Metabolism Open 26 (2025) 100365

Contents lists available at ScienceDirect

Metabolism Open

journal homepage: www.sciencedirect.com/journal/metabolism-open

The potential role of adipokines and hepatokines in age-related ocular diseases

Stavroula Almpanidou *, Ilias D. Vachliotis, Antonis Goulas, Stergios A. Polyzos **

First Laboratory of Pharmacology, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

ARTICLE INFO

Keywords:
Ocular disease
Adipokines
Obesity
Hepatokines
Metabolic dysfunction-associated steatotic liver disease
Nonalcoholic fatty liver disease

ABSTRACT

Age-related ocular diseases, including diabetic retinopathy (DR), age-related macular degeneration (AMD), cataract and glaucoma may lead to visual impairment and even to blindness. Metabolic diseases, such as obesity and metabolic dysfunction-associated steatotic liver disease (MASLD) have emerged as potential risk factors of age-related ocular diseases, especially DR. Visceral adiposity has been associated with increased risk of DR and AMD in most clinical studies, although body mass index has to-date provided conflicting association with DR and AMD. In addition, obesity is recognized as a risk factor of cataract and glaucoma. Similarly to obesity, MASLD appears to be associated with DR in patients with type 1 diabetes mellitus, but probably not in those with type 2 diabetes mellitus. A potential positive association between MASLD and AMD, glaucoma and cataract is supported by limited evidence to-date, thus needing further investigation. Altered secretion patterns of adipokines (adiponectin, leptin, lipocalin-2, resistin) and hepatokines [adropin, fetuin-A, fibroblast growth factor (FGF)-21, retinol binding protein (RBP)-4] seem to disrupt ocular homeostasis and contribute to the development of age-related ocular diseases in the context of obesity and MASLD. In this regard, novel adipokine-based and hepatokine-based therapies may be added to the treatment options for ocular diseases in the future. This narrative review aimed to summarize evidence on the interconnection of obesity and MASLD with age-related ocular diseases, with a specific focus on the roles of adipokines and hepatokines as mediators of these potential associations.

1. Introduction

Age-related ocular diseases, such as age-related macular degeneration (AMD), cataract, diabetic retinopathy (DR) and glaucoma, are leading causes of visual impairment and blindness worldwide, affecting patients' quality of life and increasing morbidity [1]. Importantly, their prevalence is expected to increase in the context of the increasing prevalence of obesity, type 2 diabetes mellitus (T2DM) and metabolic

Abbreviations: AH, aqueous humor; AdipoR, adiponectin receptor; AMD, age-related macular degeneration; AMPK, adenosine monophosphate-activated protein kinase; APN, adiponectin; BMI, body mass index; BRB, blood-retinal barrier; CI, confidence interval; CNS, central nervous system; CRP, C-reactive protein; DHA, docosahexaenoic acid; DM, diabetes mellitus; DR, diabetic retinopathy; EGR4, early growth response factor 4; ELOVL2, elongase enzyme responsible for very long-chain fatty acids 2; ERRα, estrogen-related receptor α; FGF-21, fibroblast growth factor-21; FIB-4, fibrosis-4; GLP-1RAs, glucagon-like peptide-1 receptor agonists; HMW, high molecular weight; HR, hazard ratio; HSI, hepatic steatosis index; IL, interleukin; IOP, intraocular pressure; IR, insulin resistance; KNHANES, Korea National Health and Nutrition Examination Survey; LCN-2, lipocalin-2; MAFLD, metabolic dysfunction-associated fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; NF-κB, nuclear factor kappa B; NFS, NAFLD fibrosis score; NPDR, non-proliferative diabetic retinopathy; OR, odds ratio; PDR, proliferative diabetic retinopathy; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; POAG, primary open-angle glaucoma; PSC, posterior subcapsular cataract; PVR, proliferative vitreoretinopathy; RBP-4, retinol binding protein-4; RGCs, retinal ganglion cells; ROS, reactive oxygen species; RPE, retinal pigment epithelium; RR, relative risk; RVO, retinal vein occlusion; STAT-1, signal transducer and activator of transcription 1; SD, standard deviation; SIRT1, sirtuin 1; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TE, transient elastography; TFAM, mitochondrial transcription factor A; TLR4, toll-like receptor 4; US, ultrasound; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; VH, vitreous humor; WC, waist circumference; WHR, waist-to-hip ratio.

This article is part of a special issue entitled: Cancer, Inflammation and Metabolism published in Metabolism Open.

* Corresponding author. First Laboratory of Pharmacology, School of Medicine Campus of Aristotle University of Thessaloniki, 54124, Thessaloniki, Greece.
** Corresponding author. First Laboratory of Pharmacology, School of Medicine Campus of Aristotle University of Thessaloniki, 54124, Thessaloniki, Greece.
E-mail addresses: almpstav@auth.gr (S. Almpanidou), spolyzos@auth.gr (S.A. Polyzos).

https://doi.org/10.1016/j.metop.2025.100365
Received 30 December 2024; Received in revised form 2 April 2025; Accepted 14 April 2025
Available online 16 April 2025
2589-9368/© 2025 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

dysfunction-associated steatotic liver disease (MASLD), since a growing number of epidemiological studies identify metabolic comorbidities as important modifiable risk factors of age-related ocular diseases [2,3].

The interplay of obesity and MASLD with ocular diseases appears to be mediated, at least in part, by adipokines and hepatokines, i.e., mainly peptides secreted predominantly by the adipose tissue and the liver, respectively. Dysregulated secretion patterns of adipokines and hepatokines in obesity and MASLD have been implicated in chronic low-grade inflammation, insulin resistance (IR), oxidative stress and vascular dysfunction [4], all of which are key contributors to the pathogenesis of AMD, DR and other age-related ocular diseases [5,6].

This narrative review aimed to summarize evidence on the interconnection of obesity and MASLD with age-related ocular diseases, with a specific focus on the roles of adipokines, which are primarily produced by the adipose tissue, and hepatokines, which are primarily produced by the liver, as mediators of these potential associations. To this aim, first, we provided a concise overview of the current epidemiological evidence linking obesity and MASLD with age-related ocular diseases and next, we focused on experimental and clinical studies having investigated the potential associations of specific adipokines and hepatokines with age-related ocular diseases. Understanding these molecular pathways may open novel therapeutic approaches, i.e., ocular diseases associated with aging and metabolic disorders may be prevented or mitigated by targeting adipokines or hepatokines.

2. Cross-talk between the adipose tissue and the eye

2.1. Association between obesity and age-related ocular diseases

Obesity and visual impairment have emerged over the last decades as primary public health challenges, requiring more effective interventions [7,8]. Obesity accelerates aging processes and in turn aging is linked to increased visceral obesity, i.e., possibly indicating a bidirectional association [9,10]. Hereby, evidence on the association of obesity with age-related ocular diseases are summarized. Major relevant studies are summarized in Table 1.

2.1.1. Diabetic retinopathy

In the context of prolonged and inadequately controlled diabetes mellitus (DM), DR may lead to progressive vision loss and eventually blindness. Obesity is considered to be a major risk factor of the onset and progression of DM; thus, the association between obesity and DR has been investigated beyond DM. Most data investigating this association are derived from cohort studies and few meta-analyses, generally indicating a positive association. A meta-analysis exploring the risk factors of DR, highlighted that obesity is associated with the incidence of non-proliferative DR (NPDR), but not with that of proliferative DR (PDR) [28]. In the same line, a prospective analysis of 2305 patients with T2DM showed greater prevalence of DR among patients with greater body mass index (BMI) [odds ratio (OR) 1.26, 95 % confidence interval (CI) 0.93–1.70] or waist-to-hip ratio (WHR) (OR 2.17, 95 % CI 1.13–4.17) [29]. Interestingly, visceral obesity was independently associated with new-onset DR in Chinese patients with T2DM [30]. A nested case-control study also reported that increased WHR was associated with the development of DR (OR 1.65, 95 % CI 1.17–2.33), reinforcing the aspect that visceral obesity may contribute to the pathogenesis of DR [31]. Nonetheless, there are studies that paradoxically suggest an inverse association of obesity and DR within patients with T2DM [32]. In particular, BMI was inversely associated with incident DR in both Swedish and Asian populations with T2DM [33,34], while WHR showed a positive association with DR in the latter population [34]. Data from Korean patients with T2DM also supported an inverse association between BMI, waist circumference (WC), percentage of body fat and vision-threatening DR [35]. This inverse association between BMI and DR, as supported by some but not all authors, reflects what has been termed the “obesity paradox”, wherein individuals with low or normal BMI may be at higher risk of developing DR than those with obesity [32]. In this regard, WHR has emerged as a better associate with DR, since it reflects better than BMI the visceral adiposity, which is more pathogenic than subcutaneous adiposity [36,37].

The above considering, most data favor a positive association of central adiposity with DR. In contrast, BMI does not seem to be an ideal index to explore this association, because different studies have provided conflicting data. Ethnic differences may also exist, e.g., differences in central adiposity between Caucasians and Asians with the same BMI, or differences in susceptibility to DR. Regarding the mediators of this potential association, chronic inflammation, insulin resistance, oxidative stress and altered secretion of adipokines have been reportedly involved [38].

2.1.2. Age-related macular degeneration

A systematic review on the association between obesity indices and age-related ocular diseases reported that not only obesity, but also a BMI <22 kg/m^2 were associated with higher incidence of AMD [relative risk (RR) 2.15, 95 % CI 1.35–3.45 and RR 1.43, 95 % CI 1.01–2.04, respectively] [2]. This meta-analysis also identified WHR as a risk factor of AMD, with an OR of 1.13 per 0.1 increase in WHR (95 % CI 1.01–1.26) [2]. In another study, WHR was positively associated with both early and late AMD in men, but not in women [39]. Furthermore, the Atherosclerosis Risk in Communities (ARIC) study indicated that a reduction of $\geq$3 % in WHR overtime was protective against early AMD, particularly in obese individuals at baseline [40]. Concerning BMI-defined obesity, a relevant prospective study in 2868 participants found that BMI was associated with incident AMD, but not with its progression [41]. Other studies, however, in Asian and Indian populations did not demonstrate an association between obesity and AMD [42–46]. It seems that the association between obesity and AMD is demonstrated when an index of central adiposity is used (e.g., WHR), whereas conflicting data exist from the studies having used BMI as a measure of adiposity, as in the case of DR mentioned above.

2.1.3. Cataract

Most studies suggest positive association between obesity and cataract formation, with BMI thresholds more frequently used to explore this association. A study investigating metabolic and lifestyle factors associated with the development of senile cataract showed that the OR of developing senile cataract increased by 1.19 for each 1 standard deviation (SD) rise in BMI (95 % CI 1.09–1.29) [47]. Other authors supported obesity, T2DM, arterial hypertension and metabolic syndrome (MetS) as independent associates of cataract development [48]. In another study, T2DM and arterial hypertension were primarily shown to be linked to cortical and posterior subcapsular cataract (PSC), whereas dyslipidemia, obesity and MetS were most strongly associated with cortical cataract [49]. On the contrary, the above mentioned systematic review supported that obesity was predominantly associated with nuclear cataract and PSC in Western populations [2]. Surprisingly, a similar study in an Afro-Caribbean population reported an inverse association between obesity and cataract; however, malnutrition observed in this population may be a stronger associate with cataract than obesity [50]. Two meta-analyses reported positive association between obesity and the incidence of maturity-onset cataract [51,52]. Oxidative stress and chronic inflammation are known contributors to the pathogenesis of age-related cataract [53]. Obesity is linked to arterial hypertension, DM and IR, all of which promote oxidative stress, thus possibly resulting in oxidative damage to the eye lens [54–57].

2.1.4. Glaucoma

Most studies suggest a positive association between obesity and primary open-angle glaucoma (POAG), the most prevalent form of glaucoma [58,59], with hazard ratio (HR) being 1.10 (95 % CI 1.00–1.21) in one of them [59]. In line, another meta-analysis reported that higher BMI was associated with increased intraocular pressure

Table 1
Clinical studies linking selected adipokines with age-related ocular diseases[a].

First author [reference]	Year	Origin	Type of study	Characteristics	Ocular disease	Main findings
Adiponectin (APN)						
Kaarnirantaa [11]	2012	Finland	Case-control	312 patients with advanced AMD *Wet AMD* (268) *Severe atrophic AMD (44)* 166 controls	AMD	rs10753929 AdipoR1 variant was associated with advanced AMD (OR 1.699, 95 % CI 1.192–2.423)
Cao [12]	2015	China	Case-control	189 patients with advanced AMD 168 controls	AMD	ADIPOQ genetic variant rs822396 was associated with higher risk of advanced AMD in a dominant model
Mao [13]	2012	China, USA	Case-control	20 patients with T2DM and PDR 20 controls	DR	AH APN was higher in PDR versus controls (5.29 ± 4.09 versus 1.26 ± 0.56 ng/ml)
Srinivasan [14]	2014	India	Case-control	26 patients with T2DM and PDR 11 controls	DR	VH APN, VEGF and IGF-1 were higher in patients with PDR VH APN was inversely associated with VEGF after laser treatment in patients PDR
Omae [15]	2015	Japan	Case-control	64 patients with T2DM without or with mild NPDR	DR	Circulating APN was positively associated with RBF and negatively associated with retinal arterial vascular resistance in men
Yang [16]	2021	South Korea	Case-control	98 patients with T2DM *DR (59)* *Non-DR (39)* 35 controls	DR	Circulating and AH APN were higher in T2DM versus controls (5.99 ± 3.89 versus 3.51 ± 1.44 μg/ml and 10.94 ± 11.74 versus 3.65 ± 3.33 ng/ml, respectively)
Sutkowy [17]	2023	Poland	Case-control	24 patients with cataract 33 controls	Cataract	Circulating IL-6 and resistin were higher (by 30 % and by 64.9 %, respectively), whereas omentin-1 and APN were lower (by 35.2 %, and by 22.3 %, respectively) in controls versus patients with cataract
Gencoglu [[18]]	2022	Turkey	Case-control	40 patients with POAG 38 XFG 40 healthy controls	Glaucoma	Circulating SIRT1 was lower in POAG patients versus controls No significant difference in circulating APN between the three groups Circulating SIRT1 may have a role in neuroprotection and modulation of oxidative stress in POAG
Leptin						
Evereklioglu [19]	2003	Turkey	Case-control	32 patients with AMD 20 controls	AMD	Circulating leptin was lower in AMD patients versus controls (6.01 ± 2.55 versus 13.21 ± 2.27 ng/ml) Circulating leptin was lower in late-AMD patients versus early-AMD patients (3.81 ± 0.58 versus 8.21 ± 1.68 ng/ml)
Seshasai [20]	2015	Singapore	Case-control	426 patients with AMD 927 controls	AMD	Circulating leptin was lower in AMD versus controls (10.0 ± 11.5 versus 12.9 ± 16.4 ng/ml) Circulating leptin was associated with lower risk of AMD (OR 0.56, 95 % CI 0.34–0.92)
Hernandez [21]	2004	Spain	Case-control	25 patients with T2DM and PDR 32 controls	DR	No difference in VH leptin between PDR and controls
Maberley [22]	2006	Canada	Case-control	7 patients with PDR 12 patients with maculopathies 6 patients with RD and PVR 7 controls with RD without PVR	Retinal diseases	Average VH leptin was significantly higher in PDR than in PVR patients (37.4 versus <1.0 ng/ml)
Lipocalin-2 (LCN-2)						
Rezar-Dreindl [23]	2016	Austria	Case-control	40 eyes with nAMD 15 control eyes	AMD	AH LCN-2/NGAL were higher in nAMD patients versus controls (8791 ± 4913 versus 5395 ± 1582 pg/mL)
Zhang [24]	2023	China	Case-control	237 patients with T2DM	DR	Circulating LCN-2 was higher in overweight/obese versus controls Circulating LCN-2 was higher in DR versus non-DR Higher circulating LCN-2 was associated with higher risk of developing DR (OR 4.198, 95 % CI 1.676–10.516)
Luo [25]	2020	China	Case-control	52 patients with RVO 20 patients with senile cataract (controls)	RVO	AH LCN-2 and resistin were higher in RVO versus controls; (Median: 8476.50 versus 6802.50 pg/ml and 120.42 versus 42.04 pg/ml) AH LCN-2 and resistin were negatively associated with visual improvement following anti-VEGF therapy in patients with CRVO but not in those with BRVO
Resistin						
Osawa [26]	2007	Japan	Case-control	238 patients with T2DM	DR	Circulating resistin was higher in advanced DR versus non-advanced DR (20.4 ± 1.6 versus 15.8 ± 0.8 ng/ml)
Gurlevik [27]	2019	Turkey	Case-control	45 eyes with PDR 22 control eyes	DR	No difference in circulating resistin between PDR and controls

Abbreviations: AdipoR1, adiponectin receptor 1; ADIPOQ, adiponectin, C1Q and collagen domain containing; AH, aqueous humor; AMD, age-related macular degeneration; APN, adiponectin; BRVO, branch retinal vein occlusion; CI, confidence interval; CRVO, central retinal vein occlusion; DR, diabetic retinopathy; HDL-C, high-density lipoprotein cholesterol; IGF-1, insulin-like growth factor-1; IL-6, interleukin-6; LCN-2, lipocalin-2; nAMD, neovascular age-related macular degeneration; NGAL, neutrophil gelatinase-associated lipocalin; NPDR, non-proliferative diabetic retinopathy; OR, odds ratio; PDR, proliferative diabetic retinopathy; POAG, primary open angle glaucoma; PVR, proliferative vitreoretinopathy; RBF, retinal blood flow; RD, retinal detachment; RVO, retinal vein occlusion; SIRT-1, sirtuin-1; T2DM, type 2 diabetes mellitus; VEGF, vascular endothelial growth factor; VH, vitreous humor; XFG, exfoliation glaucoma.

[a] Studies are primarily sorted by the respective adipokine, secondarily by the type of age-related ocular disease and subsequently by the year of publication.

(IOP) (RR 1.06, 95 % CI 1.04–1.07) [60]. One of these meta-analyses also identified over 20 genomic loci associated with both IOP and BMI [59]; however, even the latter does not prove a cause-effect association. In this regard, a Mendelian randomization study, supported a potentially causal association between BMI or hip circumference and POAG [61]. Similarly, other studies reported positive association between abdominal obesity and the incidence of glaucoma [62–64]. In Asian populations, most studies reported positive association between BMI-defined obesity and increased IOP [65–68]. Interestingly, BMI-defined obesity was also associated with the progression of the disease from suspect POAG to definite POAG [62]. Similarly to BMI, WC was positively associated with POAG [64]. The association between glaucoma and obesity may be partly explained by the presence of excess intraorbital adipose tissue and elevated blood viscosity in individuals with obesity, both of which increase episcleral venous pressure, decrease aqueous humor (AH) outflow and subsequently raise IOP [69]. Another prevailing hypothesis suggests that DNA damage due to oxidative stress may lead to degeneration of the trabecular meshwork, thus increasing aqueous outflow resistance [70]. On the contrary, there are studies reporting no association between BMI-defined obesity and POAG [71,72]. Even more, there is a study reporting that each unit increase in BMI resulted in a 7 % decrease in the risk of developing incident open angle glaucoma in women, but not in men [73]. Other authors supported that underweight individuals had higher risk of POAG, suggesting a reverse J-shaped association between BMI and POAG, which was most pronounced in individuals with DM [74]. This seemingly paradoxical association may reflect a potentially favorable effect of obesity, which was based on the hypothesis that higher cerebrospinal fluid pressure, observed in individuals with higher BMI, may possibly provide counter-pressure against IOP [75]. The above considering, mechanistic studies are required to definitely clarify whether obesity, and more specifically visceral obesity, is associated with glaucoma and elucidate the specific mechanisms possibly linking them.

2.2. Adipokines in age-related ocular diseases

The term adipokines refers to peptides or proteins secreted predominately from the adipocytes to maintain metabolic homeostasis [76]. Adipokine profile changes in obesity and their dysregulation may have adverse pathophysiological consequences. Thus, it was shown that adipokines are associated with systemic, central nervous system (CNS) and ocular diseases, mostly the age-related and neurodegenerative ones [77]. Adiponectin (APN), leptin, lipocalin-2 (LCN-2) and resistin are adipokines that are studied in ocular diseases and relevant data are summarized hereby.

2.2.1. Adiponectin

APN circulates in high levels, which diminish in obesity and related diseases, contrary to most adipokines which increase in obesity [78]. APN plays a significant role in metabolic and cardiovascular regulation by enhancing insulin sensitivity, promoting glucose uptake and lipid metabolism, and exhibiting anti-inflammatory properties through its receptors, adiponectin receptor (AdipoR)1 and AdipoR2 [78]. Both APN and its receptors, AdipoR1 and AdipoR2, are expressed in the retina, particularly in the outer nuclear layer, in which rods and cones reside. Nonetheless, the precise role of APN in the pathogenesis of age-related ocular diseases remains under investigation. The circulating APN levels were linked to DR [79], the retinopathy of prematurity [80] and AMD [81]. Interestingly, smoking, a known risk factor of AMD, was also shown to reduce circulating APN levels. The expression of AdipoR1 in the retina is believed to be critical for inducing the elongase enzyme responsible for very long-chain fatty acids (ELOVL2), which may be essential for the adequate supply of docosahexaenoic acid (DHA), the last being necessary for the appropriate function and survival of photoreceptor cells [82]. Furthermore, APN may influence retinal lipid metabolism by facilitating the removal of excess cholesterol, reducing acid sphingomyelinase activation, or converting ceramide to sphingosine-1-phosphate [83,84].

Oxidative stress plays a critical role in the pathogenesis of age-related ocular diseases, particularly DR, AMD, cataract and glaucoma. APN seems to mitigate oxidative stress by downregulating the generation of reactive oxygen species (ROS), attenuating lipid peroxidation and enhancing antioxidant defense mechanisms [85]. Furthermore, APN plays a role in inhibiting the inflammatory response, promoting vasodilation and triggering autophagic clearance through the activation of 5′ adenosine monophosphate-activated protein kinase (AMPK) [86,87]. The association of APN with autophagy seems to be important, because impaired autophagy was associated with retinal pigment epithelium (RPE) damage and the development of AMD [85].

Polymorphisms in APN and its receptors were associated with various metabolic diseases [88,89] and also with the development of AMD. Notably, the rs10753929 variant of AdipoR1 was associated with AMD in a Finnish cohort [11]. In a Chinese study, the APN genetic variant rs822396 was associated with advanced stages of AMD [12]. Another genetic variant of APN, the rs822396, was associated with the susceptibility to AMD, thereby being proposed as a potential genetic biomarker of the early detection of the disease [12].

Investigation of the association between APN and DR was conducted using plasma and vitreous humor (VH) samples from patients with PDR, who had undergone vitrectomy, revealing elevated VH APN levels. Notably, VH APN was negatively associated with vascular endothelial growth factor (VEGF) levels in those who underwent laser treatment prior to vitrectomy [14]. Another study compared APN levels in the serum and AH between diabetic patients with and without DR, indicating strong association of AH APN levels with the development and progression of DR. In the same study, serum APN was associated with intraocular cytokines, including VEGF [16]. An additional study showed positive associations between serum APN levels and retinal blood flow in men, but not in women, with T2DM and early-stage DR [15]. To explain this gender difference, it was speculated that the expression of AdipoR1 and AdipoR2 may differ between men and women and may account for such differences [15]. Some authors hypothesized that high levels of APN in AH may be a protective, compensatory mechanism in PDR, which may promote increased nitric oxide production, insulin sensitivity and may exhibit anti-inflammatory effects [13]. The variation in APN levels between serum and AH was reportedly linked to the critical role of the blood-retinal barrier (BRB) in regulating intraocular homeostasis [13]. Another study in a Japanese population with T2DM found a positive association of serum APN and high molecular weight (HMW) APN with the severity of DR [90]. Additionally, other authors reported an association between serum APN levels and genetic variations in APN receptors with DR in patients with T2DM [91]. In line, another group showed that serum APN levels were increased in patients with DR and they were positively associated with the severity of DR [92]. On the contrary, other authors supported that patients with T2DM and DR exhibited lower serum APN levels compared to those without DR [93,94]. Some of them also supported that serum APN levels were inversely associated with the severity of DR [93], a finding contradicting the results of all the above mentioned studies.

Retinal edema and neovascularization are the main causes of vision loss in DR and other retinal vascular diseases, including retinal vein occlusion (RVO). Increased expression and localization of APN at the occluded site of retinal veins was positively associated with the development of retinal edema in RVO mice [95]. Thus, APN may be a potential target for the treatment of neovascularization and retinal edema, which, however, remains to be shown [95]. Another driver of many vision-threatening ocular diseases, such as glaucoma, cataract, AMD, PDR and proliferative vitreoretinopathy (PVR), is fibrosis [96]. A relevant study supported that APN levels were elevated in the vitreous and subretinal fluid of patients with PDR and PVR, respectively [97]. In this regard, APN may play a role in regulating the vascular-fibrotic switch in ocular fibrosis by reducing VEGF and shifting the balance towards

fibrosis [97]. Given that APN has shown antifibrotic effects in some extraocular sites, such as the liver, whereas profibrotic effects in the kidney and the retina, it was speculated that the role of APN as a antifibrotic or profibrotic mediator is largely determined by the cell type, the pathological context and its receptor interactions [97]. However, all these remain to be definitely shown in mechanistic studies.

Regarding glaucoma, plasma sirtuin 1 (SIRT1) and APN levels were compared among patients with POAG, exfoliative glaucoma and healthy controls. Interestingly, SIRT1 levels were lower in POAG patients compared to controls, whereas there was no significant difference in plasma APN levels between groups [18]. A previous animal model investigating the effects of AdipoRon, an APN analog, on glutamate-induced cell death in rat primary retinal ganglion cells (RGCs) showed that AdipoRon increased the survival rate of RGCs and decreased ROS production [98], both being potentially favorable for glaucoma. However, this action achieved through APN receptors seems to be favorable in glaucoma, in contrast with the above mentioned potentially unfavorable APN effect on retinal fibrosis. Thus, the effects of APN may be different in different ocular diseases, an hypothesis warranting further mechanistic studies.

Regarding cataract, there are limited data on APN. Serum APN levels were higher in patients with cataract than controls in a study [17]. Another study reported no differences in plasma APN levels when comparing patients with senile cataract with patients with PDR; however, the AH APN levels were higher in the latter than the former group [13]; however, the pathophysiologic effect of APN in cataract, if any, remains to be shown.

2.2.2. Leptin

Leptin is the first identified adipokine and is secreted mainly by the white adipose tissue; its serum levels are positively associated with total fat mass, thus reflecting primarily the amount of energy stored in adipose tissue [99]. Among its associations with multiple diseases, leptin has been linked to a reduced incidence of dementia and Alzheimer's disease [100–102], the latter sharing several clinical and pathological features with AMD [20]. More specifically, participants with AMD exhibited lower serum leptin levels compared to controls; *vice versa*, higher leptin levels were inversely associated with AMD, particularly in women, individuals of Indian ethnicity and former smokers [20]. A smaller hospital-based study similarly reported lower serum leptin levels in patients with AMD compared to controls; more importantly, patients with advanced AMD had lower leptin levels than those with early disease [19], possibly indicating progressive decrease of leptin levels from the controls to early AMD and then to advanced AMD.

Several mechanisms have been proposed to explain the inverse association between leptin and AMD. First, leptin promotes the clearance of extracellular amyloid [103] and participates in lipid metabolism. Of note, accumulation of nonfibrillar amyloid-beta, long chain fatty acid cholesterol esters, non-esterified cholesterol, and apolipoproteins B100, A-I and E between Bruch's membrane and the RPE form the drusen deposits, which are hallmark of AMD [104,105].

The wet form of AMD is primarily characterized by choroidal neovascularization. The presence of leptin in choroidal neovascular membranes surgically excised from patients with AMD, idiopathic choroidal neovascularization and ocular histoplasmosis was reported in 2001 [106]. Later, other authors showed *in vitro* that chronic exposure to VEGF, a key angiogenic factor in the retina, enhances both the local expression and function of leptin. Since leptin can also activate VEGF mRNA and protein expression, this functional vicious cycle seems to contribute to a pro-angiogenic and pro-inflammatory milieu within the retina [107,108], favoring the development of ocular diseases.

Moreover, elevated leptin levels in VH taps were observed in patients with PDR, indicating a potential role in the pathogenesis of DR [22]. However, other authors did not find higher VH levels of leptin in patients undergoing vitrectomy for PDR compared to non-diabetic patients with non-proliferative ocular diseases. an outcome partially attributed to the exclusion of patients with vitreous hemorrhage [21].

Leptin may serve as a neuroprotective agent in glaucoma, a neurodegenerative condition characterized by the progressive loss of RGCs. This was potentially attributed to the leptin-induced prevention of RGC death by mitigating apoptosis, oxidative stress and excitotoxic damage [109], but it remains to be definitely shown.

Concerning cataract, the involvement of leptin is not straightforward. Oxidative stress and higher BMI were associated with cataract formation [110,111]. Thus, it was expected that leptin, positively associated with BMI and oxidative stress, would also have been associated with cataract. Nonetheless, in a recent study, serum leptin levels were similar in patients with cataract versus controls [17]. Given that leptin research in ocular disease is in its infancy, much more research is expected.

2.2.3. Lipocalin-2

LCN-2 has been implicated in acute and chronic inflammation and has shown to be upregulated in several ocular diseases. Notably, some studies reported higher expression of LCN-2 in the retina of human donors with AMD [112]. Circulating LCN-2 levels were elevated in overweight and obese patients with DR compared to those without DR; LCN-2 was reportedly an independent predictor of DR in this study [24]. In another study, elevated AH LCN-2 levels were observed in patients with persistent or recurrent wet AMD, suggesting a link to the chronic inflammatory process involved in the pathogenesis of chronic macular edema associated with AMD [23]. A subsequent study suggested a potential role of LCN-2 in AMD pathogenesis, proposing that nuclear factor kappa B (NF-κB) and signal transducer and activator of transcription 1 (STAT-1) may collaborate to regulate LCN-2 expression in the retina, thus stimulating an inflammatory response. These findings may indicate the NF-κB/LCN-2 signaling as a potential target for AMD treatment [113]. Furthermore, LCN-2 was linked to the pathological process underlying RVO, and was suggested by some authors as a prognostic marker for visual outcomes following intravitreal anti-VEGF therapy [25]. In the context of DR, LCN-2 was associated with impaired function of retinal photoreceptors and neurons [114]. Furthermore, LCN-2 promotes angiogenesis by inducing apoptosis in retinal vascular endothelial cells, as well as retinal inflammation, since LCN-2 was shown to recruit inflammatory cells and to trigger the secretion of pro-inflammatory cytokines [114]. Importantly, silencing LCN-2 may mitigate retinal damage, potentially through the inhibition of caspase-1-mediated pyroptosis, positioning LCN-2 as a promising target for the treatment of DR [114].

2.2.4. Resistin

Resistin seems to contribute to the pathophysiology of obesity and related diseases [115]. Resistin was shown to upregulate VEGF receptor (VEGFR)1 and VEGFR2 mRNA expression in human coronary and lung endothelial cells [[27]]. However, in the context of PDR, which is primarily driven by angiogenic mechanisms, no difference in circulating resistin levels were observed between patients with PDR and controls [27]. Based on these findings, the authors speculated that resistin may not be inserted into the VH, therefore it cannot affect retinal neovascularization [27]. On the contrary, other authors reported positive association between serum resistin levels and the grade of DR in patients with T2DM [26]. Concerning RVO, which primary affect retinal vasculature, patients with RVO seem to have lower resistin levels in the AH than patients with senile cataract [25]. Thus, existing data are considered limited to draw secure conclusions on any potential role of resistin in DR and RVO. More studies are needed, including studies focused on the potential ocular resistin expression in various ocular diseases.

3. Cross-talk between the liver and the eye

3.1. Association between MASLD and age-related ocular diseases

Similarly to obesity, MASLD has been emerged as a potential risk factor of age-related ocular diseases in an increasing number of studies, which are briefly summarized in this section. Most of the existing studies are observational ones that have investigated the link between MASLD and DR, owing to the well-established bidirectional association between MASLD and DM [116]. Therefore, there is comparatively less information on the association of MASLD with cataract, glaucoma and AMD. Major relevant studies are summarized in Table 2. Although we favor the use of the novel nomenclature of MASLD in future studies, herein we also kept the previous terms of nonalcoholic fatty liver disease (NAFLD) or metabolic dysfunction-associated fatty liver disease (MAFLD) as used in the original studies, acknowledging differences among different definitions of the disease, despite the significant overlap [117].

Observational studies regarding the association between NAFLD/

Table 2
Clinical studies linking selected hepatokines with age-related ocular diseases[a].

First author [reference]	Year	Origin	Type of study	Characteristics	Ocular disease	Main findings
Adropin						
Ornek [118]	2016	Turkey	Case-control	98 patients with AMD *Dry (51)* *Wet (47)* 78 controls	AMD	No difference in circulating adropin between patients with AMD and controls No difference in circulating adropin between patients with dry and wet AMD.
Neethu [119]	2020	India	Case-control	39 patients with AMD 39 patients with T2DM without AMD	AMD	No difference in circulating adropin between patients with AMD and patients with T2DM without AMD
Saaedi-Maleki [120]	2024	Iran	Case-control	44 patients with wet AMD 45 controls	AMD	Circulating adropin was lower in patients with wet AMD versus controls [268.75 (257.97–284.52) versus 331.00 (317.70–341.65) pg/ml]
Li [121]	2019	China	Case-control	165 patients with T2DM *Non-DR (52)* *NPDR (69)* *PDR (44)* 68 controls	DR	Circulating and VH adropin were progressively decreased from controls to patients with non-DR, to NPDR and to PDR Higher circulating and VH adropin were associated with reduced risk of DR (OR 0.046, 95 % CI 0.011–0.197)
Li [122]	2020	China	Case-control	392 patients with T2DM *Non-DR (174)* *NPDR (118)* *PDR (100)* 120 controls	DR	Circulating adropin was progressively decreased from controls to patients with non-DR, to NPDR and to PDR Higher circulating adropin was associated with lower risk of DR (OR 0.928, 95 % CI 0.898–0.960)
Fetuin-A						
Javadzadeh [123]	2015	Iran	Case-control	40 patients with AMD 49 controls	AMD	Circulating fetuin-A was higher in patients with AMD versus controls (50.27 ± 5.04 versus 44.99 ± 10.28 ng/mL)
Zhao [124]	2015	China	Case-control	224 patients with T2DM *Non-DR (68)* *NPDR (54)* *PDR (102)* 68 controls	DR	Circulating and VH fetuin-A were higher in patients with DR versus controls
Zhou [125]	2016	China	Case-control	245 patients with T2DM *Non-DR (95)* *NPDR (78)* *PDR (72)* 65 controls	DR	Circulating fetuin-A was independently and positively associated with circulating VEGF and CRP in patients with DR, but not in non-DR group or controls
Li [126]	2023	China	Cross-sectional	100 patients with T2DM *DR (50)* *Non-DR (50)*	DR	Circulating fetuin-A was higher in patients with than without DR Higher circulating fetuin-A was associated with higher risk of DR (OR 1.041, 95 % CI 1.003–1.081)
Chang [127]	2021	China	Cross-sectional	cataract + T2DM (5) cataract + smoking (5) cataract + T2DM + smoking (8) cataract-controls (9)	Cataract	Fetuin-A expression was higher in the AH of the T2DM and smoking groups, with the highest levels observed in the combined group of T2DM and smoking
FGF-21						
Lee [128]	2023	China	Prospective	4760 patients with T2DM *Incident STDR 3.6 %* *Median follow-up 9 years*	DR	Circulating FGF-21 at baseline was comparable between patients with and without development of sight-threatening DR
Jiang [129]	2024	China	Meta-analysis	15 observational studies	DR	Circulating FGF-21 was higher in patients with than without DR (SMD 2.12, 95 % CI 1.40–2.84)
RBP-4						
Chou [130]	2023	China	Case-control	32 healthy or with mild AMD 30 patients with severe AMD	AMD	Increased circulating RBP-4 was associated with severe AMD in univariate, but not in multivariate analysis after age adjustment
Han [131]	2020	China	Meta-analysis	19 observational studies 2856 patients with T2DM	DR	Circulating RBP-4 was higher in NPDR (SMD 0.72, 95 % CI 0.48–0.95) and PDR (SMD 2.68, 95 % CI 1.69–3.67) versus non-DR in patients with T2DM

Abbreviations: AH, aqueous humor; AMD, age-related macular degeneration; CI, confidence interval; CRP, C-reactive protein; DR, diabetic retinopathy; FGF-21; fibroblast growth factor-21; NPDR, non-proliferative diabetic retinopathy; OR, odds ratio; PDR, proliferative diabetic retinopathy; RBP-4, retinol binding protein-4; SMD, standardized mean difference; T2DM, type 2 diabetes mellitus; VEGF, vascular endothelial growth factor.

[a] Studies are primarily sorted by the respective hepatokine, secondarily by the type of age-related ocular disease and subsequently by the year of publication.

MAFLD/MASLD and DR have to date yielded conflicting findings. Of note, similarly to obesity, some studies have paradoxically shown an inverse association between ocular diseases and NAFLD in patients with T2DM, despite the well-established potential of NAFLD to result in the progression of DM and *vice versa* [116]. Meta-analyses on this topic have concluded that NAFLD is not a risk factor of DR in patients with T2DM, albeit race-specific differences may affect this association [132,133]. However, DR was positively associated with hepatic fibrosis determined non-invasively with either NAFLD fibrosis score (NFS) or transient elastography (TE) (OR 1.69, 95 % CI 1.30–2.20) in one of the above mentioned meta-analyses, leading the authors to suggest that ocular examination of DR may identify patients with T2DM at risk of advanced NAFLD [133]. Our updated meta-analysis comprising of 24985 individuals showed that NAFLD was associated with higher OR of retinopathy compared to non-NAFLD in T1DM (OR 2.35; 95 % CI 1.53–3.60), but not in T2DM patients [134]. More recently, MASLD with or without coexisting significant fibrosis, based on hepatic steatosis index (HSI) and fibrosis-4 (FIB-4) score, was also associated with higher percentage of retinopathy in T1DM Italian patients [135]. Interestingly, a prospective cohort study involving 4524 adults Chinese with NAFLD, MAFLD, or concomitant NAFLD/MAFLD showed that MAFLD, but not NAFLD, was associated with higher risk of multiple-site atherosclerosis, including retinal atherosclerosis (OR 1.79; 95 % CI 1.28–2.52) during a median follow-up of 2 years [136]. Among MAFLD subtypes, patients with DM-MAFLD presented the highest risk of subclinical atherosclerosis [136]. In another study, which evaluated the differential effect of MetS components on microvascular and macrovascular complications in patients with MASLD, patients with MASLD and all MetS components had the highest risk of retinopathy [137]. Owing to the close association between MASLD and other metabolic disorders, such as obesity, IR, dyslipidemia, arterial hypertension, it is practically difficult to isolate the effect of one versus the other components of MetS, thus establishing whether a causative effect of MASLD on retinopathy exists and whether this is additive to that of DM. However, by treating liver disease simultaneously with other metabolic risk factors may help prevent DR, but it remains to be shown. Besides DR, NAFLD has been recognized as a risk factor of other retinal vascular lesions, such as arteriovenous compression and arterial narrowing in the retina, which also deserves further investigation [138].

Data linking NAFLD/MAFLD/MASLD with other ocular diseases are relatively limited; for example, in a recent study using data from 4246 participants in the fifth Korea National Health and Nutrition Examination Survey (KNHANES) 2010–2011 database, the diagnosis of MAFLD exhibited a stronger association with cataract compared to the diagnosis of NAFLD (OR 1.34, 95 % CI 1.10–1.64), whereas the risk of cataract increased linearly with increasing values of FIB-4 and NFS, both being non-invasive indices of hepatic fibrosis [139]. Another large-scale cohort study of 326558 UK Biobank participants followed over a median of 13 years showed that severe NAFLD, characterized by cases requiring hospitalization, was associated with an increased risk of developing cataract (HR 1.47; 95 % CI 1.33–1.61) [140]. Additionally, moderate to severe ultrasound (US)-defined NAFLD, but not mild NAFLD, was associated with increased IOP (>15 mmHg) compared to non-NAFLD in Korean adults [141]. However, in another study having included 16240 Korean adults undergoing health examination, the association between US-defined NAFLD and higher IOP (>22 mmHg), while initially significant in unadjusted analysis, did not remain robust after adjustment for potential confounders [142], implying that the development of both NAFLD and glaucoma may have one or more common denominators, but their direct association may be limited. Finally, hints on a potential link between NAFLD and AMD were provided by one experimental study, in which mice fed a “fast food” diet for 9 months developed MetS and steatohepatitis along with retinal alterations characteristic of AMD [143]. Again, this study cannot show a direct association between steatohepatitis and AMD, since the common denominator maybe the fast-food diet in this study.

3.2. Hepatokines in age-related ocular diseases

Despite anatomically unrelated, the liver and the eye appear to cross-talk each other; clinically, this is evidenced by the fact that specific ocular manifestations, such as scleral jaundice, or Kayser–Fleischer ring result from liver dysmetabolism, such as disrupted bilirubin and copper metabolism, respectively [144]. Beyond these metabolic links, emerging evidence suggests that the liver directly communicates with the eye through the release of liver-specific molecules, collectively termed hepatokines [144]. This section provides a brief overview of the current data on the potential involvement of hepatokines in age-related ocular diseases.

3.2.1. Adropin

Adropin is a 76-amino acid polypeptide, which was initially discovered in mouse liver in 2008, participating in energy homeostasis and lipid metabolism [145]. Later, adropin was also detected in several other tissues [146,147]. Adropin, which is considered to exert beneficial metabolic effects, displays lower circulating levels in patients with NAFLD, MAFLD and T2DM compared to controls [148–151]. Circulating and VH adropin levels were shown to have progressively lower trend across different stages of DR in two case-control studies including patients with T2DM [121,122]; thus, adropin may warrant further investigation as a non-invasive biomarker of DR severity. Data on circulating adropin in AMD are conflicting; lower adropin levels were shown in patients with AMD than controls in some [120], albeit not all studies [118,119].

3.2.2. Fetuin-A

Fetuin-A is almost exclusively secreted by the liver and is increased in hepatic steatosis and inflammation [152]. Circulating fetuin-A is also higher in obesity and has been independently associated with T2DM, IR, MetS and cardiovascular diseases; however, there are conflicting data about the association between fetuin-A and NAFLD [153]. Contrary to adropin, serum and VH fetuin-A have been reported to be higher in T2DM patients with than without DR [124]. In line, circulating fetuin-A was independently associated with an increased risk of DR after adjustment for potential confounders in another study [126]. In addition, circulating fetuin-A was shown to be positively associated with serum levels of both VEGF and C-reactive protein (CRP) in DR patients, but not in non-DR patients or controls [125]. Of note, an *in vitro* study demonstrated that fetuin-A stimulates interleukin (IL)-6 and IL-8, as well as VEGF mRNA expression in retinal perivascular fat and endothelial cells [154]. Therefore, fetuin-A may promote the expression of angiogenic and inflammatory mediators in hyperglycemic and hyperinsulinemic states and may be involved in the pathogenesis of DR. Higher circulating and AH fetuin-A levels in patients with AMD or cataract were also reported by only two studies to-date, thus requiring further confirmation [123,127].

3.2.3. Fibroblast growth factor-21

Fibroblast growth factor (FGF)-21 is an important metabolic regulator of glucose and lipid metabolism [155]. Its serum levels have been reported to be elevated in NAFLD patients [156], as a potentially counterbalanced mechanism against hepatic steatosis and inflammation [157]. Experimental studies showed that FGF-21 administration prevented pathological neovascularization in the retina and choroid [158], inhibited retinal vascular leakage [159] and protected photoreceptor function in murine models of AMD [160]. Notably, these beneficial effects depend on the regulation of metabolic and inflammatory pathways: FGF-21 enhances APN expression and suppresses the activation of NF-κB and complement pathways, thereby decreasing IR, hyperglycemia and inflammation independently of VEGF-A [158]. In addition, most case-control studies reported higher circulating FGF-21 in T2DM patients with than without DR [129], although a recent prospective study found no significant difference at baseline circulating FGF-21 levels

between T2DM patients with and without sight-threatening DR [128]. Therefore, FGF-21 may be a possible therapeutic target for neovascular eye diseases, such as DR and neovascular AMD, which, however, remains to be shown.

3.2.4. Retinol binding protein-4

Retinol binding protein (RBP)-4 is a transporter protein responsible for delivering vitamin A (retinol) from the liver to the retina [161]. Loss of RBP-4 function due to genetic mutations in human was associated with retinal dystrophy [162]. Although this is not a constant finding [163], elevated RBP-4 levels were linked to obesity, IR and NAFLD by some authors [164,165]; RBP-4 were also linked to progressive retinal degeneration through microglial activation and loss of RGCs and bipolar cells in diabetic mice and transgenic mice overexpressing RBP-4 (RBP-4-Tg) [166,167]. In this regard, either low or high levels of RBP-4 seem to have undesirable ocular consequences, which was supported to be true for most adipokines and hepatokines [168]. In this regard, it was hypothesized that high RBP-4 may elicit retinal neurodegeneration through a retinol-independent proinflammatory mechanism, mediated by Toll-like receptor 4 (TLR4) [166]. In the clinical context, a meta-analysis of 19 studies of patients with T2DM showed that circulating RBP-4 was higher in both non-proliferative and proliferative DR versus patients without DR [131]. Furthermore, RBP-4 antagonists have been developed and tested for the treatment of the dry form of AMD in preclinical studies that may hopefully be applicable to human AMD, in which a higher trend of circulating RBP-4 has been observed [130].

4. Potential therapeutic implications

To-date, cataract is surgically managed, whereas the management of glaucoma typically begins with topical drug administration targeting to reduce IOP, while surgical management is reserved for advanced or treatment-resistant cases of glaucoma [169]. For neovascular retinopathies (i.e., wet AMD, PDR), current treatment options primarily focus on the direct intravitreal inhibition of VEGF by anti-VEGF therapy, including ranibizumab, aflibercept and bevacizumab, which are considered the standard of care [170]. Although, anti-VEGF therapy is considered to be safe and effective, challenges remain, as some patients exhibit resistance to treatment, the protocols often require repeated injections that pose a risk of complications (e.g., infection) and anti-VEGF therapy is ineffective in addressing progressive forms of other retinopathies (i.e., dry AMD, NPDR) [171]. Therefore, given the limited therapeutic options, especially for neovascular retinopathies, targeting specific adipokines and/or hepatokines, may hopefully mitigate or prevent certain age-related ocular diseases based on the above-mentioned potential implication in the pathogenesis of these diseases. Although relevant research is at its infancy, some attempts are summarized hereby.

AdipoRon, an adiponectin agonist, has recently gained attention for its potential therapeutic effects on DR and glaucoma [98,172]. It appears to offer neuroprotection against RGC death, a hallmark of glaucoma. AdipoRon may mitigate oxidative stress by upregulating peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), estrogen-related receptor α (ERRα) and mitochondrial transcription factor A (TFAM) in rat models of glaucoma [98]. In DR models, AdipoRon promoted the synthesis and expression of early growth response factor 4 (EGR4) and alleviated oxidative stress and apoptosis of cells and tissues in AMPK dependent pathways [172].

Fenretinide, an RBP-4 inhibitor, has been investigated in clinical trials as a potential treatment for dry AMD [173]. In a 2-year randomized controlled trial involving 246 patients with advanced dry AMD (geographic atrophy), treatment with fenretinide showed a reduction in the incidence of choroidal neovascularization, particularly in the higher-dose group [173]. Ongoing clinical trials continue to explore the therapeutic effects of targeting RBP-4 (clinicaltrials.gov identifier: NCT03735810).

Long-acting FGF-21 demonstrated potential in counteracting VEGF-induced retinal vascular leakages in DR by increasing the expression of inter-endothelial tight junction protein Claudin-1 [159]. FGF-21 also showed promise in inhibiting retinal neovascularization and inflammation in AMD animal models, likely through an APN-dependent mechanism [158].

Furthermore, given the potential association between obesity and ocular disease, preventive measures for the development and progression of age-related eye diseases should include lifestyle modifications, such as weight loss, a balanced diet and a regular physical activity [38]. In selected patients with morbid obesity, bariatric surgery may prove effective against POAG, AMD and cataracts [38]. Studies with patients undergoing bariatric surgeries (mini gastric bypass, laparoscopic sleeve gastrectomy) found that reduced BMI after surgery was associated with reduction in IOP and increase in retinal nerve fiber layer thickness, suggesting that bariatric surgery may have favorable effects on patients with morbid obesity and POAG [174,175]. Additionally, in a prospective study including young patients with morbid obesity, sleeve gastrectomy improved macular and peripapillary choroidal thickness, which may be beneficial for patients with AMD [176]. Another study reported that weight loss achieved after bariatric surgery is associated with a reduced risk of cataract, especially in patients younger than 60 years [177]. However, bariatric surgery cannot be performed to all patients with obesity, but only in selected ones and there is high need for active long-term surveillance after surgery [178].

Notably, it is equally important to take into consideration potentially ocular adverse effects of the medications used for the treatment of obesity, T2DM and MASLD in clinical practice. In this regard, in a meta-analysis of randomized clinical trials, glucagon-like peptide-1 receptor agonists (GLP-1RAs) were associated with increased risk of early-stage DR [179]. Although this finding needs verification by other studies, it simultaneously underscores the need for further research in the field, as well as for careful consideration and active surveillance to ensure that anti-obesity, anti-T2DM and anti-MASLD medications do not complicate ocular diseases.

5. Conclusions

Obesity, MASLD and ocular diseases seem to share common age-related pathophysiological processes orchestrated, in part, by alterations in the secretion patterns of adipokines, primarily by the adipose tissue that dysfunctions in obesity, and hepatokines, primarily by the liver that dysfunctions in MASLD (Fig. 1). Although obesity and MASLD are strongly associated and share common pathogenetic mechanisms, they are distinct pathogenic entities that affect each other [180]. It should be highlighted that about 10–15 % of patients with MASLD are not obese, a subgroup characterized as lean MASLD that also has high morbidity and mortality, maybe higher than patients with MASLD and obesity [181]. In this regard, MASLD is regarded as a multisystem disease that may affect various organs, and be affected be various organs in a bidirectional way; this may occur either directly or indirectly through obesity, dysglycemia, dyslipidemia and/or arterial hypertension that are common in MASLD [182].

Regarding the association between obesity and ocular disease, visceral adiposity seems to be associated with age-related ocular diseases more consistently than BMI-defined obesity. Regarding adipokines, altered APN levels, both circulating and in ocular fluids, as well as gene polymorphisms have been associated with AMD and PDR, whereas evidence linking APN with glaucoma and cataract are limited. Some of the other adipokines were found to be associated with AMD and DR whereas further research is guaranteed to draw secure conclusions for adipokines as potential mediators between obesity and the ocular diseases. Regarding the association between MASLD and ocular disease, most clinical data concur that MASLD is probably associated with increased risk of DR in T1DM, whereas not in those with T2DM. The

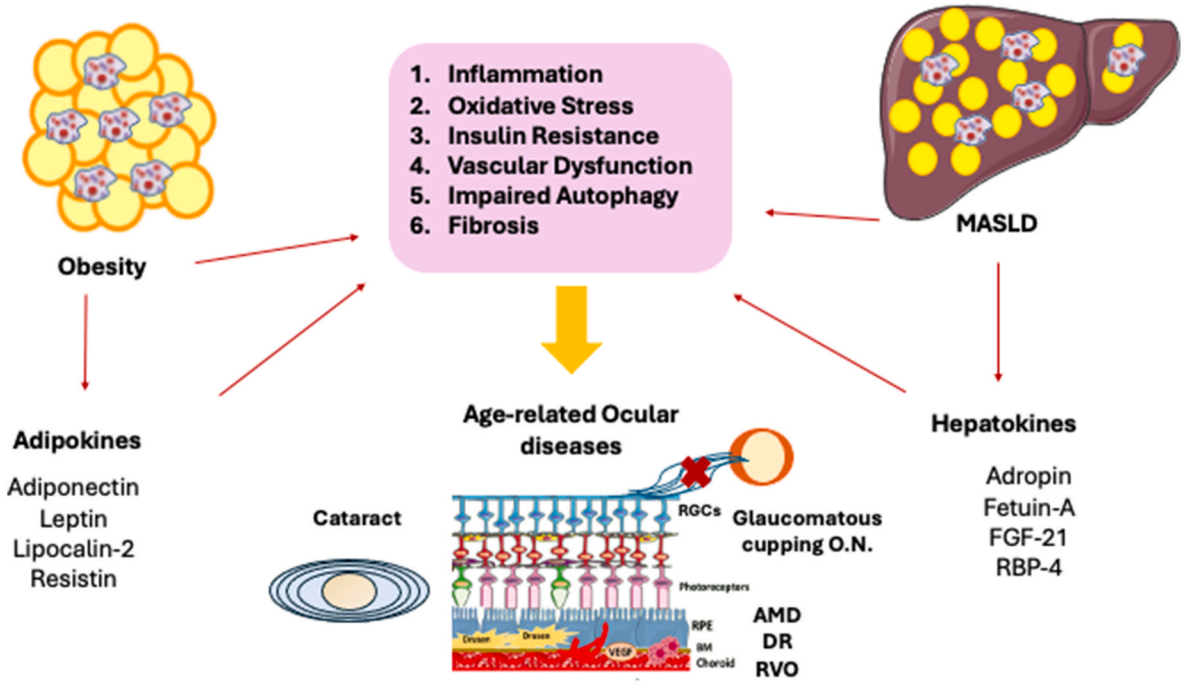

Fig. 1. Interplay between obesity, MASLD and age-related ocular diseases. Schematic representation of the consequences of obesity and MASLD on ocular homeostasis directly and through the effects of adipokines and hepatokines, respectively. AMD, age-related macular degeneration; DR, diabetic retinopathy; FGF-21: fibroblast growth factor-21; MASLD, metabolic dysfunction-associated steatotic liver disease; O.N., optic nerve; RBP-4, plasma retinol-binding protein 4; RGCs, retinal ganglion cells; RVO, retinal vein occlusion.

association between MASLD and AMD, glaucoma and cataract needs further investigation. Regarding hepatokines, low adropin levels were associated with DR severity in T2DM, while high serum fetuin-A and FGF-21 levels were observed in patients with DR. Furthermore, serum RBP-4 seems to be higher in patients with than without DR; notably RBP-4 was shown to promote retinal neurodegeneration in animal models of DR. In this regard, potentially novel adipokine-based and hepatokine-based therapies, including AdipoRon, fenretinide and FGF-21 agonist may prove to be beneficial for ocular diseases in the near future.

CRediT authorship contribution statement

Stavroula Almpanidou: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Conceptualization. **Ilias D. Vachliotis:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Conceptualization. **Antonis Goulas:** Writing – review & editing. **Stergios A. Polyzos:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Conceptualization.

Declaration of generative AI in scientific writing

No form of AI was used for the preparation of this manuscript.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors have nothing to declare.

References

[1] Chu J, Shaia JK, Sharma N, Russell MW, Rachitskaya AV, Talcott KE, et al. Characterization and prevalence of ocular comorbidities and risk of legal blindness across the United States. Early Years Educat 2024;38:3118–24. https://doi.org/10.1038/s41433-024-03238-3.
[2] Ng Yin Ling C, Lim SC, Jonas JB, Sabanayagam C. Obesity and risk of age-related eye diseases: a systematic review of prospective population-based studies. Int J Obes 2021;45:1863–85. https://doi.org/10.1038/s41366-021-00829-y.
[3] Wu J, Duan C, Yang Y, Wang Z, Tan C, Han C, et al. Insights into the liver-eyes connections, from epidemiological, mechanical studies to clinical translation. J Transl Med 2023;21:712. https://doi.org/10.1186/s12967-023-04543-3.
[4] Polyzos SA, Kountouras J, Mantzoros CS. Adipose tissue, obesity and non-alcoholic fatty liver disease. Minerva Endocrinol 2017;42:92–108. https://doi.org/10.23736/s0391-1977.16.02563-3.
[5] Dammak A, Huete-Toral F, Carpena-Torres C, Martin-Gil A, Pastrana C, Carracedo G. From oxidative stress to inflammation in the posterior ocular diseases: diagnosis and treatment. Pharmaceutics 2021;13:1376. https://doi.org/10.3390/pharmaceutics13091376.
[6] Zheng Z, Yu X. Insulin resistance in the retina: possible implications for certain ocular diseases. Front Endocrinol 2024;15:1415521. https://doi.org/10.3389/fendo.2024.1415521.
[7] Finkelstein EA, Khavjou OA, Thompson H, Trogdon JG, Pan L, Sherry B, et al. Obesity and severe obesity forecasts through 2030. Am J Prev Med 2012;42:563–70. https://doi.org/10.1016/j.amepre.2011.10.026.
[8] Bourne RRA, Flaxman SR, Braithwaite T, Cicinelli MV, Das A, Jonas JB, et al. Magnitude, temporal trends, and projections of the global prevalence of blindness and distance and near vision impairment: a systematic review and meta-analysis. Lancet Global Health 2017;5:e888–97. https://doi.org/10.1016/S2214-109X(17)30293-0.
[9] Jura M, Kozak LP. Obesity and related consequences to ageing. Age (Dordr) 2016;38. https://doi.org/10.1007/s11357-016-9884-3.
[10] Malandrino N, Bhat SZ, Alfaraidhy M, Grewal RS, Kalyani RR. Obesity and aging. Endocrinol Metab Clin N Am 2023;52:317–39. https://doi.org/10.1016/j.ecl.2022.10.001.
[11] Kaarniranta K, Paananen J, Nevalainen T, Sorri I, Seitsonen S, Immonen I, et al. Adiponectin receptor 1 gene (ADIPOR1) variant is associated with advanced age-related macular degeneration in Finnish population. Neurosci Lett 2012;513:233–7. https://doi.org/10.1016/j.neulet.2012.02.050.
[12] Cao G, Chen Y, Zhang J, Liu Y, Zhang M, Zhang K, et al. Effects of adiponectin polymorphisms on the risk of advanced age-related macular degeneration. Biomarkers 2015;20:266–70. https://doi.org/10.3109/1354750X.2015.1068857.
[13] Mao D, Peng H, Li Q, Wang J, Li P, Hu K, et al. Aqueous humor and plasma adiponectin levels in proliferative diabetic retinopathy patients. Curr Eye Res 2012;37:803–8. https://doi.org/10.3109/02713683.2012.676700.

[14] Srinivasan V, Chidambaram S, Karunakaran C, Rishi P, Konerirajapuram S. Measurement of adiponectin in vitreous and plasma of patients with proliferative diabetic retinopathy and its correlation with vascular endothelial growth factor, pigment epithelial derived factor and insulin like growth factor-1. Int J Pharm Biol Sci 2013;4:B993–1005.
[15] Omae T, Nagaoka T, Yoshida A. Relationship between retinal blood flow and serum adiponectin concentrations in patients with type 2 diabetes mellitus. Investig Ophthalmol Vis Sci 2015;56:4143. https://doi.org/10.1167/iovs.15-16447.
[16] Yang HS, Choi YJ, Han HY, Kim HS, Park SH, Lee KS, et al. Serum and aqueous humor adiponectin levels correlate with diabetic retinopathy development and progression. PLoS One 2021;16:e0259683. https://doi.org/10.1371/journal.pone.0259683.
[17] Sutkowy P, Lesiewska H, Woźniak A, Malukiewicz G. Inflammation-involved proteins in blood serum of cataract patients—a preliminary study. Biomedicines 2023;11:2607. https://doi.org/10.3390/biomedicines11102607.
[18] Gencoglu Y, Irkec M, Kocabeyoglu S, Dikmen ZG, Karakaya J, Konstas AGP. Plasma levels of sirtuin and adiponectin in patients with primary open-angle glaucoma, exfoliative glaucoma, and healthy controls. Eur J Ophthalmol 2022;32:2893–8. https://doi.org/10.1177/11206721211065216.
[19] Evereklioglu C, Doganay S, Er H, Cekmen M, Ozerol E, Otlu B. Serum leptin concentrations are decreased and correlated with disease severity in age-related macular degeneration: a preliminary study. Early Years Educat 2003;17:350–5. https://doi.org/10.1038/sj.eye.6700345.
[20] Seshasai S, Liao J, Toh QC, Cheng C-Y, Cheung GCM, Sethi S, et al. Serum Leptin and age-related macular degeneration. Investig Ophthalmol Vis Sci 2015;56:1880. https://doi.org/10.1167/iovs.14-15933.
[21] Hernández C, Lecube A, Castellanos JM, Segura RM, Garat M, García-Arumí J, et al. Intravitreous Leptin concentrations in patients with proliferative diabetic retinopathy. Retina 2004;24:30–5. https://doi.org/10.1097/00006982-200402000-00005.
[22] Maberley D, Cui JZ, Matsubara JA. Vitreous leptin levels in retinal disease. Early Years Educat 2006;20:801–4. https://doi.org/10.1038/sj.eye.6702011.
[23] Rezar-Dreindl S, Sacu S, Eibenberger K, Pollreisz A, Bühl W, Georgopoulos M, et al. The intraocular cytokine profile and therapeutic response in persistent neovascular age-related macular degeneration. Investig Ophthalmol Vis Sci 2016;57:4144–50. https://doi.org/10.1167/iovs.16-19772.
[24] Zhang Y, Song X, Qi T, Gao S, Sun C, Yang J, et al. Association between lipocalin-2 levels and diabetic retinopathy in patients with overweight/obese type 2 diabetes mellitus. Ir J Med Sci 2023;192:2785–92. https://doi.org/10.1007/s11845-023-03365-y.
[25] Luo Y, Wan J, Luo C, Liu H, Zhou Y, Chen J, et al. Higher aqueous levels of resistin and lipocalin-2 indicated worse visual improvement following anti-VEGF therapy in patients with retinal vein occlusion. Curr Eye Res 2021;46:845–54. https://doi.org/10.1080/02713683.2020.1842462.
[26] Osawa H, Ochi M, Kato K, Yamauchi J, Nishida W, Takata Y, et al. Serum resistin is associated with the severity of microangiopathies in type 2 diabetes. Biochem Biophys Res Commun 2007;355:342–6. https://doi.org/10.1016/j.bbrc.2007.01.144.
[27] Gurlevik U, Ozdamar Erol Y, Yasar E. Serum and vitreous resistin levels in patıents with proliferative diabetic retinopathy. Diabetes Res Clin Pract 2019;155:107803. https://doi.org/10.1016/j.diabres.2019.107803.
[28] Zhu W, Wu Y, Meng Y-F, Xing Q, Tao J-J, Lu J. Association of obesity and risk of diabetic retinopathy in diabetes patients: a meta-analysis of prospective cohort studies. Medicine (Baltim) 2018;97:e11807. https://doi.org/10.1097/MD.0000000000011807.
[29] Li W, Gong X, Wang W, Xiong K, Meng J, Li Y, et al. Association of different kinds of obesity with diabetic retinopathy in patients with type 2 diabetes. BMJ Open 2022;12:e056332. https://doi.org/10.1136/bmjopen-2021-056332.
[30] Chen J, Li YT, Niu Z, He Z, Xie YJ, Hernandez J, et al. Association of visceral obesity indices with incident diabetic retinopathy in patients with diabetes: prospective cohort study. JMIR Public Health Surveill 2024;10:e48120. https://doi.org/10.2196/48120.
[31] Chen J, Wan Y, Su J, Zhu Z, Pan E, Shen C, et al. Association of generalized and abdominal obesity with diabetic retinopathy in Chinese type 2 diabetic patients. Acta Diabetol 2022;59:359–67. https://doi.org/10.1007/s00592-021-01806-7.
[32] Ades PA, Savage PD. The obesity paradox: perception vs knowledge. Mayo Clin Proc 2010;85:112–4. https://doi.org/10.4065/mcp.2009.0777.
[33] Garberg G, Lövestam-Adrian M, Nasic S, Boström KB. The prognosis of diabetic retinopathy in patients with type 2 diabetes since 1996-1998: the Skaraborg Diabetes Register. Int Ophthalmol 2015;35:503–11. https://doi.org/10.1007/s10792-014-9976-y.
[34] Chan JCY, Chee ML, Tan NYQ, Cheng C-Y, Wong TY, Sabanayagam C. Differential effect of body mass index on the incidence of diabetes and diabetic retinopathy in two Asian populations. Nutr Diabetes 2018;8:16. https://doi.org/10.1038/s41387-018-0018-0.
[35] Hwang IC, Bae JH, Kim JM. Relationship between body fat and diabetic retinopathy in patients with type 2 diabetes: a nationwide survey in Korea. Early Years Educat 2019;33:980–7. https://doi.org/10.1038/s41433-019-0352-z.
[36] Wong TY, Klein R, Islam FMA, Cotch MF, Folsom AR, Klein BEK, et al. Diabetic retinopathy in a multi-ethnic cohort in the United States. Am J Ophthalmol 2006;141:446–55. https://doi.org/10.1016/j.ajo.2005.08.063.
[37] Man REK, Sabanayagam C, Chiang PP-C, Li L-J, Noonan JE, Wang JJ, et al. Differential association of generalized and abdominal obesity with diabetic retinopathy in Asian patients with type 2 diabetes. JAMA Ophthalmol 2016;134:251–7. https://doi.org/10.1001/jamaophthalmol.2015.5103.
[38] Lam S, Lindsey J, Carranza Leon BG, Takkouche S. Shedding light on eye disease in obesity: a review. Clin Obes 2024;14:e12616. https://doi.org/10.1111/cob.12616.
[39] Adams MKM, Simpson JA, Aung KZ, Makeyeva GA, Giles GG, English DR, et al. Abdominal obesity and age-related macular degeneration. Am J Epidemiol 2011;173:1246–55. https://doi.org/10.1093/aje/kwr005.
[40] Peeters A, Magliano DJ, Stevens J, Duncan BB, Klein R, Wong TY. Changes in abdominal obesity and age-related macular degeneration: the Atherosclerosis Risk in Communities Study. Arch Ophthalmol 2008;126:1554–60. https://doi.org/10.1001/archopht.126.11.1554.
[41] Jonasson F, Fisher DE, Eiriksdottir G, Sigurdsson S, Klein R, Launer LJ, et al. Five-year incidence, progression, and risk factors for age-related macular degeneration: the age, gene/environment susceptibility study. Ophthalmology 2014;121:1766–72. https://doi.org/10.1016/j.ophtha.2014.03.013.
[42] You QS, Xu L, Yang H, Li YB, Wang S, Wang JD. Fiveyear incidence of age-related macular degeneration: the Beijing Eye Study. Ophthalmology 2012;119:2519–25. https://doi.org/10.1016/j.ophtha.2012.06.043.
[43] Miyazaki M, Kiyohara Y, Yoshida A, Iida M, Nose Y, Ishibashi T. The 5-year incidence and risk factors for age-related maculopathy in a general Japanese population: the Hisayama study. Investig Ophthalmol Vis Sci 2005;46:1907–10. https://doi.org/10.1167/iovs.04-0923.
[44] Cheung CMG, Ong PG, Neelam K, Tan PC, Shi Y, Mitchell P, et al. Six-year incidence of age-related macular degeneration in Asian Malays: the Singapore Malay eye study. Ophthalmology 2017;124:1305–13. https://doi.org/10.1016/j.ophtha.2017.03.056.
[45] Foo V, Yanagi Y, Nguyen QD, Sabanayagam C, Lim SH, Neelam K. Six-year incidence and risk factors of age related macular degeneration in Singaporean Indians: the Singapore Indian Eye Study. Sci Rep 2018;8:8869. doi:10.1038/s41598-018-27202-w.
[46] Raman R, Jaisankar D, Swaminathan G, Roy R, Kulothungan V, Sharma T. Association of obesity and age-related macular degeneration in Indian population. Indian J Ophthalmol 2018;66:976. https://doi.org/10.4103/ijo.ijo_1265_17.
[47] Yuan S, Wolk A, Larsson SC. Metabolic and lifestyle factors in relation to senile cataract: a Mendelian randomization study. Sci Rep 2022;12:409. https://doi.org/10.1038/s41598-021-04515-x.
[48] Ang MJ, Afshari NA. Cataract and systemic disease: a review. Clin Exp Ophthalmol 2021;49:118–27. https://doi.org/10.1111/ceo.13892.
[49] Sabanayagam C, Wang JJ, Mitchell P, Tan AG, Tai ES, Aung T, et al. Metabolic syndrome components and age-related cataract: the Singapore Malay eye study. Investig Ophthalmol Vis Sci 2011;52:2397–404. https://doi.org/10.1167/iovs.10-6373.
[50] Leske M.C., Wu S.Y., Nemesure B., Hennis A. Barbados Eye Studies G. Risk factors for incident nuclear opacities. Ophthalmology 2002;109:1303–1308. doi: 10.1016/s0161-6420(2)01094-1.
[51] Pan C-W, Lin Y. Overweight, obesity, and age-related cataract: a meta-analysis. Optom Vis Sci 2014;91:478–83. https://doi.org/10.1097/OPX.0000000000000243.
[52] Ye J, Lou LX, He JJ, Xu YF. Body mass index and risk of age-related cataract: a meta-analysis of prospective cohort studies. PLoS One 2014;9:e89923. https://doi.org/10.1371/journal.pone. 0089923.
[53] Schaumberg DA, Ridker PM, Glynn RJ, Christen WG, Dana MR, Hennekens CH. High levels of plasma C-reactive protein and future risk of age-related cataract. Ann Epidemiol 1999;9:166–71. https://doi.org/10.1016/s1047-2797(98)00049-0.
[54] Varma SD, Chand D, Sharma YR, Kuck JF Jr, Richards RD. Oxidative stress on lens and cataract formation: role of light and oxygen. Curr Eye Res 1984;3:35–57. https://doi.org/10.3109/02713688408997186.
[55] Klein BE, Klein R, Jensen SC, Linton KL. Hypertension and lens opacities from the beaver dam eye study. Am J Ophthalmol 1995;119:640–6. https://doi.org/10.1016/s0002-9394(14)70223-5.
[56] Machan CM, Hrynchak PK, Irving EL. Age-related cataract is associated with type 2 diabetes and statin use. Optom Vis Sci 2012;89:1165–71. https://doi.org/10.1097/OPX.0b013e3182644cd1.
[57] Rowe NG, Mitchell PG, Cumming RG, Wans JJ. Diabetes, fasting blood glucose and age-related cataract: the Blue Mountains Eye Study. Ophthalmic Epidemiol 2000;7:103–14. https://doi.org/10.1076/0928-6586(200006)721-zft103.
[58] Jung Y, Kim GN, Oh EB, Ohn K, Moon JI. Metabolic health, obesity, and intraocular pressure. J Clin Med 2023;12:2066. https://doi.org/10.3390/jcm12052066.
[59] Rong SS, Yu X. Phenotypic and genetic links between body fat measurements and primary open-angle glaucoma. Int J Mol Sci 2023;24:3925. https://doi.org/10.3390/IJMS240439.
[60] Khan S, Kirubarajan A, Lee M, Pitha I, Buckey Jr JC. The Correlation Between Body Weight and Intraocular Pressure. Aerosp Med Hum Perform 2021;92:886–97. https://doi.org/10.3357/AMHP.5769.2021.
[61] Lin Y, Zhu X, Luo W, Jiang B, Lin Q, Tang M, et al. The causal association between obesity and primary open-angle glaucoma: a two-sample Mendelian randomization study. Front Genet 2022;13:835524. https://doi.org/10.3389/fgene.2022.835524.
[62] Kim YK, Choi HJ, Jeoung JW, Park KH, Kim DM. Five-year incidence of primary open-angle glaucoma and rate of progression in health center-based Korean population: the Gangnam EyeStudy. PLoS One 2014;9:e114058. doi: 10.1371/journal.pone.0114058.
[63] Jiang X, Varma R, Wu S, Torres M, Azen SP, Francis BA, et al. Baseline risk factors that predict the development of open-angle glaucoma in a population: the Los

Angeles Latino Eye Study. Ophthalmology 2012;119:2245–53. https://doi.org/10.1016/j.ophtha.2012.05.030.
[64] Wise LA, Rosenberg L, Radin RG, Mattox C, Yang EB, Palmer JR, et al. A prospective study of diabetes, lifestyle factors, and glaucoma among African-American women. Ann Epidemiol 2011;21:430–9. https://doi.org/10.1016/j.annepidem.2011.03.006.
[65] Han X, Yang T, Zhang J, Yu S, Guo X, Yan W, et al. Longitudinal changes in intraocular pressure and association with systemic factors and refractive error: lingtou Eye Cohort Study. BMJ Open 2018;8:e019416. https://doi.org/10.1136/bmjopen-2017-019416.
[66] Yoshida M, Ishikawa M, Karita K, Kokaze A, Harada M, Take S, et al. Association of blood pressure and body mass index with intraocular pressure in middle-aged and older Japanese residents: a cross-sectional and longitudinal study. Acta Med Okayama 2014;68:27–34. https://doi.org/10.18926/AMO/52141.
[67] Zhao D, Kim MH, Pastor-Barriuso R, Chang Y, Ryu S, Zhang Y, et al. A longitudinal study of association between adiposity markers and intraocular pressure: the Kangbuk Samsung health study. PLoS One 2016;11:e0146057. https://doi.org/10.1371/journal.pone.0146057.
[68] Wang YX, Xu L, Zhang XH, You QS, Zhao L, Jonas JB. Fiveyear change in intraocular pressure associated with changes in arterial blood pressure and body mass index. The Beijing eye study. PLoS One 2013;8:e77180. https://doi.org/10.1371/journal.pone.0077180.
[69] Onaran Z, Konuk O, Oktar SÖ, Yücel C, Unal M. Intraocular pressure lowering effect of orbital decompression is related to increased venous outflow in Graves orbitopathy. Curr Eye Res 2014;39:666–72. https://doi.org/10.3109/02713683.2013.867355.
[70] Baudouin C, Kolko M, Melik-Parsadaniantz S, Messmer EM. Inflammation in Glaucoma: from the back to the front of the eye, and beyond. Prog Retin Eye Res 2021;83:100916. https://doi.org/10.1016/j.preteyeres.2020.100916.
[71] Springelkamp H, Wolfs RC, Ramdas WD, Hofman A, Vingerling JR, Klaver CC, et al. Incidence of glaucomatous visual field loss after two decades of follow-up: the Rotterdam Study. Eur J Epidemiol 2017;32:691–9. https://doi.org/10.1007/s10654-017-0270-y.
[72] Pasquale LR, Willett WC, Rosner BA, Kang JH. Anthropometric measures and their relation to incident primary open-angle glaucoma. Ophthalmology 2010;117:1521–9. https://doi.org/10.1016/j.ophtha.2009.12.017.
[73] Ramdas WD, Wolfs RCW, Hofman A, de Jong PTVM, Vingerling JR, Jansonius NM. Lifestyle and risk of developing open-angle glaucoma: the Rotterdam study. Arch Ophthalmol 2011;129:767–72. https://doi.org/10.1001/archophthalmol.2010.373.
[74] Na K-S, Kim J-H, Paik J-S, Cho W-K, Ha M, Park Y-G, et al. Underweight increases the risk of primary open-angle glaucoma in diabetes patients: a Korean nationwide cohort study. Medicine (Baltim) 2020;99:e19285. https://doi.org/10.1097/MD.0000000000019285.
[75] Berdahl JP, Fleischman D, Zaydlarova J, Stinnett S, Allingham RR, Fautsch MP. Body mass index has a linear relationship with cerebrospinal fluid pressure. Investig Ophthalmol Vis Sci 2012;53:1422–7. https://doi.org/10.1167/iovs.11-8220.
[76] Polyzos SA, Mantzoros CS. Obesity: seize the day, fight the fat. Metabolism 2019;92:1–5. https://doi.org/10.1016/j.metabol.2018.12.011.
[77] Li H-Y, Hong X, Cao Q-Q, So K-F. Adiponectin, exercise and eye diseases. Int Rev Neurobiol 2019;147:281–94. https://doi.org/10.1016/bs.irn.2019.07.006.
[78] Polyzos SA, Kountouras J, Zavos C, Tsiaousi E. The role of adiponectin in the pathogenesis and treatment of non-alcoholic fatty liver disease. Diabetes Obes Metabol 2010;12:365–83. https://doi.org/10.1111/j.1463-1326.2009.01176.x.
[79] Fan X, Wu Q, Li Y, Hao Y, Ning N, Kang Z, et al. Association between adiponectin concentrations and diabetic retinopathy in patients with type 2 diabetes: a meta analysis. Chin Med J (Engl Ed) 2014;127:765–71.
[80] Fu Z, Löfqvist CA, Liegl R, Wang Z, Sun Y, Gong Y, et al. Photoreceptor glucose metabolism determines normal retinal vascular growth. EMBO Mol Med 2018;10:76–90. https://doi.org/10.15252/emmm.201707966.
[81] Iwabu M, Okada-Iwabu M, Yamauchi T, Kadowaki T. Adiponectin/adiponectin receptor in disease and aging. NPJ Aging Mech Dis 2015;1:15013. https://doi.org/10.1038/npjamd.2015.13.
[82] Osada H, Toda E, Homma K, Guzman NA, Nagai N, Ogawa M, et al. ADIPOR1 deficiency-induced suppression of retinal ELOVL2 and docosahexaenoic acid levels during photoreceptor degeneration and visual loss. Cell Death Dis 2021;12:458. https://doi.org/10.1038/s41419-021-03741-5.
[83] Fu Z, Gong Y, Löfqvist C, Hellström A, Smith LEH. Review: adiponectin in retinopathy. Biochim Biophys Acta, Mol Basis Dis 2016;1862:1392–400. https://doi.org/10.1016/j.bbadis.2016.05.002.
[84] Wang M, Wang D, Zhang Y, Wang X, Liu Y, Xia M. Adiponectin increases macrophages cholesterol efflux and suppresses foam cell formation in patients with type 2 diabetes mellitus. Atherosclerosis 2013;229:62–70. https://doi.org/10.1016/j.atherosclerosis.2013.01.017.
[85] Choubey M, Tirumalasetty MB, Bora NS, Bora PS. Linking adiponectin and its receptors to age-related macular degeneration (AMD). Biomedicines 2023;11:3044. https://doi.org/10.3390/biomedicines11113044.
[86] Fantuzzi G. Adiponectin in inflammatory and immune-mediated diseases. Cytokine 2013;64:1–10. https://doi.org/10.1016/j.cyto.2013.06.317.
[87] Choubey M, Ranjan A, Bora PS, Krishna A. Protective role of adiponectin against testicular impairment in high-fat diet/streptozotocin-induced type 2 diabetic mice. Biochimie 2020;168:41–52. https://doi.org/10.1016/j.biochi.2019.10.014.
[88] Siitonen N, Pulkkinen L, Lindström J, Kolehmainen M, Eriksson JG, Venojärvi M, et al. Association of ADIPOQ gene variants with body weight, type 2 diabetes and serum adiponectin concentrations: the Finnish Diabetes Prevention Study. BMC Med. BMC Med Genet 2011;12:5. https://doi.org/10.1186/1471-2350-12-5.
[89] Siitonen N, Pulkkinen L, Mager U, Lindström J, Eriksson JG, Valle TT, et al. Association of sequence variations in the gene encoding adiponectin receptor 1 (ADIPOR1) with body size and insulin levels. The Finnish Diabetes Prevention Study. Diabetologia 2006;49:1795–805. https://doi.org/10.1007/s00125-006-0291-7.
[90] Kato K, Osawa H, Ochi M, Kusunoki Y, Ebisui O, Ohno K, et al. Serum total and high molecular weight adiponectin levels are correlated with the severity of diabetic retinopathy and nephropathy. Clin Endocrinol 2008;68:442–9. https://doi.org/10.1111/j.1365-2265.2007.03063.x.
[91] Liao W-L, Chen Y-H, Chen C-C, Huang Y-C, Lin H-J, Chen Y-T, et al. Effect of adiponectin level and genetic variation of its receptors on diabetic retinopathy. Medicine (Baltim) 2019;98:e14878. https://doi.org/10.1097/md.0000000000014878.
[92] Kuo JZ, Guo X, Klein R, Klein BE, Genter P, Roll K, et al. Adiponectin, insulin sensitivity and diabetic retinopathy in Latinos with type 2 diabetes. J Clin Endocrinol Metab 2015;100:3348–55. https://doi.org/10.1210/jc.2015-1221.
[93] Yilmaz MI, Sonmez A, Acikel C, Celik T, Bingol N, Pinar M, et al. Adiponectin may play a part in the pathogenesis of diabetic retinopathy. Eur J Endocrinol 2004;151:135–40. https://doi.org/10.1530/eje.0.1510135.
[94] Zietz B, Buechler C, Kobuch K, Neumeier M, Schölmerich J, Schäffler A. Serum levels of adiponectin are associated with diabetic retinopathy and with adiponectin gene mutations in Caucasian patients with diabetes mellitus type 2. Exp Clin Endocrinol Diabetes 2008;116:532–6. https://doi.org/10.1055/s-2008-1058086.
[95] Nishinaka A, Nakamura S, Tanaka M, Masuda T, Inoue Y, Yamamoto T, et al. Excess adiponectin in eyes with progressive ocular vascular diseases. FASEB J 2021;35:e21313. https://doi.org/10.1096/fj.202001740rr.
[96] Friedlander M. Fibrosis and diseases of the eye. J Clin Investig 2007;117:576–86. https://doi.org/10.1172/JCI31030.
[97] Palanisamy K, Raman R, Sulochana KN, Chidambaram S. Adiponectin: a potential candidate for treating fibrosis in posterior segment of the eye. Med Hypotheses 2019;123:9–12. https://doi.org/10.1016/j.mehy.2018.12.005.
[98] Uchida T, Ueta T, Honjo M, Aihara M. The neuroprotective effect of the adiponectin receptor agonist AdipoRon on glutamate-induced cell death in rat primary retinal ganglion cells. J Ocul Pharmacol Therapeut 2019;35:535–41. https://doi.org/10.1089/jop.2018.0152.
[99] Polyzos SA, Mantzoros CS. Leptin in health and disease: facts and expectations at its twentieth anniversary. Metabolism 2015;64:5–12. https://doi.org/10.1016/j.metabol.2014.10.017.
[100] Fewlass DC, Noboa K, Pi-Sunyer FX, Johnston JM, Yan SD, Tezapsidis N. Obesity-related leptin regulates Alzheimer's Abeta. FASEB J 2004;18:1870–8. https://doi.org/10.1096/fj.04-2572com.
[101] Irving A, Harvey J. Regulation of hippocampal synaptic function by the metabolic hormone leptin: implications for health and disease. Prog Lipid Res 2021;82:101098. https://doi.org/10.1016/j.plipres.2021.101098.
[102] Lee EB. Obesity, leptin, and Alzheimer's disease. Ann N Y Acad Sci 2011;1243:15–29. https://doi.org/10.1111/j.1749-6632.2011.06274.x.
[103] Marwarha G, Prasanthi JR, Schommer J, Dasari B, Ghribi O. Molecular interplay between leptin, insulin-like growth factor-1, and β-amyloid in organotypic slices from rabbit hippocampus. Mol Neurodegener 2011;6:41. https://doi.org/10.1186/1750-1326-6-41.
[104] Isas JM, Luibl V, Johnson LV, Kayed R, Wetzel R, Glabe CG, et al. Soluble and mature amyloid fibrils in drusen deposits. Investig Ophthalmol Vis Sci 2010;51:1304–10. https://doi.org/10.1167/iovs.09-4207.
[105] Ebrahimi KB, Handa JT. Lipids, lipoproteins, and age-related macular degeneration. J Lipids 2011;2011:802059. https://doi.org/10.1155/2011/802059.
[106] Cui JZ, Hornan D, Potter MJ, Greve MDJ, Hinz BJ, Samad A, et al. The role of leptin in choroidal neovascularization. Am J Ophthalmol 2001;132:792–4. https://doi.org/10.1016/s0002-9394(01)01105-9.
[107] Coroniti R, Fario R, Nuno DJ, Otvos L, Scolaro L, Surmacz E. Designer Leptin receptor antagonist Allo-aca inhibits VEGF effects in ophthalmic neoangiogenesis models. Front Mol Biosci 2016;3:67. https://doi.org/10.3389/fmolb.2016.00067.
[108] Miller JW. VEGF: from discovery to therapy: the champalimaud award lecture. Transl Vis Sci Technol 2016;5:9. https://doi.org/10.1167/tvst.5.2.9.
[109] Gupta A. Leptin as a neuroprotective agent in glaucoma. Med Hypotheses 2013;81:797–802. https://doi.org/10.1016/j.mehy.2013.08.023.
[110] Gómez-Ambrosi J, Salvador J, Frühbeck G. Is hyperleptinemia involved in the development of age-related lens opacities? Am J Clin Nutr 2004;79:888–9. https://doi.org/10.1093/ajcn/79.5.888.
[111] Klok MD, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. Obes Rev 2007;8:21–34. https://doi.org/10.1111/j.1467-789X.2006.00270.x.
[112] Ghosh S, Stepicheva N, Yazdankhah M, Shang P, Watson AM, Hose S, et al. The role of lipocalin-2 in age-related macular degeneration (AMD). Cell Mol Life Sci 2020;77:835–51. https://doi.org/10.1007/s00018-019-03423-8.
[113] Ghosh S, Shang P, Yazdankhah M, Bhutto I, Hose S, Montezuma SR, et al. Activating the AKT2–nuclear factor-κB–lipocalin-2 axis elicits an inflammatory response in age-related macular degeneration. J Pathol 2017;241:583–8. https://doi.org/10.1002/path.4870.
[114] Zhang Y, Song X, Qi T, Zhou X. Review of lipocalin-2-mediated effects in diabetic retinopathy. Int Ophthalmol 2024;44:78. https://doi.org/10.1007/s10792-024-03015-x.

[115] Polyzos S, Kountouras J, Zavos C. Nonalcoholic fatty liver disease: the pathogenetic roles of insulin resistance and adipocytokines. Curr Mol Med 2009; 9:299–314. https://doi.org/10.2174/156652409787847191.
[116] Athyros VG, Polyzos SA, Kountouras J, Katsiki N, Anagnostis P, Doumas M, et al. Non-alcoholic fatty liver disease treatment in patients with type 2 diabetes mellitus; New kids on the block. Curr Vasc Pharmacol 2020;18:172–81. https://doi.org/10.2174/1570161117666190405164313.
[117] Polyzos SA, Kang ES, Tsochatzis EA, Kechagias S, Ekstedt M, Xanthakos S, et al. Commentary: nonalcoholic or metabolic dysfunction-associated fatty liver disease? The epidemic of the 21st century in search of the most appropriate name. Metabolism 2020;113:154413. https://doi.org/10.1016/j.metabol.2020.154413.
[118] Örnek N, Örnek K, Aydin S, Yilmaz M, Ölmez Y. Serum vascular endothelial growth factor receptor-2 and adropin levels in age-related macular degeneration. Int J Ophthalmol 2016;9:556–60. https://doi.org/10.18240/ijo.2016.04.13.
[119] Neethu A, Jayashree K, Senthilkumar GP, Ramesh Babu K, Vadivelan M. Circulating adropin and vascular endothelial growth factor receptor-2 levels in age-related macular degeneration and T2DM patients-A cross-sectional study. J Fam Med Prim Care 2020;9:4875–9. https://doi.org/10.4103/jfmpc.jfmpc_813_20.
[120] Saeedi-Maleki Z, Javadzadeh A, Brumandpur F, Ghorbanihaghjo A, Khanzadeh S, Mousavi F. Serum adropin level in wet-type age-related macular degeneration. Int J Retina Vitreous 2024;10:27. https://doi.org/10.1186/s40942-024-00543-7.
[121] Li S, Sun J, Hu W, Liu Y, Lin D, Duan H, et al. The association of serum and vitreous adropin concentrations with diabetic retinopathy. Ann Clin Biochem 2019;56:253–8. https://doi.org/10.1177/0004563218820359.
[122] Li B, Li N, Guo S, Zhang M, Li J, Zhai N, et al. The changing features of serum adropin, copeptin, neprilysin and chitotriosidase which are associated with vascular endothelial function in type 2 diabetic retinopathy patients. J Diabet Complicat 2020;34:107686. https://doi.org/10.1016/j.jdiacomp.2020.107686.
[123] Javadzadeh A, Ghorbanihaghjo A, Heidari E, Baharivand N, Sadeghi K, Sorkhabi R, et al. Matrix γ-carboxyglutamate protein and Fetuin-A, in wet type age-related macular degeneration. Int J Ophthalmol 2015;8:556–9. https://doi.org/10.3980/j.issn.2222-3959.2015.03.21.
[124] Zhao C, Hou J, Wang S, Jiang R. Relation of serum and vitreous concentrations of fetuin-A with diabetic retinopathy. Med Sci Monit 2015;21:1839–42. https://doi.org/10.12659/MSM.893403.
[125] Zhou Z-W, Ju H-X, Sun M-Z, Fu Q-P, Chen H-M, Ji H-B, et al. Serum fetuin-A levels are independently correlated with vascular endothelial growth factor and C-reactive protein concentrations in type 2 diabetic patients with diabetic retinopathy. Clin Chim Acta 2016;455:113–7. https://doi.org/10.1016/j.cca.2016.02.003.
[126] Li M, Tian M, Wang Y, Ma H, Zhou Y, Jiang X, et al. Association of plasma galectin-3 and fetuin-A levels with diabetic retinopathy in type 2 diabetes mellitus patients. Endokrynol Pol 2023;74:536–43. https://doi.org/10.5603/ep.96300.
[127] Chang W-C, Lee C-H, Chiou S-H, Liao C-C, Cheng C-W. Proteomic analysis of aqueous humor proteins in association with cataract risks: diabetes and smoking. J Clin Med 2021;10:5731. https://doi.org/10.3390/jcm10245731.
[128] Lee C-H, Lui DT-W, Cheung CY-Y, Fong CH-Y, Yuen MM-A, Woo Y-C, et al. Circulating AFABP, FGF21, and PEDF levels as prognostic biomarkers of sight-threatening diabetic retinopathy. J Clin Endocrinol Metab 2023;108:e799–806. https://doi.org/10.1210/clinem/dgad112.
[129] Jiang Y, Zhang W, Xu Y, Zeng X, Sun X. Relationship of fibroblast growth factor 21, Klotho, and diabetic retinopathy: a meta-analysis. Front Endocrinol 2024;15: 1390035. https://doi.org/10.3389/fendo.2024.1390035.
[130] Chou H-D, Hwang Y-S, Chen K-J, Wu W-C, Liu L, Ou S-T, et al. Analysis of retinol binding protein 4 and ABCA4 gene variation in non-neovascular age-related macular degeneration. Diagnostics 2023;13:2411. https://doi.org/10.3390/diagnostics13142411.
[131] Han W, Wei H, Kong W, Wang J, Yang L, Wu H. Association between retinol binding protein 4 and diabetic retinopathy among type 2 diabetic patients: a meta-analysis. Acta Diabetol 2020;57:1203–18. https://doi.org/10.1007/s00592-020-01535-3.
[132] Song D, Li C, Wang Z, Zhao Y, Shen B, Zhao W. Association of non-alcoholic fatty liver disease with diabetic retinopathy in type 2 diabetic patients: a meta-analysis of observational studies. J Diabetes Investig 2021;12:1471–9. https://doi.org/10.1111/jdi.13489.
[133] Zhang G-H, Yuan T-H, Yue Z-S, Wang L, Dou G-R. The presence of diabetic retinopathy closely associated with the progression of non-alcoholic fatty liver disease: a meta-analysis of observational studies. Front Mol Biosci 2022;9: 1019899. https://doi.org/10.3389/fmolb.2022.1019899.
[134] Orfanidou M, Ntenti C, Evripidou K, Mataftsi A, Goulas A, Polyzos SA. Retinal vascular lesions in patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. J Personalized Med 2023;13:1148. https://doi.org/10.3390/jpm13071148.
[135] Mantovani A, Morieri ML, Aldigeri R, Palmisano L, Masulli M, Bonomo K, et al. MASLD, hepatic steatosis and fibrosis are associated with the prevalence of chronic kidney disease and retinopathy in adults with type 1 diabetes mellitus. Diabetes Metab 2024;50:101497. https://doi.org/10.1016/j.diabet.2023.101497.
[136] Wang X, Zhang R, Man S, Lv J, Yu C, Yin J, et al. Metabolic-associated fatty liver disease in relation to site-specific and multiple-site subclinical atherosclerosis. Liver Int 2023;43:1691–8. https://doi.org/10.1111/liv.15591.
[137] Henney AE, Riley DR, Hydes TJ, Anson M, Ibarburu GH, Zhao SS, et al. Metabolic syndrome traits differentially and cumulatively influence micro- and macrovascular disease risk in patients with MASLD. Liver Int 2024;44:3031-3049. https://doi.org/10.1111/liv.16086.
[138] Yang W, Xu H, Yu X, Wang Y. Association between retinal artery lesions and nonalcoholic fatty liver disease. Hepatol Int 2015;9:278–82. https://doi.org/10.1007/s12072-015-9607-3.
[139] Kang KH, Shin D, Ryu IH, Kim JK, Lee IS, Koh K, et al. Association between cataract and fatty liver diseases from a nationwide cross-sectional study in South Korea. Sci Rep 2024;14:77. https://doi.org/10.1038/s41598-023-50582-7.
[140] Chen C, Wei L, He W, Zhang Y, Xiao J, Lu Y, et al. Associations of severe liver diseases with cataract using data from UK Biobank: a prospective cohort study. EClinicalMedicine 2024;68:102424. https://doi.org/10.1016/j.eclinm.2024.102424.
[141] Kwon Y-J, Kim J-H, Jung D-H. Association between nonalcoholic fatty liver disease and intraocular pressure in Korean adults. J Glaucoma 2018;27: 1099–104. https://doi.org/10.1097/ijg.0000000000001036.
[142] Lee J-H, Kwon Y-J, Lee HS, Han JH, Joung B, Kim SJ. Fatty liver is an independent risk factor for elevated intraocular pressure. Nutrients 2022;14:4455. https://doi.org/10.3390/nu14214455.
[143] Roddy GW, Rosa RH, Viker KB, Holman BH, Hann CR, Krishnan A, et al. Diet mimicking "fast food" causes structural changes to the retina relevant to age-related macular degeneration. Curr Eye Res 2020;45:726–32. https://doi.org/10.1080/02713683.2019.1694156.
[144] Yuan T-H, Yue Z-S, Zhang G-H, Wang L, Dou G-R. Beyond the liver: liver-eye communication in clinical and experimental aspects. Front Mol Biosci 2021;8: 823277. https://doi.org/10.3389/fmolb.2021.823277.
[145] Kumar KG, Trevaskis JL, Lam DD, Sutton GM, Koza RA, Chouljenko VN, et al. Identification of adropin as a secreted factor linking dietary macronutrient intake with energy homeostasis and lipid metabolism. Cell Metab 2008;8:468–81. https://doi.org/10.1016/j.cmet.2008.10.011.
[146] Aydin S, Kuloglu T, Aydin S, Eren MN, Yilmaz M, Kalayci M, et al. Expression of adropin in rat brain, cerebellum, kidneys, heart, liver, and pancreas in streptozotocin-induced diabetes. Mol Cell Biochem 2013;380:73–81. https://doi.org/10.1007/s11010-013-1660-4.
[147] Marczuk N, Cecerska-Heryć E, Jesionowska A, Dołęgowska B. Adropin - physiological and pathophysiological role. Postepy Hig Med Dosw 2016;70: 981–8. https://doi.org/10.5604/17322693.1220082.
[148] Kutlu O, Altun Ö, Dikker O, Aktaş Ş, Özsoy N, Arman Y, et al. Serum adropin levels are reduced in adult patients with nonalcoholic fatty liver disease. Med Princ Pract 2019;28:463–9. https://doi.org/10.1159/000500106.
[149] Chen X, Sun X, Shen T, Chen Q, Chen S, Pang J, et al. Lower adropin expression is associated with oxidative stress and severity of nonalcoholic fatty liver disease. Free Radic Biol Med 2020;160:191–8. https://doi.org/10.1016/j.freeradbiomed.2020.08.005.
[150] Li N, Xie G, Zhou B, Qu A, Meng H, Liu J, et al. Serum adropin as a potential biomarker for predicting the development of type 2 diabetes mellitus in individuals with metabolic dysfunction-associated fatty liver disease. Front Physiol 2021;12:696163. https://doi.org/10.3389/fphys.2021.696163.
[151] Soltani S, Beigrezaei S, Malekahmadi M, Clark CCT, Abdollahi S. Circulating levels of adropin and diabetes: a systematic review and meta-analysis of observational studies. BMC Endocr Disord 2023;23:73. https://doi.org/10.1186/s12902-023-01327-0.
[152] Kucukoglu O, Sowa J-P, Mazzolini GD, Syn W-K, Canbay A. Hepatokines and adipokines in NASH-related hepatocellular carcinoma. J Hepatol 2021;74: 442–57. https://doi.org/10.1016/j.jhep.2020.10.030.
[153] Dogru T, Kirik A, Gurel H, Rizvi AA, Rizzo M, Sonmez A. The evolving role of fetuin-A in nonalcoholic fatty liver disease: an overview from liver to the heart. Int J Mol Sci 2021;22:6627. https://doi.org/10.3390/ijms22126627.
[154] Siegel-Axel DI, Ullrich S, Stefan N, Rittig K, Gerst F, Klingler C, et al. Fetuin-A influences vascular cell growth and production of proinflammatory and angiogenic proteins by human perivascular fat cells. Diabetologia 2014;57: 1057–66. https://doi.org/10.1007/s00125-014-3177-0.
[155] Zhao T, Wang W, Gao K, Li S, Jiang Y, Yang Z, et al. Fibroblast growth factor-21 alleviates phenotypic characteristics of dry age-related macular degeneration in mice. Exp Eye Res 2022;218:109014. https://doi.org/10.1016/j.exer.2022.109014.
[156] Tillman EJ, Rolph T. FGF21: an emerging therapeutic target for non-alcoholic steatohepatitis and related metabolic diseases. Front Endocrinol 2020;11:601290. https://doi.org/10.3389/fendo.2020.601290.
[157] Raptis DD, Mantzoros CS, Polyzos SA. Fibroblast growth factor-21 as a potential therapeutic target of nonalcoholic fatty liver disease. Therapeut Clin Risk Manag 2023;19:77–96. https://doi.org/10.2147/tcrm.s352008.
[158] Fu Z, Gong Y, Liegl R, Wang Z, Liu C-H, Meng SS, et al. FGF21 administration suppresses retinal and choroidal neovascularization in mice. Cell Rep 2017;18: 1606–13. https://doi.org/10.1016/j.celrep.2017.01.014.
[159] Tomita Y, Fu Z, Wang Z, Cakir B, Cho SS, Britton W, et al. Long-acting FGF21 inhibits retinal vascular leakage in in vivo and in vitro models. Int J Mol Sci 2020; 21:1188. https://doi.org/10.3390/ijms21041188.
[160] Fu Z, Qiu C, Cagnone G, Tomita Y, Huang S, Cakir B, et al. Retinal glial remodeling by FGF21 preserves retinal function during photoreceptor degeneration. iScience 2021;24:102376. https://doi.org/10.1016/j.isci.2021.102376.
[161] Kanai M, Raz A, Goodman DS. Retinol-binding protein: the transport protein for vitamin A in human plasma. J Clin Investig 1968;47:2025–44. https://doi.org/10.1172/JCI105889.
[162] Cukras C, Gaasterland T, Lee P, Gudiseva HV, Chavali VRM, Pullakhandam R, et al. Exome analysis identified a novel mutation in the RBP4 gene in a consanguineous pedigree with retinal dystrophy and developmental

abnormalities. PLoS One 2012;7:e50205. https://doi.org/10.1371/journal.pone.0050205.
[163] Polyzos SA, Kountouras J, Polymerou V, Papadimitriou KG, Zavos C, Katsinelos P. Vaspin, resistin, retinol-binding protein-4, interleukin-1α and interleukin-6 in patients with nonalcoholic fatty liver disease. Ann Hepatol 2016;15:705–14. https://doi.org/10.5604/16652681.1212429.
[164] Nono Nankam PA, Blüher M. Retinol-binding protein 4 in obesity and metabolic dysfunctions. Mol Cell Endocrinol 2021;531:111312. https://doi.org/10.1016/j.mce.2021.111312.
[165] Hu R, Yang X, He X, Song G. The relationship between NAFLD and retinol-binding protein 4 - an updated systematic review and meta-analysis. Lipids Health Dis 2023;22:8. https://doi.org/10.1186/s12944-022-01771-2.
[166] Du M, Phelps E, Balangue MJ, Dockins A, Moiseyev G, Shin Y, et al. Transgenic mice over-expressing RBP4 have RBP4-dependent and light-independent retinal degeneration. Investig Ophthalmol Vis Sci 2017;58:4375–83. https://doi.org/10.1167/iovs.17-22107.
[167] Xu Z, Bai S, Wu H, Fang M. Elevated retinal retinol-binding protein 4 levels in diabetic mice can induce retinal neurodegeneration through microglia. Microsc Res Tech 2023;86:223–31. https://doi.org/10.1002/jemt.24258.
[168] Polyzos SA, Kountouras J, Zavos C, Stergiopoulos C. Adipocytokines in insulin resistance and non-alcoholic fatty liver disease: the two sides of the same coin. Med Hypotheses 2010;74:1089–90. https://doi.org/10.1016/j.mehy.2009.12.028.
[169] European glaucoma society terminology and guidelines for glaucoma. Br J Ophthalmol 2021;105:1–169. https://doi.org/10.1136/bjophthalmol-2021-egsguidelines.
[170] Schmidt-Erfurth U, Chong V, Loewenstein A, Larsen M, Souied E, Schlingemann R, et al. Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). Br J Ophthalmol 2014;98:1144–67. https://doi.org/10.1136/bjophthalmol-2014-305702.
[171] Xu M, Fan R, Fan X, Shao Y, Li X. Progress and challenges of anti-VEGF agents and their sustained-release strategies for retinal angiogenesis. Drug Des Dev Ther 2022;16:3241–62. https://doi.org/10.2147/DDDT.S383101.
[172] Wang Y, Liu Y, Fang J, Xing X, Wang H, Shi X, et al. Small-molecule agonist AdipoRon alleviates diabetic retinopathy through the AdipoR1/AMPK/EGR4 pathway. J Transl Med 2024;22. https://doi.org/10.1186/s12967-023-04783-3.
[173] Mata NL, Lichter JB, Vogel R, Han Y, Bui TV, Singerman LJ. Investigation of oral fenretinide for treatment of geographic atrophy in age-related macular degeneration. Retina 2013;33:498–507. https://doi.org/10.1097/IAE.0b013e318265801d.
[174] Shimonov M, Hecht I, Yehezkeli V, Maharshak I, Achiron A, Burgansky-Eliash Z. Does bariatric surgery affect intraocular pressure? Obes Surg 2020;30:3742–6. https://doi.org/10.1007/s11695-020-04714-x.
[175] Posarelli C, Salvetti G, Piaggi P, Guido F, Ceccarini G, Santini F, et al. Ophthalmologic evaluation of severely obese patients undergoing bariatric surgery: a pilot, monocentric, prospective, open-label study. PLoS One 2019;14:e0216351. https://doi.org/10.1371/journal.pone.0216351.
[176] Ozcelik-Kose A, Imamoglu S, Aktekin A, Balci S, Yıldız MB, Ozturk Y, et al. Effect of bariatric surgery on macular and peripapillary choroidal structures in young patients with morbid obesity. Can J Ophthalmol 2022;57:370–5. https://doi.org/10.1016/j.jcjo.2022.03.009.
[177] Burkard T, Holmberg D, Thorell A, Hafezi F, Burden AM. The association between bariatric surgery and cataract: a propensity score-matched cohort study. Surg Obes Relat Dis 2022;18:217–24. https://doi.org/10.1016/j.soard.2021.10.021.
[178] Carrano FM, Iossa A, Di Lorenzo N, Silecchia G, Kontouli K-M, Mavridis D, et al. EAES rapid guideline: systematic review, network meta-analysis, CINeMA and GRADE assessment, and European consensus on bariatric surgery–extension 2022. Surg Endosc 2022;36:1709–25. https://doi.org/10.1007/s00464-022-09008-0.
[179] Kapoor I, Sarvepalli SM, D'Alessio D, Grewal DS, Hadziahmetovic M. GLP-1 receptor agonists and diabetic retinopathy: a meta-analysis of randomized clinical trials. Surv Ophthalmol 2023;68:1071–83. https://doi.org/10.1016/j.survophthal.2023.07.002.
[180] Polyzos SA, Kountouras J, Mantzoros CS. Obesity and nonalcoholic fatty liver disease: from pathophysiology to therapeutics. Metabolism 2019;92:82–97. https://doi.org/10.1016/j.metabol.2018.11.014.
[181] Souza M, Diaz I, Al-Sharif L. Liver and cardiovascular outcomes in lean non-alcoholic fatty liver disease: an updated systematic review and meta-analysis of about 1 million individuals. Hepatol Int 2024;18:1396–415. https://doi.org/10.1007/s12072-024-10716-z.
[182] Targher G, Byrne CD, Tilg H. MASLD: a systemic metabolic disorder with cardiovascular and malignant complications. Gut 2024;73:691–702. https://doi.org/10.1136/gutjnl-2023-330595.