 DOI: 10.18231/2395-1451.2017.0036

A study to determine association of serum uric acid level with age related macular degeneration

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Abstract

Aim: To study the association of serum uric acid level with age related macular degeneration, if any.

Materials and Method: In this hospital based, observational, case control study, 100 patients presenting to our out patient department over a period of one year were included. The selected participants were grouped into the ARMD group which included 50 eyes with non neovascular ARMD and neovascular ARMD) and 50 eyes in control group. All participants were undergone complete ophthalmic evaluation along with serum uric acid level determination.

Results: 50 eyes of 50 patients diagnosed as having AMD and 50 eyes of 50 patients do not having AMD who served as a control were included in this study. The mean age was 66 years (49-85years). On an average higher serum uric acid were observed amongst males as compared to females (median: male vs female kruskal Wallace test H=22.5, DF=1, p<0.001).The average serum uric acid level were higher in patients with neovascular AMD (mean=505.00 ± std dev =13.57 μmol/l, n=19), than in the non-neovascular AMD (mean=322.93 ± std dev =26.26μmol/l, n=31),as compared to control group =318.42 ± std dev =76.23 μmol/l,n=50). On comparing the standardized serum uric acid level between neovascular AMD and control group, there was a statistically significant difference was observed. (H=40.734, DF=1, p<0.001).

Conclusion: A statistically significant correlation exists between serum uric acid level and severity of age related macular degeneration. Patients with neovascular age related macular degeneration present with a higher serum uric acid level as compared to patients with non neovascular age related maculae degeneration. Also, males had a significantly higher serum uric acid level as compared to females.

Keywords: Neovascular age related macular degeneration, Non neovascular age related macular degeneration, Serum uric acid level.

Introduction

AMD is a late-onset, multifactorial neurodegenerative disease characterized by progressive degeneration of photoreceptors/retinal pigment epithelial complex primarily in macular region of the retina affecting elderly population.(1) AMD appears to be an emerging public health threat in India. The India Eye Study (INDEYE) is the most recent study on AMD study derived a prevalence of AMD of 3.4% (prevalence of early and late AMD were 2.0% and 1.4%, respectively).(2) The impact of AMD continues to increase as the population ages. In the year 2020 the number of patients will increase by 60%. There is various classification available for AMD in literature. Among these, conventional classification divides AMD into two forms 1). Dry or Non-neovascular AMD and 2). Wet or Neovascular AMD. Dry AMD is characterized by geographic atrophy, the death of cells in the macula and Wet AMD is characterized by RPE detachment and/or choroidal neovascularization. The most important risk factor for AMD is increasing age. Other than this cigarette smoking, Underlying hypertension, low levels of antioxidants and inclusion of saturated fats in diet and high body mass index are also considerable factors.(3) A wide variety of studies have been performed to evaluate the associations between serum uric acid and cataract(4) and other chronic age related diseases. However, yet no studies have demonstrated a significant association between AMD and raised serum uric acid in spite of serum uric acid being widely described as having a significant role in its pathogenesis. Hence our primary aim is to evaluate the relation between altered uric acid profile and ARMD.

Materials and Method

The study was conducted after approval from the institution ethics committee and scientific committee in this hospital based, observational, case control study, 100 patients presenting to our out patient department over a period of one year were included.

Inclusion criteria consisted of age more than 40 years, presence of ARMD and non vegetarian dietary preference. The selected participants were grouped into the ARMD group which included 50 eyes with non neovascular ARMD and neovascular ARMD) and 50 eyes in control group.

Patients with co-existing retinal pathology, any systemic inflammatory disease, known renal disease or media opacities were excluded from the study.

Recruitment of patients was done by a one-stage ophthalmologic evaluation process by the ophthalmologists in the department. Every patient underwent a comprehensive ophthalmic evaluation and diagnosis was made using slit lamp biomicroscopy with + 90D lens, fundus flourescein angiography and indocyanine green angiography.

The patient was explained about the procedure, including its side effects and known complications, following which a written informed consent was taken. Approximately 2 ml of blood was collected from patient's antecubital vein under full aseptic precautions. These blood was sent to microbiology laboratory and blood was subjected at rate of 3000/rpm for 5 minutes in R8C centrifuge following which serum was isolated. Serum uric acid level measurement was done with HITACHI 902 by enzymatic photometric test using TBHBA (2,4,6-tribromo-3-hydroxybenzoic acid).

Results

Collected data were subjected to a master tabulation in MS excel spreadsheet according to the study protocol. SAS enterprise guide 4.3 and SPSS 21.0 software were used for statistical analysis. A p value less than 0.05 was considered to be statistically significant. Data were tested using Kruskal- Wallace test and Anderson Darling and Kolmogorov Smirnov (ANNOVA) test.

50 eyes of 50 patients diagnosed as having AMD and 50 eyes of 50 patients do not having AMD who served as a control were included in this study. The mean age was 66 years (49-85years). Out of 100 participants, 61 were male and 32 were female. Mean age of cases were 67.26 years with SD 7.96 (49-83 years) and mean age of control group was 65.4 years with SD 7.86 (50-85 years) (Fig. 1). On the basis of age, there is no significant different was found among group of cases and control (p value is 0.2426 and t value is 1.176 at 95% CI and 98 DF). Non-neovascular AMD was found to be the most common type, with it being present in 31 eyes (62%) while Neovascular AMD was observed in 19 eyes (38%). (Fig. 2)

In serum uric acid level analysis, the reference range for adult male was between 208-428 µmol/l and for adult female 155-327 µmol/l. On an average higher serum uric acid were observed amongst males as compared to females (median: male vs female kruskal Wallace test H=22.5, DF=1, p<0.001). The mean and standard deviation for female population were 304±94.16µmol/l whereas for male population 387±75.98µmol/l were respectively.

Out of 100 subjects observed, The average serum uric acid level were higher in patients with neovascular AMD (mean=505.00 ± std dev =13.57 µmol/l, n=19), than in the non-neovascular AMD (mean=322.93 ± std dev =26.26µmol/l, n=31), as compared to control group =318.42 ± std dev =76.23 µmol/l,n=50) (Fig.3). The difference of serum uric acid level among all groups were analyzed by Kruskal Wallace H test the rank based non parametric test ('one-way ANOVA on rank') and it was observed that the difference among the group appears to be significant. (H=46.113; DF=2; p < 0.001). On comparing the standardized serum uric acid level between neovascular AMD and control group, there was a statistically significant difference was observed. (H=40.734, DF=1, p<0.001). On comparing the standardized serum uric acid level between Non-neovascular AMD and control group, there was a no statistically significant difference was observed. (H=0.59, DF=1, p=0.443)

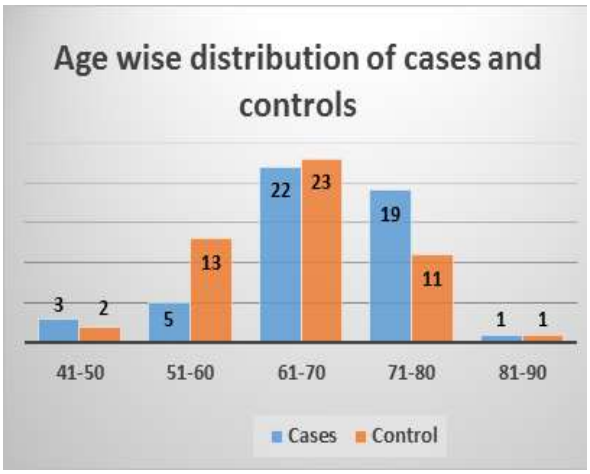

Fig. 1: Bar diagram showing age distribution

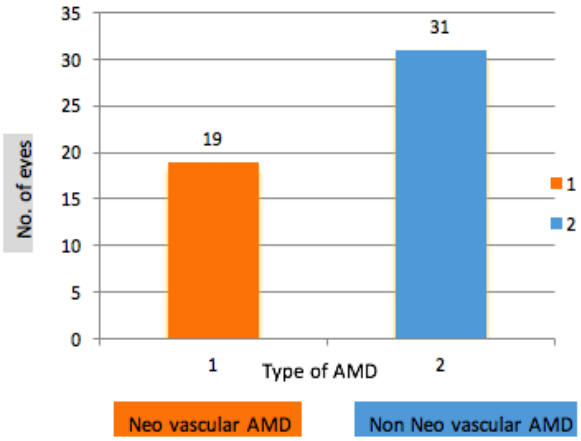

Fig. 2: Showing distribution of types of age related macular degeneration

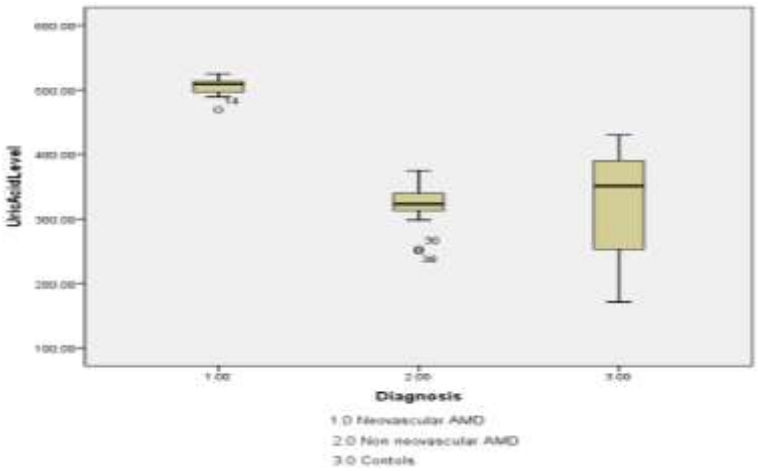

Fig. 3: showing the average serum uric acid level between groups

Discussion

The global burden of AMD is likely to double by 2020 to 6 million population. This is due to increase in life expectancy of population along with reduction in avoidable blindness caused by anterior segment abnormalities[5]. Hence, it has occupied an important place in WHO action plan to reduce global burden of avoidable blindness by 2020.[(5)] It was attempted to find out possible association between serum uric acid level and age related macular degeneration along with some other risk factors.

50 eyes of 50 subjects with AMD and 50 eyes of 50 subjects as control were included in this study.

The mean age of patients presenting with AMD and control in the present study was 67.26 ± 7.96 years and 65.6 ± 7.86 years respectively (range: 49-85). Similar age distribution was found in study by Subramani et al.[(6)] in which the mean age group in their study for AMD patients were 68.75 ± 9.23 years and for controls 64.61 ± 9.24 years. In a study by Moeini et al.[(7)] the mean age of participants were 69.9 years. In a study by Schaumberg et al[(8)] patients with AMD the range of age was 40-84 years.

In present study it has been found that mean serum uric acid level in AMD patients was 392.12 ± 91.97µmol/l and in control group was 318.42 ± 76.23µmol/l. The average serum uric acid level was higher in patients with neovascular AMD (mean=505.00 ± 13.57µmol/l), than in the non-neovascular AMD (322.93 ± 26.26µmol/l), as compared to control group (318.42 ± 76.23µmol/l). This difference between the groups appears to be significant (p<0.001). But after comparing standardized serum uric acid level in between two group of AMD and control separately, it was observed that there was a significant difference of serum uric acid level in patients with neovascular AMD than compared to control group (p<0.001). When comparing serum uric acid level amongst the non neovascular AMD and control group no significant difference was demonstrated in between this two groups (p=0.443). Similar results were noted by Subramani et al.[(6)] In that study the mean serum uric level in AMD patients was 302.53 ± 80.79µmol/l and in control group 299.19 ± 89.84µmol/l which was comparable with present study. They also observed that mean serum uric acid in neovascular AMD patients was 389.67 ± 38µmol/l which was higher from non neovascular AMD patients having mean serum uric acid level 297.86 ± 80.26µmol/l and from control group 299.19 ± 89.95µmol/l. After comparing standardized serum uric acid in two AMD groups and control group separately, they observed that there was a significant difference of serum uric acid level in neovascular AMD and control group (p=0.044) but no significant difference was observed in between non neovascular AMD and control group (P=0.448). Klein et al.[(9)] conducted population based cohort study to find out association of gout, emphysema and inflammatory markers with long term incidence of age related maculopathy. It was reported that the mean serum uric level in AMD patients was 351 ± 101µmol/l and concluded that gout (a condition with high serum level of uric acid) along with other inflammatory diseases such as emphysema a modest association with age related macular degeneration independent of smoking and other risk factors was observed. Serum uric acid and AMD association in various related studies have been summarized below in Table 1.

Table 1: Serum uric acid in related studies

Various studies	Serum uric acid (µmol/l)	p value
Subramani et al.[(6)]	302.53 ± 80.79 - AMD 299.19 ± 89.84- Control	0.021
Klein et al.[(9)]	351 ± 101-AMD	<0.001
Present study	392.12 ± 91.97- AMD 318.42 ± 76.23- Control	<0.001

In present study it has been observed that mean serum uric acid level in male was 387 ± 75.98µmol/l which was significantly higher (p<0.001) than female population 304 ± 94.16µmol/l. Similar results were

observed by Subramani et al.[6] who found that males have higher level of serum uric acid as compared to female ($p<0.001$). In that study mean serum uric acid level in male was 328.13 ± 85.58μmol/l and in female 267.70 ± 72.7μmol/l. In the study by Patil U et al.[10] it was observed that male has significantly higher level of serum uric acid level than females. Hence based on an above mentioned findings males were more predisposed to hyperuricemia as compared to the female population. The possible explanation for this may be due to estrogen promotes excretion of uric acid from the body.[11] Serum uric acid and gender association in various related studies have been summarized below in Table 2.

Table 2: Serum uric acid and gender in related studies

Various studies	Serum uric acid (μmol/l)	p value
Subramani et al.[6]	328.13 ± 85.58- Male 267.70 ± 72.7 -Female	<0.001
Patil U et al.[10]	327 -Male 297 - Female	<0.005
Present study	387 ± 75.98- Male 304 ± 94.16 - Female	<0.001

Fischer et al.[4] reviewed an article suggesting that AMD is a vascular disease, part of vasculopathy. According to it endothelium is the major site of damage due to oxidative stress in retinal microvasculature by hyperuricemia and other risk factors. The ROS (reactive oxygen species) are produced by enzymatic production of uric acid and inhibiting insulin induced eNOS (endothelial nitric oxide synthatase) phosphorylation. These ROS anion causes uncoupling of eNOS leading to generation of superoxide anion peroxynitrate subsequently leading to reduced NO (nitric oxide) bioavailability and hence inducing hypoxia leading to VEGF (vascular endothelial growth factor) production which leads to neovascular AMD.

Recent studies have brought to light the role of NLRP3 inflammasome in pathogenesis of AMD. NLRP3 is also known as cryopyrin belong NOD-like receptor family. They provide a scaffold for activation of autocatalytic process of breakdown of inactive procaspase-1. NLRP3 is activated in response to variety of stimuli one of them being uric acid.[12] Caspase-1 enzymes in RPE cell is activated by inflammsome pathway activation; this in turn leads to lysosomal destabilization and release of cathepsin which leads to cytotoxicity.[13] According to current literature NLRP3 activation further leads to induction IL-1BETA and IL-18 in a two process step. Hence nlrp3 is considered more of oxidative marker since the level of m-RNA are up regulated in response of oxidative stress.[14]

Limitations of present study are as following; since the present study does not categorize the patients according to the stage of AMD (Early and Late), the effect of the risk factor on progression of the disease could not be established clearly, the absence of follow up did not allow to see the persistence of the association between the modifiable risk factors and disease, A prospective cohort study design would have been more conclusive regarding the association.

Conclusion

A statistically significant correlation exists between serum uric acid level and severity of age related macular degeneration. Patients with neovascular age related macular degeneration present with a higher serum uric acid level as compared to patients with non neovascular age related maculae degeneration. Also, males had a significantly higher serum uric acid level as compared to females.

As is evident from the findings of the study, patients presenting with a higher serum uric acid level will benefit from regular screening to detect early changes associated with age related macular degeneration thereby helping to prevent severe vision loss associated with the pathology.

References

1. Ratnapriya R, Chew EY. Age-related macular degeneration -clinical review and genetics update. Clin Genet. 2013;84(2):160-166.
2. Gupta SK, Murthy GV, Morrison N, Price GM, Dherani M, John N, et al. Prevalence of early and late age-related macular degeneration in a rural population in northern India: the INDEYE Feasibility Study. Invest Ophthalmol Vis Sci. 2007;48(3):1007-1011.
3. Khan JC, Thurlby DA, Shahid H, Clayton DG, Yates JR, Bradley M, et al. Smoking and age related macular degeneration: the number of pack years of cigarette smoking is a major determinant of risk for both geographic atrophy and choroidal neovascularisation. Br J Ophthalmol. 2006;90(1):75-80.
4. Fischer TS. Age related macular degeneration is a vascular disease, part of vasculopathy: holistic approach of the AMD s pathophysiology, prevention and preventive treatment. J Pharm Sci Innov. 2012;1(6):15-35.
5. Age Related Macular Degeneration: Disease control and prevention of visual impairment in global initiative for the elimination of Avoidable Blindness Action Plan 2006–2011. World Health Organization: http://www.who.int/blindness/Vision2020_report.pdf as accessed on 26/11/2010. p. 32-32.
6. Subramani S, Khor SE, Livingstone BI, Kulkarni UV. Serum uric acid levels and its association with age-related macular degeneration (ARMD). Med J Malaysia. 2010;65(1):36-40.
7. Moeini HA, Masoudpour H, Ghanbari H. A study of the relation between body mass index and the incidence of age related macular degeneration. Br J Ophthalmol. 2005;89:964-966.
8. Schaumberg DA, Christen WG, Hankinson SE, Glynn RJ. Body mass index and the incidence of visually significant age-related maculopathy in men. Arch Ophthalmol. 2001;119(9):1259-64.
9. Klein R, Klein BE, Tomay SC, Cruickshanks KJ. Association of gout, emphysema and inflamamtory markers with long term incidence of age related maculopathy. Arch Opthal. 2003;121:674-78.
10. Patil U, Divekar S, Vaidya S, Ruikar VM, Patwardhan

MS. Study of serum uric acid and its correlation with intelligence quotient and other parameters in normal healthy adults. Int J Rec Tren Sci Tech. 2013;6(2):64-66.
11. Chen L, Zhu W, Chen Z, DAI H, Ren J, Chen J, et al. Relationship between hyperuricemia and metabolic syndrome. J Zhejiang Univ Sci B. 2007;8(8):593-598.
12. Celkova L, Doyle S L, Campbell M. NLRP3 Inflammasome and Pathobiology in AMD. J Clin Med. 2015;4:172-192.
13. Tseng WA, Thein T, Kinnunen K, Lashkari K, Gregory MS, D'Amore PA, et al. NLRP3 inflammasome activation in retinal pigment epithelial cells by lysosomal destabilization: Implications for age-related macular degeneration. Investig Ophthalmol Vis Sci. 2013;54:110–120.
14. Kauppinen A, Niskanen H, Suuronen T, Kinnunen K, Salminen A, Kaarniranta K. Oxidative stress activates NLRP3 inflammasomes in ARPE-19 cells- Implications for age-related macular degeneration (AMD). Immunol Lett. 2012;147:29–33.