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Long-Term Exposure to Solar Ultraviolet Radiation as a Risk Factor for Age-Related Macular Degeneration

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A B S T R A C T

A clinical epidemiological study has been conducted as a part of research project investigating chronic exposure to solar ultraviolet radiation (UVR) as a factor contributing to the onset of age-related macular degeneration (ARMD). The study included 623 subjects older than 50 from two different geographic areas, one with high solar radiation (the island of Šolta – Region 1) and the other (Zagreb and its surroundings – Region 2) with low solar radiation. Individual exposure to UVR was assessed according to global exposure to sunlight, on the basis detailed history of life-long exposure to sunlight, with special reference to professional history and geophysical specificities of the respective areas. Different grades of ARMD were based on the fundus photographs and flourescein angiography. Statistically significant relation was found between ARMD and mean daily exposure (in hours) to solar radiation in Region 1 (χ^2=186.22; p=0.000), Region 2 (χ^2=25.66; p=0.000) and in both regions together (χ^2=216.43; p=0.000). ARMD is more frequent in the subjects belonging to the Region 1 and with the same exposure to sunlight (8 hours and more) which goes in favor of their increased UVR exposure. The results support a relationship between long-term sunlight exposure and increased risk of ARMD.

***Key words**: ultraviolet radiation, age-related macular degeneration*

Introduction

Age-related macular degeneration (ARMD) is the leading cause of legal blindness in people over 50 years in the western world. Despite its importance, relatively little is known about its etiology, pathogenesis and its prevention, and specific treatment is possible only for selected patients with the neovascular stage. It is believed that ARMD, like other biological processes can be influenced by number of complex biochemical, immunogenetic and environmental mechanisms. One of them seems to be solar radiation.

The adverse effect of solar radiation on the vision has been known since the times of Plato[1–4]. It is well known that the intensive short-term exposure of the retina to the sunlight causes solar retinopathy (solar eclipse blindness)[2,3]. However, very little is known about long-term exposure to sunlight and about thus induced damage to the retina, primarily to the macula lutea retinae.

Recently, numerous animal experiments have demonstrated that longer wavelengths of ultraviolet radiation (UVR) and shorter wavelengths of visible radiation (especially blue light) can cause retinal damage that closely resembles those seen of ARMD in humans[5–7].

Light can cause retinal damage by mechanical, thermal or photochemical mechanisms. Mechanical and thermal injuries require a very intense light exposure, but photochemical injury is caused by a prolonged exposure to light levels that probably would be well tolerated in experienced only transiently.

The mechanism of phototoxicity has not been fully elucidated yet. One of possible mechanisms is that a long-term exposure to sunlight causes a photochemical damage to retinal pigment epithelium (RPE)-photoreceptor complex by producing toxic superoxide radicals

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damaging the cell membranes rich in polyunsaturated fatty acids, which in turn results in peroksidation and destruction of plasmalemma and dysfunction and death of the cell[1–8]. Repeated doses of UVR below the noxious threshold cumulate over years before inducing damage to the retina.

The spectrum of UV radiation is divided into three parts: UV-A (300–400 nm), UV-B (290–320 nm) and UV-C rays (bellow 290 nm). The rays bellow 290 nm are completely absorbed by the stratosphere ozone layer, so they do not reach the Earth at all. The ozone layer absorbs about 70% of UV-B radiation too. Only 5% of the sun radiation reaching the Earth belongs to UV radiation, and only 2–17% of the ambient sun radiation reaches the human eye. Not all the UVR that reach the eye pass back to the retina. In young adults, almost all the wavelengths below 360 nm appear to be absorbed by cornea and lens[1–3], but experiments have shown that retina is damaged even though less than 1% of the UV-B light penetrates to it[1–3,9–11].

Till today neither epidemiologic nor clinical investigations have produced any satisfactory answer to the question whether the risk of ARMD increases with exposure to high cumulative doses of solar (UV and short wavelength visible light) radiation, but relationship between the two entities has been suggested. The purpose of this study is to try to address this question.

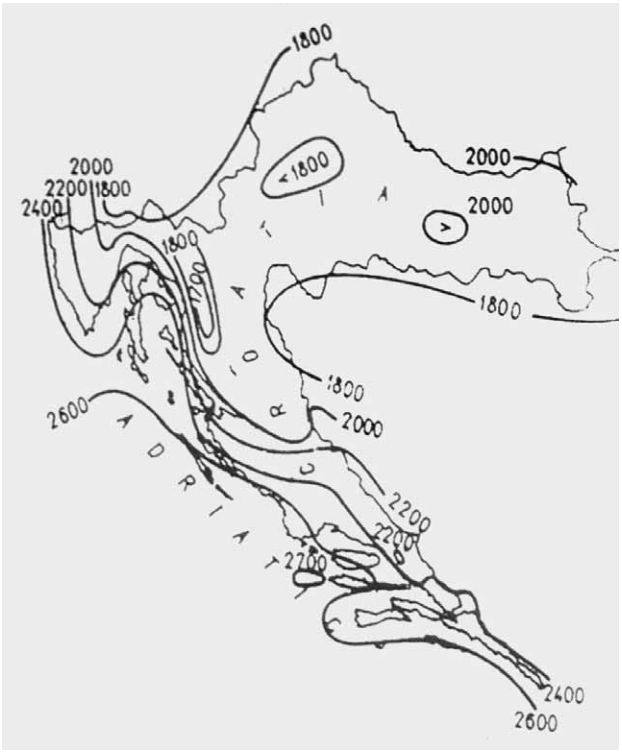

Fig. 1a. Mean annular number of sunny hours in each area of Croatia for the period 1961-1990. (According to: Poje, et al.)

Subjects and Methods

A study included 632 subjects over 50 years from two different geographic areas, one with high (the island of Šolta: 420 subjects) and the other with low (Zagreb and its surroundings: 212 subjects) solar radiation.

The groups were similar regarding the age, sex and outdoor working status.

The island of Šolta was chosen for a very high proportion of elderly people in the population and their high life-long exposure to sunlight. In the early childhood, during World War II, most of them had spent a year and a half in the El Shatt camp for refugees. Many of them are fishermen, seamen and farmers, spending most of the time outdoors, usually without any protection from sunlight, occasionally wearing a hat or, more frequently a kerchief.

A questionnaire containing all relevant risk factors for ARMD, with particular reference to life-long exposure to solar radiation (based on detailed professional history, leisure activities and also information of hat or sun-glasses or other sun-protective items used), was designed to be filled-in by each studied subject.

As UVR was not measured in Croatia, so fare individual exposure to UV rays (which makes 5% of global solar radiation) was assessed intermediately according to the global exposure to sunlight, taking the geophysical characteristics of the respective area in consideration: the average number of sunny hours (Figure 1a), global solar irradiation upon a horizontal surface (Figure 1b), daily

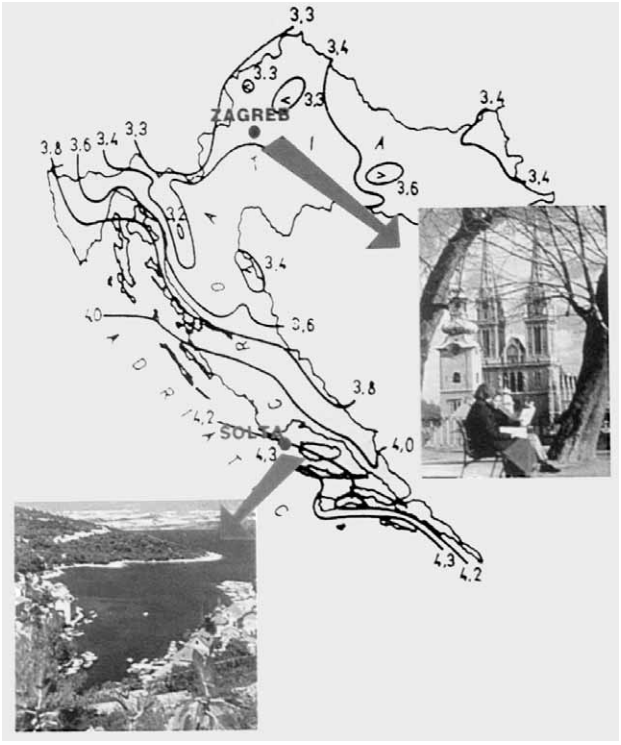

Fig. 1b. Annular mean daily global solar radiation upon a horizontal surface (kWhm^{-2}) in the each area of Croatia for the period 1961–1990. (According to: Žibrant et al.)

and seasonally variation of solar UV exposure with geographical latitude and possibility of reflectivity of UVR from water (3–13%) and sand (7–18%).

The subjects underwent detailed ophthalmologic examination including fundus color photography and fluorescein angiography which were placed at the central assessment site.

Degeneration of the maculae was graded as follows:

Grade 1 – five or more small drusen within 1500 μm from the foveola;

Grade 2 – many small drusen within 1500 μm from the foveola;

Grade 3 – large confluent drusen or focal RPE hyperpigmentation and

Grade 4 – geographic atrophy of RPE or exudative alternations (e.g. chorioidal neovascularisation, serious or hemorrhagic detachments of RPE, disciform scarring.

Grade 0 – referred to eyes without changes in terms of ARMD according to the grading scheme.

For the purpose of this study the grading scheme has been adjusted from Bressler et al. that they had used in grading of waterman in Maryland and applied to this population study[12]. None of the subjects in this analysis was aphakic. Some subjects did not have photographs taken. The most frequent reason for that was that some of them could not come to the clinic and they were examined on the island, and some of them had severe lens opacities that obscured macular details.

The subjects were classified according to findings in their worse eye, if the both eyes were affected. If only one eye had photographs, he was classified on the basis of findings in the single eye. In friendly user program SPSS comprehensive analysis has been performed, and following results were obtained.

Results

The prevalence rate of ARMD in the Region 1 was 34.28% and 16.02% in the Region 2. The prevalence of ARMD was strongly age-related with various age groups and between the respective regions. ARMD appears in Region 1 at statistically significant earlier age (Figure 2). It is more prevalent in man than in woman in the Region 1, but not in the Region 2 (Table 1 and 2).

Statistically significant association was found between ARMD and mean daily exposure to solar radiation in Region 1 (^{2}=186.22; p=0.000) (Table 3) and in Region 2 (^{2}=25.66; p=0.000) (Table 4) and in both regions together (^{2}=216.43; p=0.000).

TABLE 1
DISTRIBUTIONS OF SUBJECTS IN REGION 1 ACCORDING TO SEX AND DIFFERENT GRADES OF ARMD

ARMD (grades)	Male (N)	Female (N)	Total (N)
0	93	183	276
1,2,3,4	89	55	144
Total	182	238	420

^{2} = 30.2, p<0.001
Region 1 – the island of Šolta, ARMD – Age related macular degeneration

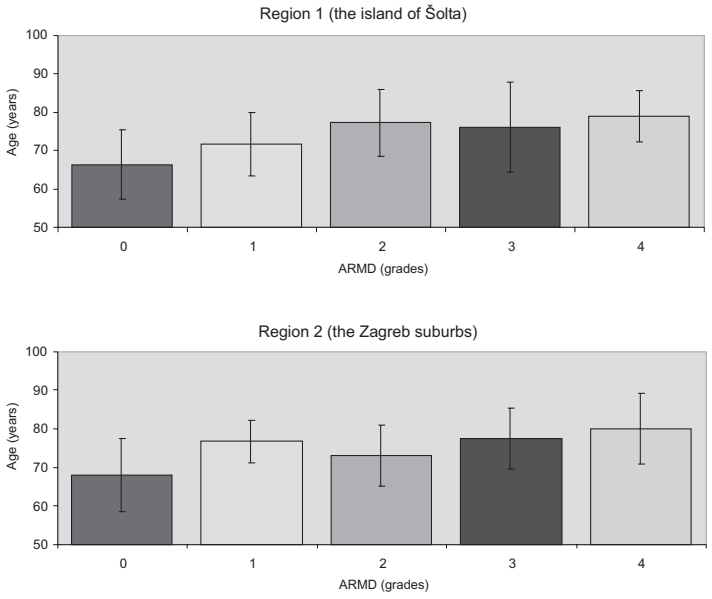

*Fig. 2. Average age of subjects in Region 1 and Region 2 according to different grades (1 through 4) of ARMD (*t=2.95; p= 0.005). Region 1- the island of Šolta, Region 2 – Zagreb and its surroundings, ARMD – age-related macular degeneration. (see further comment on ARMD grades in the Methods and Subjects section)*

TABLE 2
DISTRIBUTIONS OF SUBJECTS IN REGION 2 ACCORDING TO SEX AND DIFFERENT GRADES OF ARMD

ARMD (grades)	Male (N)	Female (N)	Total (N)
0	78	100	178
1,2,3,4	16	18	34
Total	94	118	212

^{2} = 0.137, p<0.7113
Region 2 – Zagreb and its surroundings, ARMD – Age related macular degeneration

TABLE 3
DISTRIBUTIONS OF SUBJECTS IN REGION 1 ACCORDING TO DIFFERENT ARMD GRADES AND MEAN DAILY EXPOSURE TO SOLAR RADIATION

ARMD (grades)	Mean daily exposure to sun (hours)			Total
	< 4	4–7	> 8	
0	176.00	61.00	39.00	276.00
1,2,3,4	6.00	25.00	113.00	140.00
Total	182.00	86.00	152.00	420.00

^{2} = 186.22, p<0.001
Region 1 – the island of Šolta, ARMD – Age related macular degeneration

TABLE 4
DISTRIBUTIONS OF SUBJECTS IN REGION 2 ACCORDING TO DIFFERENT ARMD GRADES AND MEAN DAILY EXPOSURE TO SOLAR RADIATION

ARMD (grades)	Mean daily exposure to sun (hours)			Total
	< 4	4–7	> 8	
0	90.00	42.00	46.00	178.00
1,2,3,4	2.00	11.00	21.00	34.00
Total	92.00	53.00	67.00	212.00

^{2} = 25.66, p<0.001; Region 2 – Zagreb and its surroundings, ARMD – Age related macular degeneration

TABLE 5
DISTRIBUTIONS OF SUBJECTS EXPOSED TO SOLAR RADIATION 8 OR MORE HOURS A DAY ACCORDING TO ARMD GRADES AND RESPECTIVE REGIONS

ARMD (grades)	Region 1 (N)	Region 2 (N)	Total (N)
0	39.00	46.00	85.00
1,2,3,4	113.00	21.00	134.00
Total	152.00	67.00	219.00

^{2} = 34.44, p<0.01
Region 1 – the island of Šolta, Region 2 – Zagreb and its surroundings, ARMD – Age related macular degeneration

TABLE 6
DISTRIBUTION OF SUBJECTS IN REGION 1 ACCORDING TO DIFFERENT GRADES OF ARMD AND REFUGE TO EL SHATT

Refuge to El Shatt	ARMD (grades)					Total
	0	1	2	3	4	
Yes	40	16	23	3	7	89
No	236	33	36	15	11	331
Total	276	49	59	18	18	420

^{2} = 26.05, p<0.0001
Region 1 – the island of Šolta, ARMD – Age related macular degeneration

ARMD is more frequent with the subjects in Region 1 and with same exposure to light (8 hours or more) (Table 5). In the case of shorter exposure of subjects to sun (4 hours or less) there was no difference in appearance of ARMD between the respective regions. Statistically significant association was found between ARMD and high exposure to sunlight early in the life (refugees to El Shatt from the island of Šolta) (Table 6).

Other potential risk factors for the onset of ARMD were evaluated (Table 7). Statistically significant associations were found between ARMD and eye color, sun burning, the actinic keratosis, pterygium and pinguecula. The last three of these risk factors are not directly associated with ARMD, but all three depend on the exposure of solar radiation. Significant association of ARMD was found with hyperopia and cortical cataract. Association between ARMD and hypertension disappears when the influence of sunlight on their relation was excluded.

Discussion and Conclusion

Eye as a sight, visual, organ is very exposed to the light. During the day thousands of rodopsine molecules change under the influence of sunlight.

There has been an increasing number of proofs that place the sun radiation on the first place among the potential etiologic factors causing ARMD, which is the main cause of blindness in people over 60's in Western countries (with the prevalence of 17% in population over 60 and 30% if they are over 75). More than 10 million

TABLE 7
OTHER POTENTIAL RISK FACTORS FOR THE ONSET OF ARMD (STATISTICAL SIGNIFICANCE)

Potential risk factor	^{2}	p
fair eyes	10.66	0.0048
getting dark on the sun	28.07	0.0000
actinic keratosis	18.00	0.0000
pterygium and/or pinguecula	4.99	0.0255
cataract	9.71	0.0211
glaucoma	2.25	0.1333
hypermetropia	48.86	0.0000
hipertensio	0.47	0.8283
smoking	1.99	0.1573
rural way of life	10.82	0.0010
education	6.32	0.2762

Americans older than 50 suffer from some form of ARMD, with 165,000 new cases every year and 16,000 new cases of legal blindness annually[13,14].

It is absurd that the sunlight and the oxygen, two fundamental entities are not only the cause of all life on the Earth, but also are responsible for ageing and dying of the cells. Experiments on animals show that the repeated douses of exposure to UV radiation below the noxious threshold, accumulate over years and might damage the retina[5–7,9]. Experimentally induced exposure, causing such damage, approaches or exceeds the midday solar UV radiation of the eyes. The level of exposure needed for photobiological damage to occur can be decreased by numerous factors (e.g. temperature, oxygen concentration etc.). Exposure to UV radiation is increased by reflection. Earth and green surfaces reflect 1–5% of the solar UV radiation, water 3–12% and sand 7–18%[3].

The lens is natural filters for short wavelength UV rays of shorter wavelengths on their way to the retina. Only 1% of radiation between 320 and 340 nm and only 2% above 360 nm reaches the retina. The lens absorption of the radiation is not a statically function from the birth but an increasing phenomenon. In 5-year-old children 8% of UVB radiation reaches the retina. The lens protect from UV radiation starting from the 20's linearly increasing to the maximum of protection in the 30's[1,8].

Our results have proven a significant relation between ARMD and increased sun exposure of the subjects in early childhood, especially related to the sojourn of the subjects of the Region 1 in exile El Shatt.

According to some authors, cataract (also as sclerosis of the nucleus as a result of aging) should be considered a form of eye adaptation measures to prevent the phototoxic damage of the macula. Sperduto and Siegel think that the relation between ARMD and cataract is only apparent and that both diseases develop separately but they are both related to the higher sun exposure (that's why countries around the equator are called »cataract belt«)[1,15].

More frequent cases of pterygium and pinguecula in tropical area are also related to higher exposure to sun radiation (especially to UV-B radiation)[1,11].

Our research also shows statistically significant association of ARMD and cataract, pterygium and pinguecula.

Our results support the relationship between prolonged exposure to solar radiation (especially UV and short wavelength visible light) and increased risk of ARMD in both regions. The occurrence of ARMD is more common in the subjects in region with high solar radiation.

Prevalence and severity of ARMD rises with the increase in the mean daily life-long exposure to solar radiation. ARMD is more frequent in the subjects in region with high solar radiation than in subjects in region with low solar radiation and with same exposure to sunlight (8 hours a day or more) which speaks in favor of some other factors closely connected to that region (e.g. higher exposure to UVR, because of different geophysical specificities of the respective areas). If we take into consideration Figures 1a and 1b, we shall see differences (in the mean annular number of sunny hours and also in the mean annular daily global solar radiation upon a horizontal surface) between respective regions[16]. Difference in appearance of ARMD between regions (for the exposure to sunlight 8 hours or more) becomes clear, which it is not the case in shorter exposure to sunlight.

Unfortunately, in the future, we will face an ever increasing exposure to UVR due to changes in the Earth atmosphere. Most recent data show that chlorofluorocarbon reduced the ozone layer in the stratosphere which is the most powerful filter for UVR. Recent scientific findings show dramatic ozone depletion in the lower stratosphere over Antarctic (Antarctic ozone hole) and also diminishing ozone over the North Pole (mini ozone hole)[17–19]. A 10% reduction in ozone could lead to as much as 15–20% increases in UV exposure[18,19].

Also, recent reports suggest that in the last 40 years the world's population has doubled and it's still growing and shows a substantial increase in both: the numbers and proportions of elderly people in western societies[13–14,20]. Because of the last two reasons, ARMD in the future will be the public health problem of growing proportions[20–23].

Due to a small number of subjects examined in the study so far, no conclusive data on the actual causative relationship between exposure to solar UVR and ARMD could be obtained, but the results appear to be highly intriguing, stimulating future investigations to clarify the problem.

It seems prudent to protect the eyes from unnecessary solar radiation (especially young children without effective natural lens filter of UVR, aphakic and pseudophakic eyes lacking the filter) and in those with high levels of solar radiation, such as: seamen, fishermen, farmers, sunbathers and skiers by wearing sun-glasses with UVR filter or at least a hat.

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KRONIČNO IZLAGANJE SUNČEVOM ULTRALJUBIČASTOM ZRAČENJU KAO ČIMBENIK U NASTANKU SENILNE MAKULARNE DEGENERACIJE

SAŽETAK

U cilju istraživanja dugoročne izloženosti sunčevu ultraljubičastom (UV) zračenju kao čimbenika u nastanku senilne makularne degeneracije (SDM) poduzeli smo znanstveno istraživanje kojim su obuhvaćena 632 ispitanika iznad 50 godina starosti, iz dva različita geografska područja, područje jače sunčeve ozračenosti (Regija 1 – otok Šolta) i područje slabije ozračenosti (Regija 2 – područje grada Zagreba). Osobna izloženost ispitanika UV zračenju temeljena je na detaljno uzetoj anamnezi, s obzirom na izloženost sunčevu zračenju tijekom cijelog života. Utvrđivanje različitih stupnjeva SDM provedeno je na temelju fotografije očne pozadine i fluoresceinske angiografije. Uočena je statistički značajna povezanost pojavljivanja SDM i prosječnog broja sati izloženosti djelovanju sunca u regiji 1. Također se, uz jednaku izloženost djelovanju sunca, SDM češće javlja u ispitanika u regiji 1, a to svjedoči i o njihovoj većoj UV ozračenosti. Rezultati ukazuju na značajnu povezanost izloženosti sunčevu zračenju i povećanog rizika za nastanak SDM.