

Research Article

# Circulating salusin-beta levels in the patients with age-related macular degeneration

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## Abstract

**Purpose:** To evaluate the levels of salusin-beta ( $\beta$ -SAL) in the serum in patients with age-related macular degeneration (ARMD).

**Methods:** Our study was designed as a controlled comparative clinical study. The  $\beta$ -SAL levels in serums of age and sex-matched 20 healthy volunteers as controls (Group 1), 20 patients with dry-age related macular degeneration (d-ARMD) (Group 2) and 20 patients with wet-age related macular degeneration (w-ARMD) (Group 3) were measured with the enzyme-linked immunosorbent assay (ELISA) method.

**Results:** In our study, it was found that age and gender didn't show a statistically significant difference among the study groups ( $p > 0.05$ ). The mean serum  $\beta$ -SAL levels in Group 1, Group 2 and Group 3 were  $1372,17 \pm 1126.69$  pg/mL;  $1423,71 \pm 1196.84$  pg/mL and  $940,57 \pm 1092.05$  pg/mL, respectively. Although the mean  $\beta$ -SAL levels in w-ARMD seem numerically lower than both the control and d-ARMD groups, this difference among the study groups was not statistically significant ( $p > 0.05$ ).

**Conclusion:** Our study suggests that  $\beta$ -SAL levels in the patients with ARMD and healthy controls were not different than each other. Further studies with large numbers may reveal possible relationships between  $\beta$ -SAL and ARMD.

## Introduction

Age-related macular degeneration (ARMD) is a leading cause of irreversible visual loss in over 65 years' older subjects. The two types of ARMD are non-neovascular (dry, non-exudative) and neovascular (wet, exudative) type. Wet ARMD (w-ARMD) is characterized by choroidal neovascular membrane (CNVM) that is due to the formation of abnormal blood vessels, which grow from the choroid into or under the retina [1-10]. Although its pathogenesis is not currently well-understood, it has been considered that ARMD is a multifactorial disease [1-4]. Additionally, it has been considered that chronic low level inflammation could lead to oxidative stress and degeneration associated with ARMD [1-10].

Salusins, salusin-alpha, and salusin-beta ( $\beta$ -SAL) are

soluble peptide hormones processed from the same precursor peptide. Salusins are secreted in blood vessels, monocytes, and macrophages and exist in human body fluids. They stimulate the proliferation of vascular smooth muscle cells (VSMC) and fibroblasts.  $\beta$ -SAL has various functions including cytokine function and modulation of vascular inflammation and oxidative damage. In recent studies, it has been demonstrated that  $\beta$ -SAL could promote inflammation by increasing activation of nuclear factor kappa B (NF- $\kappa$ B) signaling pathway. Additionally, it has been reported that inhibition of  $\beta$ -SAL alleviates oxidative stress and inflammation in diabetic rats [11-25]. To the best of our knowledge, there have been no previous reports in the literature on the blood levels of salusin in patients with ARMD. However, in a recent study, it has been reported that the mean serum  $\beta$ -SAL level in the patients with

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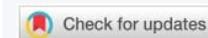
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**Keywords:** Age-related macular degeneration; Dry; Wet; Salusin beta; Serum levels



Behcet's Disease was significantly higher compared to healthy controls [26]. An experimental study by Xu, et al. showed that  $\beta$ -SAL contributes to vascular inflammation associated with pulmonary arterial hypertension [13]. In this study, based on recent evidence, we hypothesized that  $\beta$ -SAL might play a role in ARMD pathogenesis, and aimed to evaluate the levels of  $\beta$ -SAL in the serum in patients with ARMD.

## Material and methods

This study was performed in accordance with the Helsinki Declaration and approved by the institutional ethics committee. Informed consents were obtained from the participants. The study was conducted as a clinical comparative study and it included three groups:

Group 1 consisting sex- and age-matched 20 healthy control subjects presenting for routine eye examination with or without other ocular disorders, but without evidence of drusen, retina pigment epithelial (RPE) changes or choroidal neovascular membrane (CNVM).

Group 2 consisting 20 patients with d-ARMD characterized by RPE changes or/and macular drusen or the presence of geographic atrophy without CNVM or scarring documented by color fundus imaging, FFA and optical coherence tomography (OCT).

Group 3 consisting 20 patients with wet-ARMD with the CNVM or disciform scar documented by FFA and OCT.

A systemic examination and taking of a detailed medical history were obtained to identify the patients with risk factors for hypertension (HT), diabetes mellitus (DM), morbid obesity, hyperlipidemia, cardiovascular, and cerebrovascular diseases. The patients with hematological, neoplastic, connective, immune, cardiac, cerebrovascular, renal or hepatic diseases, DM, HT, vasculitis, morbid obesity and the patients with any ocular or systemic infection and inflammation, retinal vaso-occlusive disease and the patients underwent retinal laser photocoagulation and intra-vitreous injection were excluded from the study.

A full ophthalmic examination including visual acuity, biomicroscopy, tonometry, dilated ophthalmoscopy, color fundus imaging, fundus fluorescein angiography (FFA) and OCT was performed for all participants. Clinical diagnosis and classification of ARMD to d-ARMD or w-ARMD types were performed by a single retina specialist.

Blood samples were taken from participants to measure  $\beta$ -SAL levels at 08.00 hours after overnight fasting and were delivered to the laboratory within 20 min, centrifuged (2000 xg for 10 min at 4 °C) and the sera aliquot is stored at -80 °C until assayed. Commercial kit (Sunredbio, Baoshan, Shanghai) was used for  $\beta$ -SAL measurement. The samples were assayed by enzyme-linked immunosorbent test (ELISA)

according to the manufacturer's instructions. The minimum detectable level (sensitivity) was less than 8.756 pg/mL and the assay range was 10-3000 pg/mL. Intra- and interassay CVs were less than 10% and 12%, respectively. All samples were measured spectrophotometrically via EL x 800™ Absorbance Microplate Reader (BioTek Instruments, Inc., Winooski, VT, USA) at 450 nm. The biochemist was blind to the identity of samples during processing. The results were presented as "pg/mL".

## Statistical analysis

Statistical analysis of data was performed by Statistical Package for Social Sciences, version 11.0 (SPSS Inc., Chicago, IL). Results were given as means  $\pm$  SD. Individual group parameters were assessed with the one-sample Kolmogorov-Smirnov Z test and were found to be abnormally distributed ( $p < 0.05$ ). The non-parametric Kruskal-Wallis and Mann-Whitney U test were used for statistical comparisons between groups. Spearman's Rank order correlation coefficients were used to assess significant associations between  $\beta$ -SAL levels and demographic findings. For all comparisons, statistical significance was defined by  $p < 0.05$ .

## Results

It was found that there was no statistically significant difference concerning age and gender among the groups ( $p > 0.05$ ). The mean serum  $\beta$ -SAL levels in Group 1, Group 2 and Group 3 were  $1372,17 \pm 1126.69$  pg/mL;  $1423,71 \pm 1196.84$  pg/mL and  $940,57 \pm 1092.05$  pg/mL, respectively. Although the mean  $\beta$ -SAL levels in w-ARMD seem numerically lower than both the control and d-ARMD groups, this difference among the study groups was not statistically significant ( $p > 0.05$ ) (Table 1).

## Discussion

Recent clinical studies have revealed that a number of inflammatory cytokines such as IL (interleukin)-6, IL-17A, IL-18, IL-22 and TNF- $\alpha$  have been found to be elevated either systemically in the serum or locally in the ocular tissue or fluids of patients with especially w-ARMD. Additionally, it has been considered that chronic or prolonged low level inflammation can lead to oxidative stress and degeneration associated with ARMD [27-42].

Salusin- $\alpha$  and  $\beta$ -SAL are newly discovered bioactive peptides derived from prosalusin. They are expressed and synthesized by various cells in many tissues such as heart,

**Table 1:** Comparative mean  $\beta$ -Salusin levels in study groups.

Group	Number	Mean $\beta$ -Salusin levels $\pm$ SD (pg/mL)	p value
Control	20	1372,17 $\pm$ 1126.69	Controls vs. d-AMD: $p > 0.05$
d-AMD	20	1423,71 $\pm$ 1196.84	d-AMD vs. w-AMD: $p > 0.05$
w-AMD	20	940,57 $\pm$ 1092.05	w-AMD vs. controls: $p > 0.05$

Abbreviations: d-AMD: dry-Age-related Macular Degeneration; w-AMD, wet-Age-related Macular Degeneration; SD: Standard deviation



liver, brain, human vascular smooth muscle cells (VSMCs), and endothelial cells. It has been considered that  $\beta$ -SAL stimulates proliferation of VSMCs and fibroblasts through the activation of immediate response genes such as *c-myc* and *fos* in rats and humans [11-25].

Recent reports have demonstrated that circulating  $\beta$ -SAL levels in patients with coronary artery disease, DM, and cerebrovascular disease are also significantly higher levels than healthy controls [21]. Additionally, it has been reported that circulating levels of  $\beta$ -SAL are lower in patients with essential HT [11-25].

It has been reported that  $\beta$ -SAL accelerates inflammatory responses in human endothelial cells and monocyte-endothelial adhesion and that it stimulates human macrophage foam cell formation. Secretion of  $\beta$ -SAL is stimulated by inflammatory cytokines such as tumor necrosis factor- $\alpha$  and lipopolysaccharide [11-25]. In recent studies, it was demonstrated that  $\beta$ -SAL also has a stimulatory effect on pro-inflammatory and oxidative stress molecules. In those publications, it has been reported that  $\beta$ -SAL induces the expression of interleukin-1 $\beta$  (IL-1 $\beta$ ), monocyte chemoattractant protein-1 (MCP-1), acetyl-coenzyme A acetyltransferase 1 (ACAT-1), vascular cell adhesion molecule-1 (VCAM-1), and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2 (Nox2), a potent source of reactive oxygen species in human umbilical vein ECs (HUVECs), the adhesion of THP-1 monocytes onto HUVECs via nuclear factor- $\kappa$ B (NF- $\kappa$ B)-mediated VCAM-1 induction [17-21]. It has been reported that  $\beta$ -SAL increased the ROS production attenuated by NAC, apocynin or NOX2 siRNA [20].

To the best of our knowledge, this is the first report investigating the relation of serum  $\beta$ -SAL level in ARMD. In our study, we found that the mean  $\beta$ -SAL levels in w-ARMD were numerically lower than both the control and d-ARMD groups, and however, this difference among the study groups was not statistically significant. We consider that the fact that small sample size in our study may result in this statistical insignificance. We also think that theoretically,  $\beta$ -SAL may contribute to the pathogenesis of ARMD because it may play a significant role through its stimulatory effects on pro-inflammatory and oxidative stress molecules. Thus, in the studies having large patient number, the significant results on the relationship between salusins and ARMD or other retinal diseases might be revealed in the future.

In the beginning of this study, we hypothesized that the levels of  $\beta$ -SAL in the serum in patients with ARMD may be higher than those of healthy controls because  $\beta$ -SAL has a pro-inflammatory and possibly angiogenic effects. The insignificant results concerning the serum levels of  $\beta$ -SAL in our study may be due to a choroidal (local) vascular disease but a systemic vascular disease such as diabetes or hypertension. Additionally, the levels of  $\beta$ -SAL in vitreous may be different in ARMD patients than those in healthy controls and also may be lower or higher in these samples compared to serum.

The main lack of our study is lower sample number. But yet, in the light of literature, we speculate that  $\beta$ -SAL may contribute to the pathogenesis of ARMD. Thus, as a next step, the measurement of both vitreous and surgical removed CNVMs of levels of  $\beta$ -SAL in ARMD patients with and without treatment may support this theory and may give marked evidence regarding the exact role of  $\beta$ -SAL in ARMD pathogenesis. Further research is needed to have more information on the effects of  $\beta$ -SAL, and to investigate the levels of free and bound  $\beta$ -SAL and to determine the exact role of  $\beta$ -SAL in the pathogenesis of ARMD.

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