reduces the plasma levels of VLDRs by promoting their clearance. Consequently, ANGPTL3 inhibitors can potentially decrease VLDL production and accumulation [35, 45], resulting in hypertriglyceridemia and associated dyslipidemia in diabetic patients. This mechanism highlights the therapeutic potential of ANGPTL3 inhibitors in managing lipid disorders in patients with T2DM by modulating LPL activity and reducing VLDL levels.

4) ANGPTL3 and impaired HDL function in T2DM

HDL is responsible for antiatherogenic activities such as cholesterol efflux and antioxidative and anti-inflammatory functions [27, 50]. However, in T2DM, these functions are impaired due to structural modifications such as glycation and oxidation, which alter the ability of HDL to perform effectively [51]. Metabolic abnormalities, including hyperglycemia and insulin resistance, lead to increased triglyceride levels and changes in HDL composition, resulting in smaller, denser particles that are rapidly broken down [51]. Additionally, the chronic inflammatory state in diabetes transforms HDL into a proinflammatory particle, further diminishing its protective role [51]. Changes in enzymatic activity, particularly those involving cholesteryl ester transfer protein (CETP) and hepatic lipase (HL), exacerbate these issues by destabilizing HDL particles. Collectively, these alterations underscore the importance of addressing HDL dysfunction to manage cardiovascular complications in diabetic patients. Regardless of the lowering effect on HDL cholesterol, the inhibition of ANGPTL3 improves HDL-mediated reverse cholesterol transport in mice [25]. Therefore, ANGPTL3 inhibitors may also improve the impaired cholesterol efflux capacity of HDL in patients with T2DM. However, a recent study revealed that ANGPTL3 binds to HDL and is positively associated with cholesterol efflux capacity in nondiabetic individuals but not in T2DM

patients [29]. In mouse models, they reported that ANGPTL3 overexpression improved HDL functions, whereas ANGPTL3 knockdown impaired HDL functions [29]. A recent study indicated that ANGPTL3 may not necessarily affect the anti-atherosclerotic functions of HDL [52]. How ANGPTL3 inhibitors affect HDL function in patients with T2DM still requires further investigation.

Inhibition of ANGPTL3 in humans

Preclinical and human genetic studies indicate that the inhibition of ANGPTL3 is a promising therapeutic strategy for reducing ASCVD risk. Several approaches have been applied to pharmacologically inactivate ANGPTL3, including monoclonal antibodies [6], antisense oligonucleotides (ASOs) [35], mRNA interference (mRNAis) [32, 53], and vaccine-based approaches [54]. ARO-ANG3 represents a cutting-edge platform that uses GalNAc3-conjugated small interfering RNA (siRNA) to effectively and persistently suppress the mRNA transcription of the ANGPTL3 gene within hepatic cells [53]. The relevant clinical trials are summarized in Table 1.

The fully human monoclonal antibody against ANGPTL3 evinacumab has shown a robust lipid-lowering effect in healthy individuals [6]. In phase II and III studies, a reduction in LDL cholesterol of almost 50% was observed in patients with homozygous familial hypercholesterolemia (HoFH) receiving evinacumab versus placebo [55, 56], in which almost 50% of patients achieved LDL cholesterol < 100 mg/dL (< 2.6 mmol/L) [56]. Importantly, evinacumab provides robust LDL cholesterol reduction (−43.4%), even in HoFH patients with no residual LDLR function [56], indicating that unlike PCSK9 inhibitors and statins, the inhibitory effect of ANGPTL3 is independent of LDL receptor function. Given the pronounced lipid-lowering effect of ANGPTL3 inactivation in healthy individuals and HoFH patients, it is likely to have good efficacy in patients with T2DM.

Potential side effects and limitations of targeting ANGPTL3

ANGPTL3 has emerged as a significant target for therapy because of its ability to significantly reduce circulating lipoproteins, resulting in cardioprotective effects. However, the utilization of ANGPTL3-targeting therapy is accompanied by potential side effects and limitations that require careful consideration. Potential side effects may include hepatotoxicity, injection-related adverse reactions, hepatic fat accumulation, and high medication costs [47, 59]. Furthermore, targeting ANGPTL3 may result in uncertain long-term safety implications, underscoring the importance of balancing treatment benefits with potential risks in clinical decision-making. Recently, a study revealed that inhibiting hepatic ANGPTL3 synthesis with vupanorsen resulted in dose-dependent increases in liver steatosis [59]. In addition, the ANGPTL family plays pivotal roles in angiogenesis [60, 61]. Angiogenesis is critical for early repair after myocardial infarction (MI); if ANGPTL3 is essential for angiogenesis post-MI, then ANGPTL3 inhibition as a therapeutic strategy will be harmful for angiogenesis and cardiac cell repair after MI [62]. However, genetic research indicates that individuals with lifelong genetic ANGPTL3 deficiency do not exhibit significant alterations in the distribution of hepatic and extrahepatic fat [63]. The long-term genetic inhibition of ANGPTL3 seems to be safe and well tolerated, implying a favorable safety profile for pharmacological interventions targeting ANGPTL3 activity [63]. Furthermore, ANGPTL3 may have certain effects on adipose tissue and metabolism, and it remains unclear whether the inhibition of ANGPTL3 affects adipose tissue and other metabolic functions [64, 65]. In summary, while the targeting of ANGPTL3 shows promise in managing specific diseases by regulating lipid metabolism, researchers should conduct a thorough assessment of the associated side effects and limitations to make well-informed decisions regarding the use of ANGPTL3-targeting therapy in clinical practice.

Conclusions and future perspectives

Diabetic dyslipidemia plays a critical role in the development of CVD. Emerging studies have shown that current lipid-lowering therapy substantially reduces the risk of CVD in individuals with or at high risk of T2DM, but a high degree of residual risk remains in statin-treated patients with T2DM [66]. New lipid-lowering therapies are urgently needed to reduce the residual risk of CVD [67]. The development of diabetic dyslipidemia is driven by insulin resistance. Inactivation of ANGPTL3 may improve insulin resistance. Thus, it may improve the overall spectrum of dyslipidemia in patients with T2DM. The lipid abnormalities in T2DM include elevated TG-rich lipoproteins (VLDL/CM and their remnants), increased sdLDL particles, decreased HDL cholesterol, and impaired HDL function. Inhibition of ANGPTL3 can significantly reduce TG-rich lipoprotein and LDL cholesterol and improve HDL-mediated reverse cholesterol transport in mice [6, 25, 56]. Therefore, ANGPTL3 may be a promising therapeutic target for the treatment of dyslipidemia in T2DM patients and may offer new therapeutic opportunities in the future. There is no substantial evidence to support that ANGPTL3 processes are related to insulin or that ANGPTL3 changes with insulin resistance. Owing to the extremely limited literature

Table 1 Clinical trials of ANGPTL3 inhibitors

Trial (Ref. #)	ANGPTL3 inhibitors	Phase	Participants, N	Description of Participants	Duration	Glucose metabolism	Maximal LDL-C Reduction	Maximal TG Reduction
Gaudet et al. 2017 [55]	Avinacumab	Phase 1	9	homozygous familial hypercholesterolemia	26-week	Not mentioned	49%	47%
Dewey et al. 2017 [6]	Avinacumab	Phase 1	83	mild to moderate dyslipidemia (fasting TG levels 150–450 mg/dL or LDL-C ≥ 100 mg/dL)	21 days	Not mentioned	23%	76%
Raal et al.2020 [56]	Avinacumab	Phase 3	65	homozygous familial hypercholesterolemia (LDL-C ≥ 70 mg per deciliter)	24-week	Not mentioned	47%	55.0%
Rosenson et al.2020 [57]	Avinacumab	Phase 2	272	refractory hypercholesterolemia	16-week	Not mentioned	56%	62%
Ahmad et al. 2019 [58]	Avinacumab	Phase 1	83	hypertriglyceridemia (triglycerides > 150 but ≤ 450 mg/dL and low-density, lipoprotein cholesterol ≥ 100 mg/dL)	126 days	Not mentioned	21%	88%
Ahmad et al.2019 [58]	Avinacumab	Phase 1	56	hypertriglyceridemia (triglycerides > 150 but ≤ 450 mg/dL and low-density, lipoprotein cholesterol ≥ 100 mg/dL)	6 months	Not mentioned	25%	88%
Graham et al. 2017 [35]	Antisense oligonucleotides	Phase 1	44	LDL-C ≥ 70 mg/dL, fasting TG ≥ 90 mg/dL	15–43 days	Not mentioned	33%	63%
Gaudet et al. 2020 [47]	Antisense oligonucleotides	Phase 2a	105	Fasting TG > 150 mg/dL, T2DM, and hepatic steatosis	25–27 weeks	No improvement	12%	44%
Bergmark et al. 2022 [59]	Antisense oligonucleotides	Phase 2b	286	Non–HDL-C ≥ 100 mg/dL and triglycerides 150 to 500 mg/dL	24 weeks	Not mentioned	17%	59%
Watts ET AL. 2023 [53]	RNA interference therapy	Phase 1	61	healthy volunteers	85 days	Not mentioned	27%	54%
Rosenson et al. [32]	RNA interference (RNAi) therapy	Phase 2b	204	mixed hyperlipidemia	24 weeks	Elevated glycated hemoglobin levels	63%	20%

supporting these associations, we did not provide a figure illustrating the potential relationship between ANGPTL3 levels and insulin resistance. We believe that in the future, more research will focus on the role and mechanism of action of NAGPTL3 in diabetic dyslipidemia, further elucidating their relationship.

Abbreviations

ANGPTL3	Angiopoietin-like 3
ApoC-III	Apolipoprotein C-III
CETP	Cholesteryl ester transfer protein
CM	Chylomicron
CVD	Cardiovascular disease
T2DM	Type 2 diabetes mellitus
HDL	High-density lipoprotein
IDL	Intermediate density lipoprotein
HoFH	Homozygous familial hypercholesterolemia
LDL	Low-density lipoprotein
LPL	Lipoprotein lipase
LXR	Liver-X receptor
MACE	Major adverse cardiac events
PCSK9	Proprotein convertase subtilisin/kexin type 9
sdLDL	Small dense low-density lipoprotein
VLDL	Very-low-density lipoprotein

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None.

Authors' contributions
Z Fang, F Luo, and P Chen conceived the study; J Chen wrote the manuscript; J Chen, Q Luo, Y Yi and J Wang collected and read the literature; and F Luo and Z Fang read through and corrected the manuscript. All the authors have read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All the authors agreed to publication.

Competing interests
The authors declare no competing interests.

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