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Adiponectin alleviates high glucose - induced retinal angiogenesis by inhibiting NLRP3 inflammasome

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脂联素通过抑制 NLRP3 炎症小体减轻高糖诱导的视网膜血管生成

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摘要

目的:探讨脂联素(ADPN)对高糖(HG)环境下人视网膜微血管内皮细胞(hRMECs)血管生成的影响,以及 NOD 样受体家族含 pyrin 结构域蛋白 3(NLRP3)炎症小体的作用。

方法:将人视网膜微血管内皮细胞分为 6 组:对照组(不做处理);高糖组:用 D-葡萄糖孵育;脂联素组:先用脂联素预处理,再用 D-葡萄糖孵育;CY-09 组:先用 NLRP3 抑制剂 CY-09 预处理,再用 D-葡萄糖孵育;尼日利亚菌素组:先用 NLRP3 激活剂尼日利亚菌素预处理,再用 D-葡萄糖孵育;尼日利亚菌素+脂联素组:先后用尼日利亚菌素和脂联素预处理,再用 D-葡萄糖孵育。采用蛋白质印迹法(Western blot)检测 NLRP3 水平;细胞划痕实验检测人视网膜微血管内皮细胞迁移能力;基质胶(Matrigel)实验检测细胞管样形成能力。

结果:高糖环境下人视网膜微血管内皮细胞中 NLRP3 表达显著升高($P<0.01$),而脂联素和 CY-09 可降低升高的 NLRP3(与高糖组比较,均 $P<0.05$)。尼日利亚菌素可显著升高 NLRP3 水平(与对照组比较,$P<0.01$),而脂联素可逆转该作用(与尼日利亚菌素组比较,$P=0.032$)。高糖组细胞迁移能力增强($P<0.001$),总主干段长度和网格数增加($P<0.001$);脂联素组和 CY-09 组上述指标均降低(与高糖组比较,均 $P<0.01$)。尼日利亚菌素可显著提高高糖环境下细胞迁移及管样形成能力(总主干段长度、网格数)($P=0.003$),而脂联素可逆转该变化。

结论:脂联素可改善高糖条件下人视网膜微血管内皮细胞的迁移及血管生成。

关键词:脂联素;视网膜微血管内皮细胞;血管新生;高糖;NLRP3 炎症小体

Abstract

• AIM: To explore the effect of adiponectin (ADPN) on angiogenesis of human retinal microvascular endothelial cells (hRMECs) in high glucose (HG) environment and role of NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome.

• METHODS: The hRMECs were divided into six groups, including control group (without treatment), HG group: incubated with D-glucose, ADPN group: pretreatment with ADPN and then incubated with D-glucose, CY-09 group: pretreatment with CY-09 (an NLRP3 inhibitor) and then incubated with D-glucose, Nigericin group: pretreatment with nigericin (an NLRP3 activator) and then incubated with D-glucose, Nigericin + ADPN group: pretreatment with nigericin and ADPN and then incubated with D-glucose. NLRP3 level was detected using Western blot analysis. hRMECs migration was measured using scratch wound healing assay. The tube formation of hRMECs was detected using Matrigel.

• RESULTS: The NLRP3 expression in hRMECs cultured in an HG environment was significantly increased ($P<0.01$), while ADPN and CY-09 reduced the elevated NLRP3 (both $P<0.05$ *vs* HG group). Nigericin significantly increased NLRP3 levels ($P<0.01$ *vs* control group) which was reversed by ADPN ($P=0.032$ *vs* Nigericin group). hRMECs migration ability ($P<0.001$), and total master segments length and number of meshes increased in HG group ($P<0.001$) while decreased in ADPN and CY-09 groups (all $P<0.01$ *vs* HG group). The hRMECs migration ability and tube formation (total master segments length and number of meshes) in HG environment were significantly increased by nigericin ($P=0.003$), while ADPN inversed the change.

• CONCLUSION: ADPN alleviates the migration and angiogenesis of hRMECs under HG conditions.

• KEYWORDS: adiponectin; retinal microvascular endothelial cells; angiogenesis; high glucose; NLRP3 inflammasome
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INTRODUCTION

Diabetic retinopathy (DR) is one of the most common microvascular complications of diabetes. Diabetes leads to retinal microvascular leakage and occlusion, resulting in a series of fundus diseases, such as microangioma, hard exudation, cotton wool spots, neovascularization, macular edema and even retinal detachment, which result in visual impairment. The International Diabetes Federation (IDF) Diabetes Atlas (2021) reports that 10.5% of the adult population (20-79 y) has diabetes. Among individuals with diabetes, more than one fifth suffered from DR[1]. The prevention and treatment of DR had attracted the attention of researchers in recent years.

NOD-like receptor family pyrin domain containing 3 inflammasome (NLRP3) was considered a contributing factor in pathogenesis of DR[2-4]. High glucose (HG) significantly increased the expression of NLRP3 in human retinal microvascular endothelial cells (hRMEC)[5]. In type 1 diabetic mice models, inhibition of NLRP3 caused a decrease of caspase 1, vascular endothelial growth factor (VEGF), and vascular permeability[5].

Adiponectin (ADPN) is an endogenous bioactive peptide or protein secreted by adipocytes. It can improve insulin resistance[6]. ADPN levels can predict the development of type 2 diabetes[7-8] and DR severity[9]. However, the mechanism of ADPN role in the formation of DR needs further study. In recent years, some studies have found that ADPN alleviated the progression of some disease by inhibiting NLRP3 such as glomerulopathy[10], oral submucosal fibrosis[11], and Alzheimer's disease[12]. Our previous research found that ADPN pretreatment can protect hRMEC from damage in HG environments[13]. Therefore, this study will explore the role of ADPN in the activation of NLRP3 in hRMEC under HG environment.

MATERIALS AND METHODS

Cell Culture and Grouping hRMECs (Shanghai Zhong Qiao Xin Zhou Biotechnology Co., Ltd., China) were cultured in M199 (Procell, China) complete medium (supplement with 10% fetal bovine serum and 1% penicillin/streptomycin) and incubated at 37 ℃ in humidified incubator with 5% CO_2.

The hRMECs were divided into six groups, including control group (without treatment), HG group: incubated with 25 mmol/L D-glucose for 24 h, ADPN group: pretreatment with 10 μg/mL ADPN (GenScript, China) for 2 h and then incubated with 25 mmol/L D-glucose for 24 h[13], NLRP3 inhibiting group (CY-09 group): pretreatment with 10 mmol/L CY-09 (an NLRP3 inhibitor; Selleckchem, USA) for 2 h and then incubated with 25 mmol/L D-glucose for 24 h, NLRP3 activation group (Nigericin group): pretreatment with 10 μmol/L nigericin sodium salt (an NLRP3 activator; Selleckchem, USA) for 2 h and then incubated with 25 mmol/L D-glucose for 24 h, Nigericin+ADPN group: pretreatment with 10 μmol/L nigericin sodium salt and 10 μg/mL ADPN for 2h and then incubated with 25 mmol/L D-glucose for 24 h.

Scratch Wound Healing Assay hRMECs migration was measured using scratch wound healing assay. After 24 h of different treatment, the cells in each group were digested using 0.25% trypsin (Procell, China) and seeded on a 6-well plate. When the cell reached about 90%, the pipette tip was perpendicular to the plate and a straight line was drawn. The cells were rinsed three times using phosphate buffer saline (PBS) to remove the detached cells and incubated in at 37 ℃ for 24 h. The distance between the scratch boundaries of cells before and after processing was measured using Photoshop software. Relative migration rates = (distance at 0 h-distance at 24 h)/distance at 0 h×100%.

Tube Formation Assay The tube formation of hRMECs was detected using Matrigel. Matrigel thawed overnight at 4 ℃ and pre cool the 24-well plate and pipette tips. Dilute the Matrigel with Dulbecco's modified Eagle's medium (DMEM) medium 1∶1 and add to 24-well plate with a volume of 200 μL per well. Remove bubbles by low-speed sterile centrifugation and incubate at 37 ℃ for 30 min. hRMECs suspensions were prepared using serum-free medium, and then inoculated into 24-well plates preplaced with Matrigel with 1×10^5 cells per well. The cells were cultured overnight at 37 ℃, 5% CO_2. Image J software was used to count the total master segments length and number of meshes.

Western Blot Analysis NLRP3 level was detected using Western blot analysis. After 24 h of different treatments, the hRMECs in each group were added radio-immunoprecipitation assay (RIPA) lysis solution containing protease inhibitors and centrifuged at 12 000 r/min at 4 ℃ for 5 min. The protein concentration was measured using bicinchoninic acid (BCA) method (Beyotime Biotech Inc, China). The supernatant was boiled for 10 min with 5× sodium dodecyl sulfate (SDS) sample buffer and separated using 12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). The gel-separated protein was transferred to polyvinylidene fluoride (PVDF) membrane (0.45 μm; Millipore, USA). The PVDF membranes were incubated with Tris buffered saline with Tween-20 (TBST) containing 5% non-fat milk powder at room temperature for 2 h and then incubated with rabbit anti-NLRP3 (ab263899, 1∶1000, Abcam, USA) and rabbit anti-glyceraldehyde-3-phosphate dehydrogenase (GAPDH, AB-P-R001, 1∶1000, Goodhere Biotech, Hangzhou, China) at 4 ℃ overnight, followed by soaking

with horseradish peroxidase-labeled anti-rabbit secondary antibody (BA1054, 1∶10000, Boster Biological Technology Co., Ltd., Wuhan, China) at room temperature for 2 h. The protein bands were visualized with enhanced chemiluminescence (ECL). Grayscale values were analysis with Image J software.

Statistical Analysis SPSS 25.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for data analysis. All experiments were repeated at least three times. Continuous data were tested by Shapiro-Wilktest and homogeneity of variance and presented as mean±standard deviation (SD). Univariate analysis of variance was used for comparison of all groups, and least significant difference(LSD)-t test was used for multiple comparisons. $P<0.05$ was considered statistical significance.

RESULTS

ADPN on NLRP3 Expression Levels in hRMECs Cultured with HG There were significant differences of NLRP3 expression levels in hRMECs among the six groups ($F=11.02$, $P<0.001$; Figure 1). The NLRP3 expression in hRMECs cultured in HG environment was significantly increased ($P<0.01$), while ADPN reduced the elevated NLRP3 ($P=0.030$ *vs* HG group). NLRP3 inhibitor, CY-09, had the same effect on hRMECs ($P=0.005$ *vs* HG group). nigericin (an NLRP3 activator) significantly increased NLRP3 levels ($P<0.01$ *vs* control group) which was reversed by ADPN ($P=0.032$ *vs* Nigericin group).

ADPN on hRMECs Migration Cultured with HG Scratch wound healing assay showed a significant difference in hRMECs migration rates of the six groups ($F=70.45$, $P<0.001$; Figure 2). HG environment significantly enhanced hRMECs migration ability ($P<0.01$). ADPN and CY-09 (an NLRP3 inhibitor) weakened the enhancing migration ability which obtained in HG environment (both $P<0.01$ *vs* HG group). The hRMECs migration ability in HG environment were significantly increased by nigericin (an NLRP3 activator; $P=0.003$), while ADPN decreased this ability ($P<0.01$).

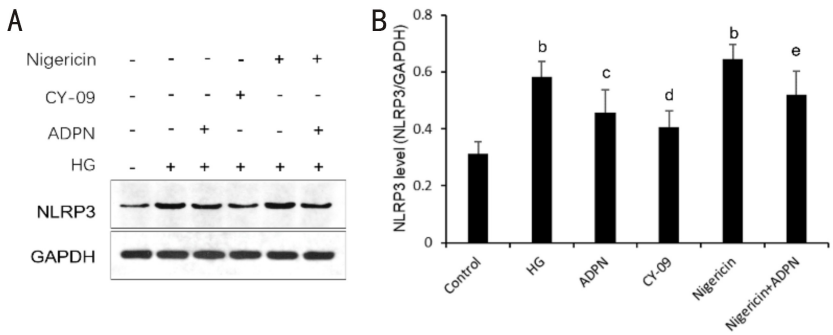

Figure 1 Effect of ADPN on NLRP3 expression levels in hRMECs cultured with HG NLRP3 expression in HG group was significantly increased, while ADPN reduced the elevated NLRP3 NLRP3 inhibitor, CY-09, also reduced the elevated NLRP3. Nigericin (an NLRP3 activator) significantly increased NLRP3 levels which was reversed by ADPN. A: NLRP3 expression levels in hRMECs using Western blot; B: Semiquantitative of NLRP3 expression. $^{b}P<0.01$ *vs* control group; $^{c}P<0.05$, $^{d}P<0.01$ *vs* HG group; $^{e}P<0.05$ *vs* Nigericin group. Error bar was standard deviation; $n=3$ independent experiments. HG: High glucose; ADPN: Adiponectin; NLRP3: NOD-like receptor family pyrin domain containing 3; hRMECs: Human retinal microvascular endothelial cells; GAPDH: Glyceraldehyde-3-phosphate dehydrogenase.

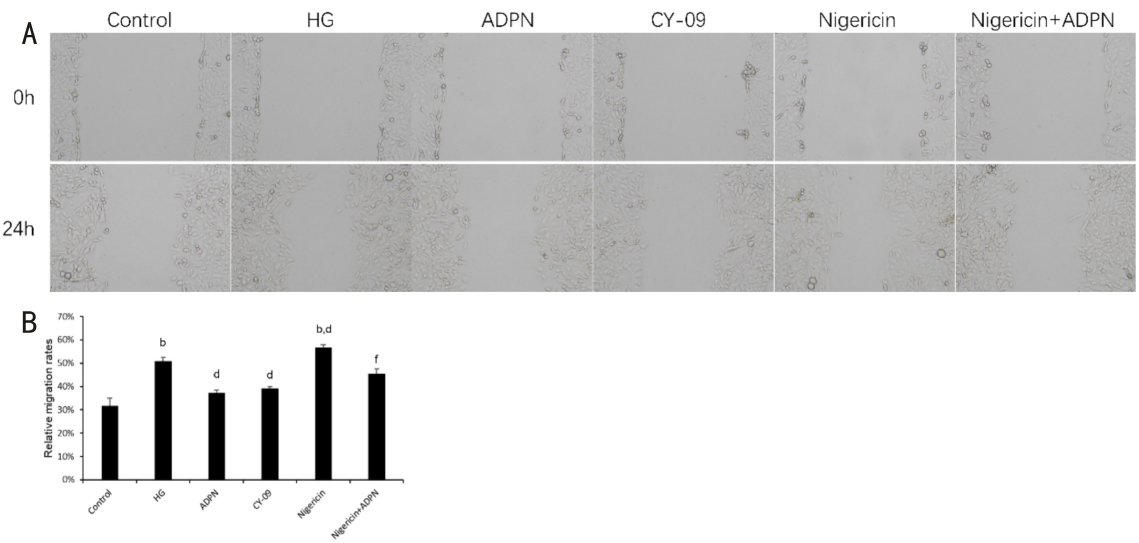

Figure 2 Effect of ADPN on hRMECs migration cultured with HG A: Scratch wound healing assay showed a significant difference in hRMECs migration rates of the six groups; B: Relative migration rates of six groups. Relative migration rates=(distance at 0 h-distance at 24 h)/distance at 0 h×100%. $^{b}P<0.01$ *vs* control group; $^{d}P<0.01$ *vs* HG group; $^{f}P<0.01$ *vs* Nigericin group. Error bar was standard deviation; $n=3$ independent experiments. HG: High glucose; ADPN: Adiponectin; hRMECs: Human retinal microvascular endothelial cells.

ADPN on Tube Formation of hRMECs Cultured with HG

According to tube formation assay, there were significant differences in total master segments length ($F=37.26$, $P<0.001$) and number of meshes ($F=37.41$, $P<0.001$) in six groups (Figure 3). Under HG culture conditions, total master segments length and number of meshes significantly increased (both $P<0.001$). In ADPN and CY-09 groups, total master segments length and number of meshes significantly decreased compared to HG group (all $P<0.001$). In Nigericin group, total master segments length increased comparing to control group ($P<0.001$) but similar to HG group ($P=0.54$); number of meshes were more than both control and HG groups (both $P<0.01$). In Nigericin + ADPN group, total master segments length decreased comparing to Nigericin group, but there was no statistically significant difference ($P=0.062$); while number of meshes were significantly less than Nigericin group ($P<0.001$).

DISCUSSION

ADPN is a 244 amino acid endogenous protein primarily secreted by adipocytes and regulates fatty acid oxidation and glucosemetabolism[14]. *In vivo* studies have found that ADPN levels can predict the development of type 2 diabetes and coronary heart disease[6-7], and show the potential of anti-diabetes, anti-atherosclerosis and anti-inflammation in clinical trials[8-11]. Human ADPN is encoded by *Adipo Q* gene located on chromosome 3q27. Researchers have found that there are susceptible genes of type 2 diabetes and metabolic syndrome also located in 3q27[15-16]. ADPN concentration in fasting plasma is significantly correlated with insulin sensitivity[17]. Ag and Chaitanya Kumar[18] found that the ADPN level in type 2 diabetic patients was lower than healthy control. ADPN in the blood circulation is not only secreted by adipocytes, but also by skeletal muscles, endothelial cells, and myocardial cells[14]. The serum ADPN level was significantly decreased in type 2 diabetes patients, especially in type 2 diabetes patients with macrovascular complications[19] and also related to the aging of renal cells in diabetes[20].

Our previous study results showed that the ADPN was involved in autophagy and retinal angiogenesis[21]. We found that ADPN had a protective effect on HG-induced RF/6A cell injury and prevented cell angiogenesis by inhibiting the autophagy. Yilmaz *et al*'s[22] study including 74 patients with type 2 diabetes and 54 age and body mass index-matched healthy controls showed that ADPN concentrations in plasma were significantly lower in proliferative (mean 3.16 μg/mL) or non-proliferative (mean 3.97 μg/mL) DR patients than in those healthy controls (mean 6.30 μg/mL) and ADPN concentration was associated with the severity of DR. Therefore, ADPN may be a new target for the treatment of microangiopathy in DR. We used 25 mmol/L D-glucose cultured hRMECs to simulate HG environment. The results showed that hRMECs migration ability, total master segments length, and number of meshes were significant increased than control, while these were decreased in the ADPN group. These results indicated that ADPN is involved in the migration and angiogenesis of hRMECs under HG conditions.

Inflammasomes are multi protein complexes assembled by cytoplasmic pattern recognition receptors (PRRs) and are an important component of the innate immune system. Inflammasomes can recognize pathogen-associated molecular patterns (PAMPs) or host derived damage-associated molecular patterns (DAMPs), recruit and activate pro-inflammatory protease Caspase-1. Activated Caspase-1 cleaves the precursors of interleukin (IL)-1β and IL-18, producing corresponding mature cytokines. NLRP3 inflammasome, as an important component of innate immunity, plays an important role in a variety of disease, including type 2 diabetes, Alzheimer's disease, atherosclerosis, as well as diabetic retinopathy[23-25]. In

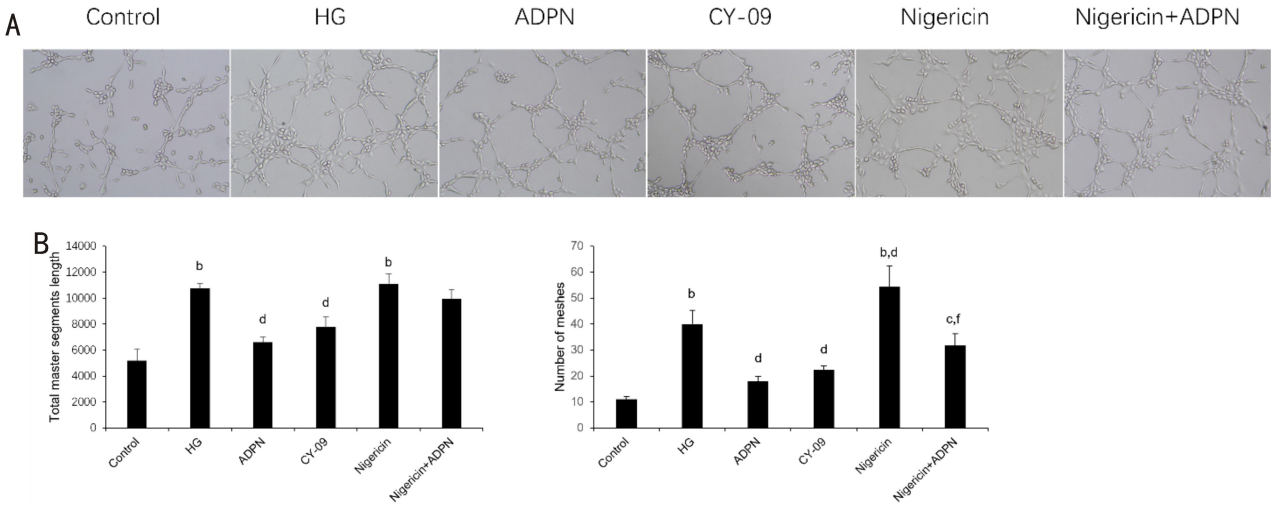

Figure 3 ADPN on tube formation of hRMECs cultured with HG A: Tube formation assay showed a significant difference of tube formation of hRMECs in six groups; B: Total master segments length and number of meshes of six groups. $^{b}P<0.01$ *vs* control group; $^{c}P<0.05$, $^{d}P<0.01$ *vs* HG group; $^{f}P<0.01$ *vs* Nigericin group. Error bar was standard deviation; $n=3$ independent experiments. HG: High glucose; ADPN: Adiponectin; hRMECs: Human retinal microvascular endothelial cells.

streptozocin (STZ)-induced diabetic rats model, *NLRP3*-targeted shRNA decreased VEGF levels in retina, and over-expression of NLRP3 increased VEGF level in retinal endothelial cells[26]. We used inhibitor (CY-09) and activator (nigericin) of NLRP3 inflammasome to pre-treat hRMECs separately. CY-09 significantly inhibited cell migration and angiogenesis of hRMECs in HG environments and the effect of Nigerian was exactly the opposite. Therefore, HG may regulate hRMECs migration and angiogenesis through NLRP3 inflammasomes.

Dong *et al*[27] found that a high-fat diet for 12 wk resulted in more hepatic steatosis and elevated NLRP3 inflammasome in ADPN knockout mice compared to the wild-type group. In astrocytes of oxygen-glucose deprivation and reintroduction model *in vitro*, ADPN peptide suppressed the activation of the NLRP3 inflammasome[28]. ADPN reduced the secretion of IL-18 and IL-1β by inhibiting the activation of NLRP3 inflammasomes in monocytic THP-1 cells[29]. Recently, Ng *et al*[12] explored the possibility of ADPN gene therapy for Alzheimer's disease. They transfected adeno-associated virus carrying ADPN gene segments into the Alzheimer's disease model mice's liver and generated low-molecular-weight trimeric ADPN. The level of ADPN in plasma and cerebral cortex increased. Pretreated with ADPN also reduced IL-18 and IL-1β by suppressing NLRP3-inflammasome activation in microglia model of Alzheimer's disease. These results indicated that ADPN can pass the blood-brain barrier and can be used as a gene therapy method[12]. Therefore, we speculated that ADPN may pass the blood-retinal barrier and act on NLRP3 inflammasomes to regulate angiogenesis of hRMECs in HG environment. In our study, nigericin significantly increased NLRP3 levels which was reversed by ADPN. The hRMECs migration ability in HG environment were significantly increased by nigericin, while ADPN decreased this ability. In Nigericin+ADPN group, total master segments length decreased comparing to Nigericin group, but there was no statistically significant difference ($P=0.062$); while number of meshes were significantly less than Nigericin group ($P<0.001$). These results indicated that ADPN exerted anti vascular effects by inhibiting the activation of NLRP3 inflammasomes.

In conclusion, ADPN alleviates the migration and angiogenesis of hRMECs under HG conditions. Its alleviative effect may be achieved by inhibiting the activation of NLRP3 inflammasomes. These results may provide new ideas and approaches for the clinical treatment of retinal neovascularization in DR.

Conflicts of Interest: Zhang Y, None; Wang XD, None; Zhang YX, None; Yao GM, None.

REFERENCES

[1] Teo ZL, Tham YC, Yu M, et al. Global prevalence of diabetic retinopathy and projection of burden through 2045 systematic review and meta-analysis. Ophthalmology, 2021,128(11):1580-1591.

[2] Sepehri Z, Kiani Z, Afshari M, et al. Inflammasomes and type 2 diabetes: an updated systematic review. Immunol Lett, 2017, 192: 97-103.

[3] Raman KS, Matsubara JA. Dysregulation of the NLRP3 inflammasome in diabetic retinopathy and potential therapeutic targets. Ocul Immunol Inflamm, 2022,30(2):470-478.

[4] Zheng XQ, Wan J, Tan G. The mechanisms of NLRP3 inflammasome/pyroptosis activation and their role in diabetic retinopathy. Front Immunol, 2023,14:1151185.

[5] Shi Y, Chen HM, Liu AH, et al. Fenofibrate mitigates the dysfunction of high glucose-driven human retinal microvascular endothelial cells by suppressing NLRP3 inflammasome. Int J Ophthalmol, 2025,18(5):792-801.

[6] Yadav A, Kataria MA, Saini V, et al. Role of leptin and adiponectin in insulin resistance. Clin Chim Acta, 2013,417:80-84.

[7] Li SS, Shin HJ, Ding EL, et al. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA, 2009, 302(2):179.

[8] Habib SS, Al-Khlaiwi T, Al-Khliwi H, et al. Adiponectin and TNFα in relation to glucometabolic control in patients with type 2 diabetes mellitus. J Family Med Prim Care, 2024,13(7):2741-2745.

[9] Min F, Li ZR, Li YL, et al. The contribution of adiponectin to diabetic retinopathy progression: association with the AGEs-RAGE pathway. Heliyon, 2024,10(17):e36111.

[10] Xu XH, Huang XL, Zhang LX, et al. Adiponectin protects obesity-related glomerulopathy by inhibiting ROS/NF-κB/NLRP3 inflammation pathway. BMC Nephrol, 2021,22(1):218.

[11] Zeng YY, Luo MS, Yao ZL, et al. Adiponectin inhibits ROS/NLRP3 inflammatory pathway through FOXO3A to ameliorate oral submucosal fibrosis. Odontology, 2024,112(3):811-825.

[12] Ng RC, Jian M, Ma OK, et al. Liver-specific adiponectin gene therapy suppresses microglial NLRP3-inflammasome activation for treating Alzheimer's disease. J Neuroinflammation, 2024,21(1):77.

[13] Yao G, Li R, Deng, Y, et al. Protective effect of adiponectin pretreatment against high glucose-induced human retinal microvascular endothelial cell damage. J Shanxi Med Univ 2022;53(9):1157-1161.

[14] Achari AE, Jain SK. Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction. Int J Mol Sci, 2017,18(6):1321.

[15] Mori Y, Otabe S, Dina C, et al. Genome-wide search for type 2 diabetes in Japanese affected sib-pairs confirms susceptibility genes on 3q, 15q, and 20q and identifies two new candidate Loci on 7p and 11p. Diabetes, 2002,51(4):1247-1255.

[16] Kissebah AH, Sonnenberg GE, Myklebust J, et al. Quantitative trait loci on chromosomes 3 and 17 influence phenotypes of the metabolic syndrome. Proc Natl Acad Sci U S A, 2000,97(26):14478-14483.

[17] Putz DM, Goldner WS, Bar RS, et al. Adiponectin and C-reactive protein in obesity, type 2 diabetes, andmonodrug therapy. Metabolism, 2004,53(11):1454-1461.

[18] Ag P, Chaitanya Kumar S. Evaluation of adiponectin levels in patients with diabetes mellitus. J Assoc Physicians India. 2022,70(4): 11-12.

[19] Su N, Zhao N, Wang G, et al. The effects of adiponectin and adiponectin receptor 1 levels on macrovascular complications among patients with type 2 diabetes mellitus. Cell Physiol Biochem. 2019, 52(2):225-231.

[20] Karamian M, Moossavi M, Hemmati M. From diabetes to renal aging: the therapeutic potential of adiponectin. J Physiol Biochem, 2021, 77(2):205-214.

[21] Li R, Du JH, Yao Y, et al. Adiponectin inhibits high glucose-induced angiogenesis *via* inhibiting autophagy in RF/6A cells. J Cell Physiol, 2019,234(11):20566-20576.
[22] Yilmaz MI, Sonmez A, Acikel C, et al. Adiponectin may play a part in the pathogenesis of diabetic retinopathy. Eur J Endocrinol, 2004:135-140.
[23] Kelley N, Jeltema D, Duan YH, et al. The NLRP3 inflammasome: an overview of mechanisms of activation and regulation. Int J Mol Sci, 2019,20(13):3328.
[24] Yang YX, Jiang GC, Huang RC, et al. Targeting the NLRP3 inflammasome in diabetic retinopathy: From pathogenesis to therapeutic strategies. Biochem Pharmacol, 2023,212:115569.
[25] Kuo CY, Maran JJ, Jamieson EG, et al. Characterization of NLRP3 inflammasome activation in the onset of diabetic retinopathy. Int J Mol Sci, 2022,23(22):14471.
[26] Chai GR, Liu S, Yang HW, et al. NLRP3 blockade suppresses pro-inflammatory and pro-angiogenic cytokine secretion in diabetic retinopathy. Diabetes Metab Syndr Obes, 2020,13:3047-3058.
[27] Dong ZX, Zhuang Q, Ye X, et al. Adiponectin inhibits NLRP3 inflammasome activation in nonalcoholic steatohepatitis *via* AMPK-JNK/ErK1/2-NFκB/ROS signaling pathways. Front Med, 2020,7:546445.
[28] Liu HX, Wu X, Luo JN, et al. Adiponectin peptide alleviates oxidative stress and NLRP3 inflammasome activation after cerebral ischemia-reperfusion injury by regulating AMPK/GSK-3β. Exp Neurol, 2020,329:113302.
[29] Wang F, Liu Y, Yang W, et al. Adiponectin inhibits NLRP3 inflammasome by modulating the AMPK-ROS pathway. Int J Clin Exp Pathol. 2018,11(7):3338-3347.