# VEGF and MMP-2 Changes in Physiological Aging Processes in the Eyeball

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***Abstract*— In the elderly, loss of vision significantly affects quality of life, and the most common cause of this malady is age-related macular degeneration (AMD). In AMD, the pathological processes begin with deposit accumulation in Brush's membrane which then progress and continue ultimately resulting in a vascularity increase in the choroid layer, retinal separation and blindness. There is still a lot to be learned about how and when the changes occurring in the physiological aging processes transform into pathological processes. The aim of the study was to examine eyeball tissues in old and young male Sprague Dawley rats to determine the changes in the MMP-2 and VEGF levels as these are closely related to AMD pathogenesis. The measurements of the old rats' eye tissues indicated that the testosterone level decreased, MMP-2 level increased, and VEGF levels did not change. In previous studies, loss of MMP-2 activity and increase in VEGF levels was reported in AMD. It was suggested that in the physiological aging process, high MMP-2 levels may prevent deposit accumulation in Bruch's membrane, and the unelevated VEGF levels may prevent choroidal vascularization.**

***Keywords*— eye; VEGF; MMP-2; testosterone; age-related macular degeneration**

## I. INTRODUCTION

Elderly people experience both cognitive and physical discomfort and impairments in the functions of their sensory organs and this affects their quality of life. Visual inability was reported in one out of every three people over the age of 65 [1]. Visual impairment can lead to psychological problems such as depression and anxiety, general health problems related to loss of physical activity, and social problems such as loneliness [2]. AMD, which is the most common cause of visual inability over the age of 50, is caused by photoreceptor damage in the macula [3, 4].

In the elderly, atrophy of the retinal pigment epithelium (RPE) between the retina and the choroid layer, which is the blood-retinal barrier, causes the dry type AMD. In wet AMD, neovascularization, fluid extravasation and retinal detachment can occur in the choroidal layer [5, 6]. In AMD, deterioration in Bruch's membrane (BM), the innermost layer in the choroid layer, also occurs. The degenerations in BM are diffuse membrane thickening, lipid increase in the membrane, accumulation of extracellular material (drusen deposits) between BM and retinal pigment epithelium (RPE), increase in collagen cross-linking, calcification and fragmentation; however, the mechanisms of these changes are not fully clarified at the molecular level [6-9]. Due to an increase in collagen crosslinks, the decrease in enzymatic breakdown and decreased solubility of collagen, the accumulation of extracellular drusen containing lipids, mucoprotein and mucopolysaccharides occurs in the early stage of AMD [5, 10]. In the late stage of AMD, choroidal neovascularization, which follows atrophy in the RPE and photoreceptors, retinal detachment and eventually vision loss occurs [9, 11]. In the choroidal layer, the density of large choroidal vessels decreases, capillary density increases, endothelial dysfunction occurs and eventually blood flow is impaired due to vascular changes. These pathological processes are associated with extracellular matrix reorganization and angiogenesis. Extracellular matrix structuring and angiogenesis are processes which affect one another; both MMP and VEGF play an important role in the management of these processes [12, 13].

VEGF is the most powerful known mediator for the proliferation and differentiation of endothelial cells, increased vascular permeability, and management of angiogenesis [14]. Although anti-VEGF treatments are currently used in the treatments of age-related vascular AMD or diabetic retinopathy, more effective molecules targeting the isoforms, receptors and downstream signaling pathways of VEGF-A continue to be investigated [15, 16]. MMPs have a significant function in the regulation of VEGF activity and the neovascularization process as well as extracellular matrix structuring [17]. It is not known at what point the matrix and vascular changes shift from aging to the pathological processes. Consequently, it is important to understand how these two mediators contribute to the changes in the physiological aging process.

The aim of the study is to examine the changes due to aging that are observed in the physiological levels of VEGF and MMPs in vivo in the eyeball.

## II. METHOD

### A. Animals and Sample Collection

The Sprague Dawley male rats were obtained from the animal laboratory of our institution. The rats were housed in a standard room temperature (22 ± 2 ° C) and humidity (60%) environment and were fed with standard laboratory feed. The study was approved by the animal experiments ethics committee of our institution (the tissues used in this study were obtained from study number 40/2018 approved on 5.4.2018). The animal experiments were implemented in accordance with the "Guide for the Care and Use of Laboratory Animals, Eighth Edition". In this study, two groups of rats were examined, the first had an average age of 28 months [old rat (OR) group, n = 6] and the others rats were an average of 9 months [young rat (YR) group]. Sacrification was performed by decapitation after a blood sample had been taken from the right ventricle under CO2 anesthesia. The complete eyeballs of the rats were removed from the skull and rapidly placed in a -85 °C freezer for storage pending analysis. Blood samples were centrifuged at 1000 g for 10 minutes and their serum was separated. Serums were stored in a -85 °C freezer for analysis.

### B. Biochemical Analysis

For analysis, tissues taken from the freezer were homogenized in 10 volumes iced cold PBS (HyClone Phosphate Buffered Saline solution, cat no: SH30256.01). Homogenization was performed with BioSpec mini beadbeater-16 (BioSpec Products Inc., USA) at 60 Hz and 3450 oscillation/min using steel beads. After the homogenates were centrifuged for 15 minutes at 5000 g, the supernatants were separated, and these were used for MMP-2 and VEGF ELISA measurements. In ELISA measurements, specific kits for rats were studied in accordance with the kit protocol. Rat specific MMP-2 kit (Catalog No E-EL-R0618, Elabscience®, USA; with assay sensitivity: 0.19 ng/mL and detection range 0.31~20 ng/ml), rat specific VEGF kit (Catalog No EK0540, BOSTER Biological Technology, USA; with assay sensitivity <1 pg/mL and detection range 15.6-1000 pg/mL) were used for measurements. All results were calculated with µg/mg protein per tissue. Protein analysis performed according to manufacturer guide of BCA protein Assay kit (Catalog Number 23227, PierceTM BCA Protein Assay Kit,USA). The absorbency changes were measured with a microplate reader (ELx800, BioTek Instruments, Inc., Winooski, VT, USA) at 450 nm for the ELISA kit and 560 nm for the protein assay kit. Serum total Testosterone measurements were conducted in the biochemistry laboratory using an analyzer (Beckman Coulter DXI 800) in accordance with the kit protocol (reference range: 1.75-7.81 ng/ml).

### C. Statistical Analysis

The SPSS version 22 (IBM, Turkey) was used for statistical analysis. The suitability of variables to normal distribution was evaluated using the Shapiro-Wilk test. Variables suitable for normal distribution were tested using the student-t test, and unsuitable variables by the Mann-Whitney U test. p values <0.05 were considered statistically significant. Individual data points were presented with mean values in a graph. The mean, standard error mean and p values of the inter-group evaluations of the groups are provided in a table.

## III. RESULTS

In the biochemical evaluation of the eyeball, we observed that in the OR group, MMP-2 levels were higher compared to the YR group [t (5,4) =2,54, p=0.048, Figure 1 and Table]. When the VEGF levels in the eyeball were measured, there was no significant difference between the groups [U=11,50, p=0.29, Figure 2 and Table]. When the testosterone levels in the serum of the subjects were measured, it was observed that the testosterone levels of the OR group were lower than the YR group [t (10) =-4,61, p=0.001, Figure 3 and Table].

TABLE: Testosterone, MMP-2 and VEGF protein measurements in eyeball tissues. Data were presented as mean+standard error mean. *P<0.05 was determined significant.

| | **Old Group** | **Young Group** | ***p* value** |
|---|---|---|---|
| **Testosterone Levels** | 2.53±0.34 | 5.49±0.53 | *0.001 |
| **MMP-2 Levels** | 2.94±0.79 | 0.88±0.16 | *0.048 |
| **VEGF Levels** | 0.10±0.014 | 0.16±0.05 | 0.29 |

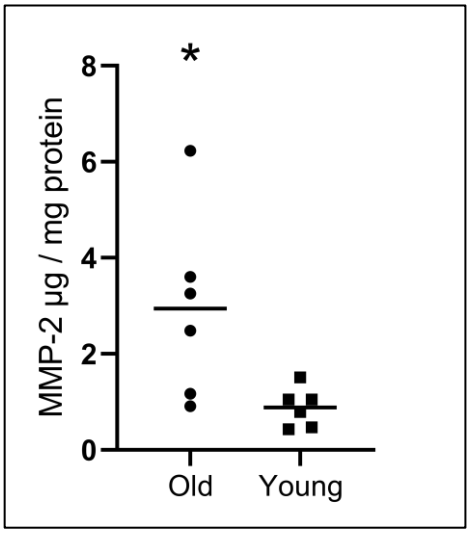


*Figure 1. MMP-2 levels in the eyeballs:* MMP-2 level was significantly increased in the old rat group in comparison to the young rat group (Data points were presented with mean, *p=0.048).

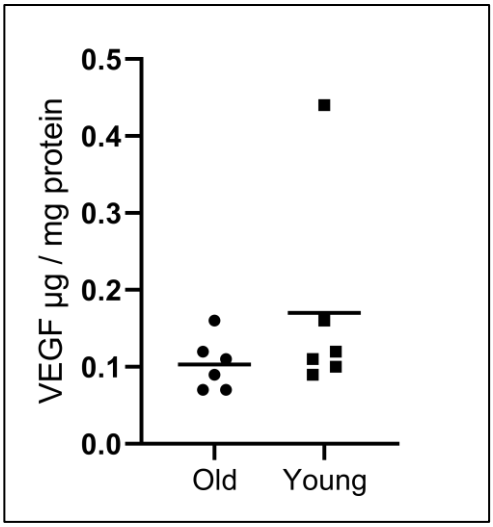


*Figure 2. VEGF levels in the eyeballs:* VEGF level did not change in the intergroup evaluation (Data points were presented with mean).

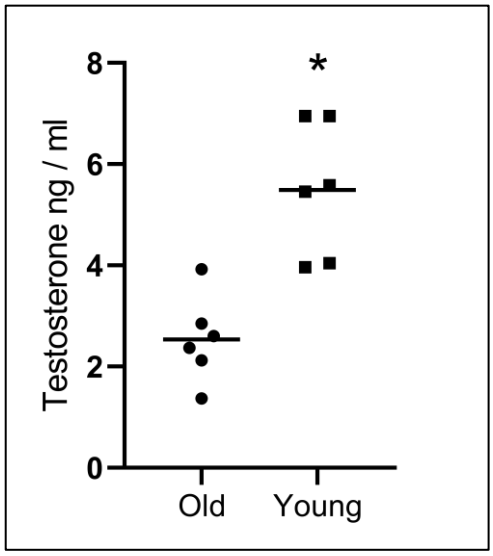


*Figure 3. Testosterone levels in the eyeballs:* Testosterone levels were lower in the old rat group compared to the young rat group (Data points were presented with mean, *p=0.001).

## IV. DISCUSSION

Age-related changes in the eye can occur in the lens (cataract), cornea (keratopathy), optic nerve (glaucoma), retina (diabetic retinopathy), and choroidal layer (AMD). Age-related changes are clearly observed in the retina where visual stimuli are transformed into neural stimulation and transferred to the optic nerve. Electrophysiological recordings obtained from rod and cone receptor cells in the retina showed that electrical stimuli decreased in those over the age of 40 [18]. During aging, cell loss in the retina, intracellular and extracellular deposit accumulation in the neuronal and non-neuronal cells (RPE cells) may occur, and these changes translate into a predisposition to AMD [19]. It has been reported that in elderly eyes, age-related ischemia and complement activity increase occurs; these complements may lead to drusen accumulation in RPE [11]. The regulation of the extracellular matrix plays a crucial role in both the deposit accumulation in the early stage of AMD and in late progressive neovascularization.

MMPs are responsible for the degradation of the extracellular matrix and the release of many biological active mediators and growth factors such as VEGF stored in the matrix [20]. In relation to age, the accumulation of abnormal matrix components, and thickening in BM, an increase in proMMP-2 and proMMP-9, which are inactive forms attached to BM, were detected [21]. A study indicated that the active form of MMP2 was present in the BM obtained from the macular and peri macular area in the elderly, and this was interpreted as the continuation of ECM remodeling [22]. In the same study, it was observed that the active form of MMP-2 was lower in the macula than the peripheral region. It has been suggested that this may worsen extracellular degradation function in the macula [22]. An imbalance in MMPs may disrupt the regulation of the extracellular matrix and MMP-2 may be the predominant cause of this situation [23]. Since MMP-2 levels in the eyeball are the active form of MMP-2, the increase in MMP-2 levels detected in the elderly compared to young people may be to facilitate the degradation of deposits formed due to aging.

MMP-2 plays a fundamental role in the regulation of both intracellular and intercellular signals and in maintaining the delicate balance of inflammatory and immune processes [20, 24]. MMPs can inhibit mediators such as monocyte chemoattractant protein 3 (MCP3), alarmine (DAMP), or their receptors by proteolytic cleavage, reducing their activity, reversing and suppressing inflammation [25, 26]. DAMPs contribute to chronic, sterile, low-intensity inflammatory processes which occur in pathologies such as AMD [27]. Vascular insufficiencies, tendency to ischemia, increased DAMP, and ongoing inflammatory tone in old age require MMP-2 activity. In cases where the increase in MMP-2 levels cannot maintain the physiological balances, the transition to pathological processes may occur.

MMP2 is critical in the physiological and pathological angiogenesis processes (such as cancer angiogenesis and choroidal vascularization) [24]. In the choroidal vascularization model created by laser application in rodents, it was observed that vascularization was milder in those with MMP2 gene expression deficiency [28]. It was suggested that MMP-2 and MMP-9 gene expression increased with hypoxia in RPE cell culture, and the combined effect on VEGF in hypoxic conditions increased regulation [29]. Normally, during physiological aging, the dysfunction in endothelial cells, a decrease in nitric oxide levels, an increase in vascular tone and a decrease in microcirculatory blood flow and consequently hypoxic conditions occur [30]. VEGF expression and angiogenesis are expected to be stimulated in aged eye tissues as a result of hypoxia and MMP-2 levels. In addition, although there were hypoxic conditions in the elderly eyeball, a decrease in capillary density and thinning was observed in the choroid layer [30]. These findings are inconsistent with elevated VEGF levels. We found no significant

difference in VEGF levels between old and young subjects. It has been reported that an increase in VEGF levels leads to pathological processes such as cataracts, dry and wet AMD; consequently, anti-VEGF treatments are implemented in age-related eye diseases [31]. In our study, we observed non-elevated VEGF levels consistent with changes in the eye based on physiological aging. Increased physiological VEGF level and activity may lead to choroidal vascularization, leading to the development of wet AMD.

MMP-2 and VEGF may interfere with one another in the physiological aging processes in the eye. In H2O2 induced RPE monolayer, it was shown that MMP-2 expression and activity increased, VEGF secretion increased, and transepithelial resistance decreased [5]. The positive regulation of MMP-2 on VEGF expression via direct or indirect pathways (receptor, signaling pathways HIF1-$\alpha$ interactions) has been observed in many tumoral and non-tumoral tissues [32]. We did not observe an increase in VEGF levels regarding an increase in MMP-2 levels in vivo. However, there may have been an increase in the activity of VEGF even though the levels did not change. The first synthesized long chain VEGF converted into active form by enzymatic degradation of MMPs, and VEGFs attached to the matrix has shown to be mobilized via MMPs [17, 33, 34]. Even if there is an increase in VEGF activity under physiological conditions, this increase should not be at a level inducing choroidal vascularization. The transition from physiological aging to pathological AMD may also be related to the interaction with MMP-2 and the increases in the level and/or activity of VEGF. The unresponsiveness or poor response to anti-VEGF treatments used in the treatment of AMD, determined by the unchanged fluid sequestration in some patients, may also be related to high MMP-2 activities in these patients [35].

In aging men, the levels of testosterone secreted into the circulation are reduced due to decreased function of Leydig cells and decreased GnRH secretion from the hypothalamus [36]. The role of testosterone in extracellular matrix construction and preventing fibrotic processes is well known [37, 38]. Exogenous testosterone administration has been reported to improve extracellular matrix enhancement and decrease MMP2 and MMP9 expressions in the renal fibrosis model [39]. In this study, on the contrary, we observed that MMP-2 levels were high in elderly subjects with low testosterone levels. The increase in MMM-2 levels in the eye tissue despite the decreased testosterone suggests the presence of strong triggers on MMP-2 expression in the eye tissues. Triggers in the eye for MMP-2 expression or activity may be extracellular accumulations, photo stimulants, chronic low-level inflammation, chronic hypoxia, complement activation, and reactive oxygen species and other unknown reasons [40-43].

In this study, the change between AMD developed and non-developed old rats was not examined. However, the VEGF and MMP-2 changes we detected in the old rats can provide a basis for the presence of a pathological shift to AMD. As a result, increased MMP-2 expressions visible in physiological aging may facilitate a preventive effect on drusen accumulation in the BM. Except for hypoxia, normal VEGF levels in physiological aging may impede choroidal vascularization. Attempts to preserve the levels and activities of MMP-2 and VEGF in physiological aging can help prevent AMD.

## REFERENCES

[1] Quillen DA. Common causes of vision loss in elderly patients. American family physician. 1999;60(1):99-108.
[2] Swenor BK, Lee MJ, Varadaraj V, Whitson HE, Ramulu PY. Aging With Vision Loss: A Framework for Assessing the Impact of Visual Impairment on Older Adults. The Gerontologist. 2019;60(6):989-95.
[3] Jager RD, Mieler WF, Miller JW. Age-Related Macular Degeneration. 2008;358(24):2606-17.
[4] Singh M, Tyagi SC. Metalloproteinases as mediators of inflammation and the eyes: molecular genetic underpinnings governing ocular pathophysiology. Int J Ophthalmol. 2017;10(8):1308-18.
[5] Bandyopadhyay M, Rohrer B. Matrix Metalloproteinase Activity Creates Pro-Angiogenic Environment in Primary Human Retinal Pigment Epithelial Cells Exposed to Complement. Investigative Ophthalmology & Visual Science. 2012;53(4):1953-61.
[6] Spraul CW, Lang GE, Grossniklaus HE, Lang GK. Histologic and Morphometric Analysis of the Choroid, Bruch's Membrane, and Retinal Pigment Epithelium in Postmortem Eyes With Age-Related Macular Degeneration and Histologic Examination of Surgically Excised Choroidal Neovascular Membranes. Survey of Ophthalmology. 1999;44:S10-S32.
[7] Fields MA, Bowrey HE, Gong J, Moreira EF, Cai H, Del Priore LV. Extracellular matrix nitration alters growth factor release and activates bioactive complement in human retinal pigment epithelial cells. PloS one. 2017;12(5):e0177763.
[8] Young RW. Pathophysiology of age-related macular degeneration. Survey of Ophthalmology. 1987;31(5):291-306.
[9] Spraul CW, Lang GE, Grossniklaus HE, Lang GK. Histologic and morphometric analysis of the choroid, Bruch's membrane, and retinal pigment epithelium in postmortem eyes with age-related macular degeneration and histologic examination of surgically excised choroidal neovascular membranes. Surv Ophthalmol. 1999;44 Suppl 1:S10-32.
[10] Karwatowski WS, Jeffries TE, Duance VC, Albon J, Bailey AJ, Easty DL. Preparation of Bruch's membrane and analysis of the age-related changes in the structural collagens. The British journal of ophthalmology. 1995;79(10):944-52.
[11] Chen M, Muckersie E, Robertson M, Forrester JV, Xu H. Up-regulation of complement factor B in retinal pigment epithelial cells is accompanied by complement activation in the aged retina. Experimental eye research. 2008;87(6):543-50.
[12] Ma Z, Mao C, Jia Y, Fu Y, Kong W. Extracellular matrix dynamics in vascular remodeling. 2020;319(3):C481-C99.
[13]Rue hle MA, Eastburn EA, LaBelle SA, Krishnan L, Weiss JA, Boerckel JD, et al. Extracellular matrix compression temporally regulates microvascular angiogenesis. 2020;6(34):eabb6351.
[14] Melincovici CS, Boşca AB, Şuşman S, Mărginean M, Mihu C, Istrate M, et al. Vascular endothelial growth factor (VEGF) - key factor in normal and pathological angiogenesis. Romanian journal of morphology and

embryology = Revue roumaine de morphologie et embryologie. 2018;59(2):455-67.
[15] Tolentino MJ, Dennrick A, John E, Tolentino MS. Drugs in Phase II clinical trials for the treatment of age-related macular degeneration. Expert Opinion on Investigational Drugs. 2015;24(2):183-99.
[16] Amadio M, Govoni S, Pascale A. Targeting VEGF in eye neovascularization: What's new?: A comprehensive review on current therapies and oligonucleotide-based interventions under development. Pharmacological Research. 2016;103:253-69.
[17] Ebrahem Q, Chaurasia SS, Vasanji A, Qi JH, Klenotic PA, Cutler A, et al. Cross-Talk between Vascular Endothelial Growth Factor and Matrix Metalloproteinases in the Induction of Neovascularization in Vivo. The American Journal of Pathology. 2010;176(1):496-503.
[18] Dimopoulos IS, Freund PR, Redel T, Dornstauder B, Gilmour G, Sauvé Y. Changes in rod and cone-driven oscillatory potentials in the aging human retina. Invest Ophthalmol Vis Sci. 2014;55(8):5058-73.
[19] Lin JB, Tsubota K, Apte RS. A glimpse at the aging eye. NPJ Aging Mech Dis. 2016;2:16003-.
[20] Wang X, Khalil RA. Matrix Metalloproteinases, Vascular Remodeling, and Vascular Disease. Adv Pharmacol. 2018;81:241-330.
[21] Kumar A, El-Osta A, Hussain AA, Marshall J. Increased Sequestration of Matrix Metalloproteinases in Ageing Human Bruch's Membrane: Implications for ECM Turnover. Investigative Ophthalmology & Visual Science. 2010;51(5):2664-70.
[22] Guo L, Hussain AA, Limb GA, Marshall J. Age-Dependent Variation in Metalloproteinase Activity of Isolated Human Bruch's Membrane and Choroid. Investigative Ophthalmology & Visual Science. 1999;40(11):2676-82.
[23] García-Onrubia L, Valentín-Bravo FJ, Coco-Martin RM, González-Sarmiento R, Pastor JC, Usategui-Martín R, et al. Matrix Metalloproteinases in Age-Related Macular Degeneration (AMD). Int J Mol Sci. 2020;21(16):5934.
[24] Quintero-Fabián S, Arreola R, Becerril-Villanueva E, Torres-Romero JC, Arana-Argáez V, Lara-Riegos J, et al. Role of Matrix Metalloproteinases in Angiogenesis and Cancer. Front Oncol. 2019;9:1370-.
[25] McQuibban GA, Gong J-H, Tam EM, McCulloch CAG, Clark-Lewis I, Overall CM. Inflammation Dampened by Gelatinase A Cleavage of Monocyte Chemoattractant Protein-3. 2000;289(5482):1202-6.
[26] Aguirre A, Blázquez-Prieto J, Amado-Rodriguez L, López-Alonso I, Batalla-Solís E, González-López A, et al. Matrix metalloproteinase-14 triggers an anti-inflammatory proteolytic cascade in endotoxemia. Journal of molecular medicine (Berlin, Germany). 2017;95(5):487-97.
[27] Feldman N, Rotter-Maskowitz A, Okun E. DAMPs as mediators of sterile inflammation in aging-related pathologies. Ageing Research Reviews. 2015;24:29-39.
[28] Lambert V, Wielockx B, Munaut C, Galopin C, Jost M, Itoh T, et al. MMP-2 and MMP-9 synergize in promoting choroidal neovascularization. 2003;17(15):2290-2.
[29] Hollborn M, Stathopoulos C, Steffen A, Wiedemann P, Kohen L, Bringmann A. Positive Feedback Regulation between MMP-9 and VEGF in Human RPE Cells. Investigative Ophthalmology & Visual Science. 2007;48(9):4360-7.
[30] Akpek EK, Smith RA. Overview of age-related ocular conditions. The American journal of managed care. 2013;19(5 Suppl):S67-75.
[31] Marneros AG. Increased VEGF-A promotes multiple distinct aging diseases of the eye through shared pathomechanisms. EMBO Mol Med. 2016;8(3):208-31.
[32] Chetty C, Lakka SS, Bhoopathi P, Rao JS. MMP-2 alters VEGF expression via alphaVbeta3 integrin-mediated PI3K/AKT signaling in A549 lung cancer cells. Int J Cancer. 2010;127(5):1081-95.
[33] Ferrara N. Binding to the extracellular matrix and proteolytic processing: two key mechanisms regulating vascular endothelial growth factor action. Mol Biol Cell. 2010;21(5):687-90.
[34] Lee S, Jilani SM, Nikolova GV, Carpizo D, Iruela-Arispe ML. Processing of VEGF-A by matrix metalloproteinases regulates bioavailability and vascular patterning in tumors. J Cell Biol. 2005;169(4):681-91.
[35] Amoaku WM, Chakravarthy U, Gale R, Gavin M, Ghanchi F, Gibson J, et al. Defining response to anti-VEGF therapies in neovascular AMD. Eye. 2015;29(6):721-31.
[36] Basaria S. Reproductive aging in men. Endocrinology and metabolism clinics of North America. 2013;42(2):255-70.
[37] Yang X, Wang Y, Yan S, Sun L, Yang G, Li Y, et al. Effect of testosterone on the proliferation and collagen synthesis of cardiac fibroblasts induced by angiotensin II in neonatal rat. Bioengineered. 2017;8(1):14-20.
[38] Sarkar M, Yates K, Suzuki A, Lavine J, Gill R, Ziegler T, et al. Low Testosterone Is Associated With Nonalcoholic Steatohepatitis (NASH) and Severity of NASH Fibrosis in Men With NAFLD. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2019.
[39] Zhang G, Kang Y, Zhou C, Cui R, Jia M, Hu S, et al. Amelioratory Effects of Testosterone Propionate on Age-related Renal Fibrosis via Suppression of TGF-β1/Smad Signaling and Activation of Nrf2-ARE Signaling. Scientific Reports. 2018;8(1):10726.
[40] Oliveira FAd, Matos AA, Matsuda SS, Buzalaf MAR, Bagnato VS, Machado MAdAM, et al. Low level laser therapy modulates viability, alkaline phosphatase and matrix metalloproteinase-2 activities of osteoblasts. Journal of Photochemistry and Photobiology B: Biology. 2017;169:35-40.
[41] Cao Q, Xiao B, Jin G, Lin J, Wang Y, Young CA, et al. Expression of transforming growth factor β and matrix metalloproteinases in the aqueous humor of patients with congenital ectopia lentis. Mol Med Rep. 2019;20(1):559-66.
[42] Ren W, Liu Y, Wang X, Piao C, Ma Y, Qiu S, et al. The Complement C3a–C3aR Axis Promotes Development of Thoracic Aortic Dissection via Regulation of MMP2 Expression. 2018;200(5):1829-38.
[43] Liu J, Khalil RA. Matrix Metalloproteinase Inhibitors as Investigational and Therapeutic Tools in Unrestrained Tissue Remodeling and Pathological Disorders. Prog Mol Biol Transl Sci. 2017;148:355-420.