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Factors Associated with Skin Carotenoid Levels in Israeli Patients with Age-Related Macular Degeneration: A Cross-Sectional Study

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Abstract

Background/Objectives: Age-related macular degeneration (AMD) is a leading cause of irreversible vision loss. Diet and carotenoid supplementation have been associated with slower AMD progression. We evaluated whether skin carotenoid (SC) levels measured by reflection spectroscopy (RS) are associated with diet and vitamin supplement use in patients with AMD. Methods: This cross-sectional study included 338 participants: 201 with AMD, 68 controls, and 69 with diabetic retinopathy (DR). SC was measured by RS, and demographic, clinical, dietary, and supplementation data were collected. Analyses included non-parametric tests and multivariable linear regression. Results: SC scores did not differ across clinical groups ($p = 0.24$). Patients with dry AMD ($n = 34$) had higher SC scores than those with neovascular AMD ($n = 159$) after adjustment for age and sex ($p = 0.009$). In the AMD cohort, fruit intake ($\beta = +30.99$ per category), vegetable intake ($\beta = +41.81$ for ≥2 servings/day), current smoking ($\beta = -61.05$), Age-Related Eye Disease Study 2 (AREDS2) supplementation ($\beta = +32.39$), and BMI ($\beta = -3.04$ per kg/m^2) were independently associated with SC scores ($R^2 = 0.313$, adjusted $R^2 = 0.277$). Mean SC in Israeli AMD patients (354.7 ± 96.3, $n = 201$) was similar to a Japanese AMD cohort (346.2 ± 146.4, $n = 435$, $p = 0.385$) and higher than a low-income US cohort (172.3 ± 77.2, $n = 153$, $p < 0.001$). Conclusions: In Israeli patients with AMD, SC scores were positively associated with dietary produce intake and AREDS2 supplementation, inversely associated with smoking and differed according to AMD subtype.

Keywords: carotenoids; Veggie Meter; age-related macular degeneration; dietary biomarker; skin carotenoid

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1. Introduction

Age-related macular degeneration (AMD) is a leading cause of irreversible blindness among older adults in developed countries [1–3]. It is a progressive degenerative retinal disease that may progress to severe vision loss through geographic atrophy (GA) involving the retinal pigment epithelium (RPE) or macular neovascularization [4]. Treatment options for the non-neovascular form of AMD remain limited to complement inhibitors and oral vitamin and mineral supplements [5,6]. Novel therapeutic approaches, including nanoparticle-based retinal drug delivery, are currently being investigated in preclinical studies [7].

AMD is a multifactorial disease influenced by genetic, immunologic, and environmental factors, with nutrition representing a key modifiable risk factor [8]. Adherence to a Mediterranean diet, characterized by high consumption of fruits and vegetables, fish, legumes, olive oil, and whole grains, has been associated with a reduced risk of AMD progression in multiple studies [9,10]. Therefore, accurate nutritional assessment is important for optimizing patient nutrition and potentially influencing disease course. While diet is traditionally evaluated using food frequency questionnaires (FFQs), this method is subject to recall bias, highlighting the need for additional reliable methods to assess dietary adequacy in clinical and research settings [11].

Objective biomarkers may provide a useful complement to self-reported dietary data in the assessment of nutritional status and retinal health. Carotenoids, which are obtained primarily through diet, are of particular interest in AMD, since these pigmented compounds protect against blue light and oxidative stress [12,13]. In the retina, they concentrate in the macula to form the macular pigment, which consists mainly of lutein and zeaxanthin, predominantly derived from dietary intake, as well as meso-zeaxanthin, which is generated in the eye from ingested carotenoids [14,15]. Patients with AMD are commonly recommended Age-Related Eye Disease Study 2 (AREDS2)-based nutritional supplements containing lutein and zeaxanthin, which have been shown to slow disease progression [16,17].

While macular pigment optical density (MPOD) directly quantifies retinal carotenoids, SC levels offer a fast, cost-effective, and non-invasive alternative for assessing total-body carotenoid status and dietary intake. Only a minority of the skin signal comes from lutein and zeaxanthin, the carotenoids that accumulate in the retina [18]. Resonance Raman spectroscopy (RRS) has been used to measure SC levels but requires specialized laser-based instrumentation that may limit clinical implementation. Portable reflection spectroscopy (RS) devices have been developed as simpler, laser-free alternatives to RRS, offering measurements that correlate with RRS-derived estimates at lower cost and with greater portability. Studies have demonstrated positive correlations between ocular and SC levels in diverse populations, including AMD cohorts [19,20]. SC scores also correlate positively with Mediterranean diet adherence in an adolescent Italian population [21].

We aimed to evaluate SC levels in Israeli patients with AMD, compare them with individuals without chronic retinal disease, and examine associations with factors potentially related to SC levels. These data may help evaluate the usefulness of SC measurements for research and clinical purposes in the retina clinic. The Israeli population presents a unique study group due to its heterogeneous population including individuals from diverse geographical and cultural backgrounds [22]. These characteristics provide an opportunity to gain important insights into the association between skin carotenoids and AMD.

2. Materials and Methods

2.1. Study Design and Participants

This cross-sectional study recruited a consecutive sample of patients and controls from the Department of Ophthalmology of the Hadassah–Hebrew University Medical Center, Jerusalem, Israel, between October 2025 and June 2026. Participants were approached by a trained staff member and received information about the study objectives. All participants provided written informed consent prior to participation. Ethical approval for the study was granted by the Institutional Review Board of the Hadassah–Hebrew University Medical Center, Jerusalem (protocol 22-03.08.07). Participants were recruited into three groups. The study group included patients with AMD. A comparison group of patients with DR was included to compare SC levels across chronic retinal diseases, and an additional control group included older individuals without chronic retinal disease.

2.2. Inclusion and Exclusion Criteria

Diagnosis and study group allocation were determined according to the results of an eye examination and optical coherence tomography (OCT) imaging. AMD diagnosis was determined according to the Age-Related Eye Disease Study (AREDS) criteria [23]. AMD subtype was determined based on clinical records. Patients were classified as dry AMD, or as neovascular AMD (including unilateral neovascular AMD or bilateral neovascular AMD). DR diagnosis and severity were classified according to the Early Treatment Diabetic Retinopathy Study (ETDRS) grading scale [24]. The control group consisted of patients attending the ophthalmology clinic for cataract evaluation and individuals accompanying patients to the clinic. The absence of chronic retinal disease was confirmed by clinical examination and OCT imaging. Participants were excluded if they declined to provide written informed consent or if the index finger could not be adequately cleaned for reliable SC measurement.

2.3. SC Measurement

SC levels were measured using the Veggie Meter device (Longevity Link Corporation, Salt Lake City, UT, USA), a portable instrument based on pressure-mediated reflection spectroscopy, in accordance with the manufacturer's instructions. The device generates a SC score on a continuous scale ranging from 0 to 800. Measurements were obtained from the index finger of the non-dominant hand after cleaning the finger with an alcohol wipe. For each participant, the SC score was calculated as the mean of three consecutive scans. The device was calibrated hourly using supplied dark and white reference sticks according to the manufacturer's recommendations. Room temperature and humidity were monitored to ensure a stable measurement environment. The device incorporates an algorithm to correct for melanin-related optical interference and has been validated across diverse racial and ethnic populations [25,26]. Skin pigmentation was not independently assessed in the present study.

2.4. Additional Data Collected

Demographic and clinical data collected from each participant included age, sex, weight, and height from which body mass index (BMI, kg/m^2) was calculated. Additional variables included smoking status (never, past, or current), and nutritional supplement use (recorded as AREDS2 formulations, vitamins other than AREDS2, minerals, and other supplements). The AREDS2 formulation contained 5 mg of lutein and 1 mg of zeaxanthin per capsule and was taken twice daily, corresponding to a daily dose of 10 mg of lutein and 2 mg of zeaxanthin. The duration of supplementation was not systematically recorded.

Self-reported daily fruit and vegetable intake was categorized according to Mediterranean Diet Adherence Screener (MEDAS) criteria, with adherence defined as consumption of ≥3 servings of fruit per day and ≥2 servings of vegetables per day [27]. Fruit intake was recorded as an ordinal variable (0 = <1 serving/day, 1 = 1 serving/day, 2 = 2 servings/day and 3 = ≥3 servings/day), whereas vegetable intake was recorded as a binary variable (≥2 servings/day = 1, otherwise 0). A supplement count variable was calculated as the number of supplement types used (AREDS2, vitamin, mineral, and other; range 0–4). The questionnaire was administered prior to SC measurement to minimize potential bias related to knowledge of results.

Country of birth was obtained from clinical records and categorized into four geographical regions: Israel, Europe and the former Soviet Union, other Middle Eastern and North African countries, and elsewhere. Socioeconomic status (SES) was assessed using area-based socioeconomic rankings published by the Central Bureau of Statistics (CBS) [28]. Participants were assigned an SES score from 1 to 10 based on their residential

address recorded in the system, with higher scores indicating higher socioeconomic status.

2.5. Comparison with International Studies

To contextualize the findings, SC scores in the present cohort were compared with values reported in two published studies using the same Veggie Meter device [29,30]. Comparisons were performed using Welch's *t*-test applied to published summary statistics (mean, SD, and n). Results in this section are presented as means and standard deviations rather than medians, because only summary statistics of this form were available for the published comparator cohorts. These comparisons are exploratory and based on published aggregate data, without adjustment for differences in demographic or clinical characteristics between cohorts.

2.6. Statistical Analysis

Statistical analyses were performed using R (version 4.5.3). Continuous variables are presented as medians and interquartile ranges (IQRs), and categorical variables as frequencies and percentages. Missing data were handled using complete-case analysis for the multivariable linear regression model (n = 162). Baseline characteristics were compared between included and excluded patients. Multiple imputation by chained equations (50 imputed datasets) was performed as a sensitivity analysis, with regression estimates pooled using Rubin's rules. The marginal distribution of SC scores departed from normality (Shapiro–Wilk W = 0.968, $p < 0.001$). Therefore, non-parametric methods were used for primary group comparisons and univariate association testing. Linear regression was used for adjusted and multivariable analyses because it assumes normality of the model residuals rather than normality of the marginal outcome distribution. Accordingly, regression assumptions were evaluated using the fitted-model residuals rather than inferred from this test.

Between-group differences across the three clinical groups (AMD, DR, and controls) were assessed to characterize the full cohort. Differences in continuous and ordinal variables were evaluated using the Kruskal–Wallis H test. Differences in categorical variables were assessed using the chi-square test. Multivariable linear regression was used to assess differences in SC scores across clinical groups and AMD subtypes, adjusting for potential confounders.

Subsequent analyses focused exclusively on the AMD cohort (n = 201). Univariate associations between potential predictors and SC scores were assessed using Spearman's rank correlation coefficient (ϱ) for continuous and ordinal variables. For binary predictors, Mann–Whitney U tests were used, with the rank-biserial correlation coefficient (r) reported as the effect size. To account for multiple comparisons, *p*-values from all univariate association tests conducted within the AMD cohort were corrected using the Benjamini–Hochberg false discovery rate (FDR) procedure, applied as a single family. Age- and sex-adjusted models were corrected separately, within that set of estimates. Where the Kruskal–Wallis test for smoking status was significant, pairwise post hoc comparisons were conducted using Dunn's test with BH-FDR correction for multiple comparisons. Exploratory analyses assessed associations between geographical region of birth and SC scores using the Kruskal–Wallis test and age- and sex-adjusted linear regression.

Age and sex adjusted linear regression models were then fitted for each predictor within the AMD cohort. A multivariable model was fitted within the AMD cohort including age, sex, BMI, smoking status, AREDS2 use, fruit intake, and vegetable intake as simultaneous predictors of SC.

Multicollinearity was assessed using generalized variance inflation factors (GVIFs).

Receiver operating characteristic (ROC) analysis was used to assess the ability of the SC score to discriminate adherence to the MEDAS fruit and vegetable targets (≥2 vegetable

servings/day and ≥3 fruit servings/day) within the AMD cohort. Discrimination was quantified using the area under the ROC curve (AUC), with a bootstrap 95% confidence interval, and was internally validated using 10-fold cross-validation. The optimal cutoff was defined by the Youden index. A secondary multivariable model including the SC score, age, sex, BMI, smoking status, and AREDS2 use was compared with the SC-only classifier.

A p-value < 0.05 was considered statistically significant for all primary tests.

3. Results

3.1. Participant Characteristics

A total of 338 participants were enrolled, including 201 patients with AMD (56.7% female, median age 79 [IQR 74.0–84.0] years), 68 controls (55.9% female, 70.5 [61.8–75.0] years), and 69 patients with DR (30.4% female; 65 [59.0–71.0] years). A total of 193 patients with AMD were classified into subtypes (17.6% dry AMD, 49.2% unilateral neovascular AMD, 33.2% bilateral neovascular AMD). Baseline characteristics by group are presented in Table 1.

Table 1. Baseline characteristics by clinical group.

Variable	AMD (*n* = 201)	Control (*n* = 68)	DR (*n* = 69)	*p*-Value
Demographics				
Age, median [IQR]	79.0 [74.0, 84.0]	70.5 [61.8, 75.0]	65.0 [59.0, 71.0]	<0.001
Female sex, *n* (%)	114 (56.7%)	38 (55.9%)	21 (30.4%)	<0.001
BMI, median [IQR]	26.6 [23.9, 29.4]	28.2 [23.9, 30.1]	28.9 [24.7, 31.7]	0.023
SES score, median [IQR]	6 [5, 8]	4 [2, 7]	3.5 [1, 7]	<0.001
Veggie Meter score, median [IQR]	345 [281, 412]	330.5 [261.8, 395.5]	331 [270, 400]	0.24
Smoking status, *n* (%)				0.002
Never	129 (64.8%)	46 (67.6%)	42 (60.9%)	
Past	56 (28.1%)	10 (14.7%)	12 (17.4%)	
Current	14 (7.0%)	12 (17.6%)	15 (21.7%)	
Any supplement use, *n* (%)	146 (72.6%)	36 (52.9%)	28 (40.6%)	<0.001
AREDS2 use, *n* (%)	92 (45.8%)	1 (1.5%)	0 (0.0%)	<0.001
Dietary intake (*n* = 297)				
≥2 vegetables/day, *n* (%)	127 (77.4%)	45 (70.3%)	49 (71.0%)	0.412
≥3 fruit servings/day, *n* (%)	39 (23.8%)	17 (26.6%)	24 (34.8%)	0.224
High produce intake: ≥2 vegetables/day and ≥3 fruit servings/day, *n* (%)	35 (21.3%)	14 (21.9%)	19 (27.5%)	0.576

Baseline characteristics. BMI = body mass index (kg/m^2); SES = socioeconomic status; AREDS2 = Age-Related Eye Disease Study 2 formulation. Kruskal–Wallis test for continuous variables; chi-square test for categorical variables. BMI was missing for 3 participants, smoking for 2, SES for 79, and dietary intake for 41.

3.2. SC Scores by Group

The overall median SC score was 339 (range 104–723). Scores did not differ significantly across the three clinical groups (Kruskal–Wallis H(2) = 2.86, p = 0.24). Median [IQR] scores were 345 [281–412] in participants with AMD, 330.5 [261.8–395.5] in controls, and 331 [270–400] in participants with DR. Scores by clinical group are shown in Figure 1. Differences remained non-significant after adjustment for age, sex, BMI, smoking status, and any supplement use (control vs. AMD, p = 0.485; DR vs. AMD, p = 0.652).

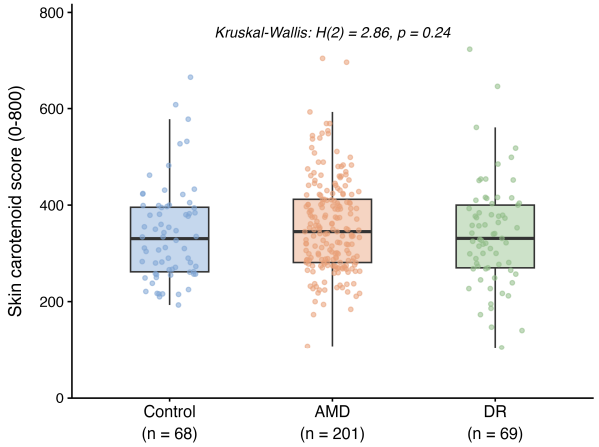

Figure 1. Skin carotenoid score by clinical group (Control, $n = 68$; AMD, $n = 201$; DR, $n = 69$). Boxes show the median and interquartile range, and the points are individual participants. Scores did not differ across groups (Kruskal–Wallis H(2) = 2.86, $p = 0.24$).

3.3. SC Scores Based on AMD Subtype

Among the 193 AMD patients with available subtype classification, 34 had dry AMD, 95 had unilateral neovascular AMD, and 64 had bilateral neovascular AMD. Mean SC scores were 390, 342, and 349 respectively. Differences across the three subgroups remained significant after adjustment for age and sex ($p = 0.027$).

When patients with neovascular AMD in at least one eye were combined into one group, those with dry AMD demonstrated higher SC scores after adjustment for age and sex ($\beta = 47.40$, $p = 0.009$; $n = 193$). To evaluate the influence of additional covariates, sequential models were fitted using a common complete-case subset ($n = 154$). Within this subset, the age- and sex-adjusted association remained significant ($\beta = 46.89$, 95% CI 10.32–83.46, $p = 0.012$). This association remained significant following additional adjustment for smoking and AREDS2 supplementation ($\beta = 37.38$, $p = 0.041$). Further adjustment for self-reported fruit and vegetable intake attenuated the association ($\beta = 24.93$, $p = 0.142$). SC scores according to AMD subtype are shown in Figure 2.

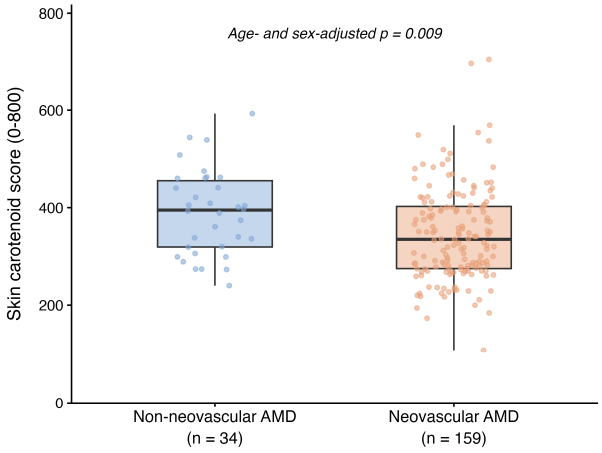

Figure 2. Skin carotenoid scores according to AMD subtype. Boxes show the median and interquartile range, and the points are individual participants. Patients with dry AMD exhibited higher SC scores than patients with neovascular AMD in at least one eye.

3.4. Univariate Associations with SC Scores in the AMD Group

Subsequent analyses focused exclusively on the AMD cohort ($n = 201$), which is the focus of the study.

3.4.1. Dietary Intake

Within the AMD group, based on the binary MEDAS classification, participants consuming at least two servings of vegetables per day had higher SC scores than those who did not (374 vs. 290, Mann–Whitney U test, r rank-biserial= 0.441, FDR-adjusted $p < 0.001$). Similarly, participants consuming at least three servings of fruit per day had higher scores (397 vs. 335, r rank-biserial= 0.331, FDR-adjusted $p = 0.006$).

Participants meeting both MEDAS recommendations (≥2 vegetables/day and ≥3 fruit servings/day) had substantially higher scores than those who did not (median 400 vs. 328, r rank-biserial= 0.401, FDR-adjusted p= 0.002). SC scores according to fruit and vegetable intake categories are presented in Figure 3.

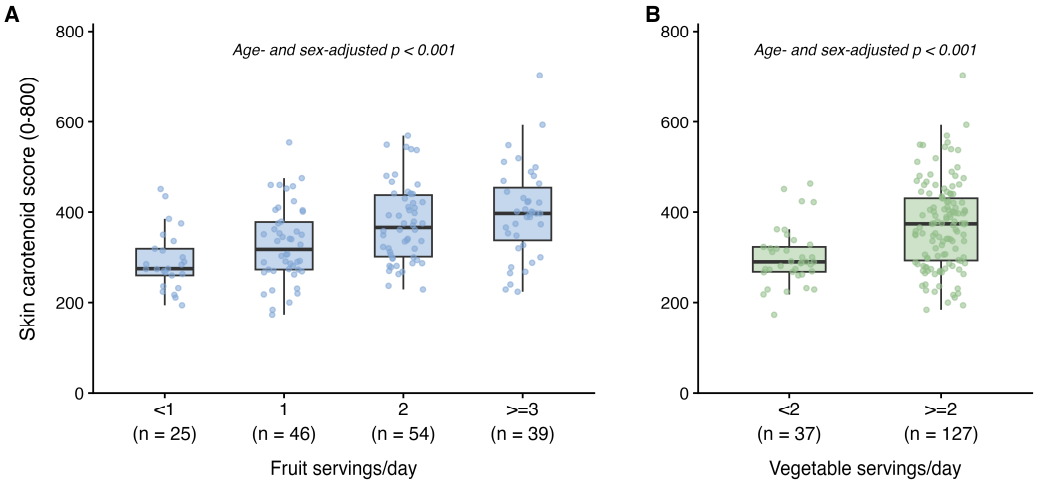

Figure 3. Skin carotenoid scores according to self-reported daily fruit (**A**) and vegetable (**B**) intake categories in the AMD cohort.

3.4.2. Discrimination of MEDAS Fruit and Vegetable Adherence

The ability of the SC score to discriminate participants who met both MEDAS fruit and vegetable recommendations (≥2 vegetable servings/day and ≥3 fruit servings/day) was evaluated among the 164 participants with available dietary data. Thirty-five participants (21.3%) met both recommendations. The SC score demonstrated moderate discrimination, with an AUC of 0.70 (bootstrap 95% CI, 0.60–0.79), which was maintained with 10-fold cross-validation (mean AUC, 0.70). The Youden-optimal cutoff was an SC score of 366, corresponding to 74% sensitivity and 65% specificity. At the observed prevalence of adherence (21.3%), the positive and negative predictive values were 36.6% and 90.3%, respectively. The ROC curve is shown in Figure 4. The addition of age, sex, BMI, smoking status, and AREDS2 use did not improve cross-validated discrimination compared with the SC score alone.

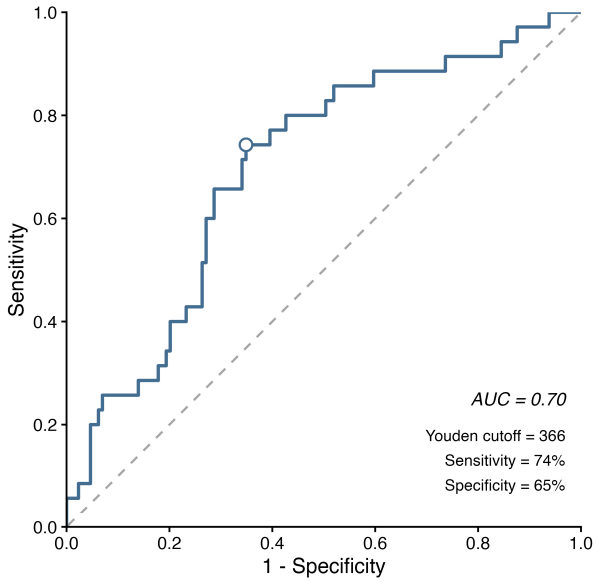

Figure 4. Receiver operating characteristic (ROC) curve for the skin carotenoid (SC) score for classifying adherence to MEDAS fruit and vegetable targets (≥2 vegetable servings/day and ≥3 fruit servings/day) in the AMD cohort (n = 164). The circle marks the Youden-optimal cutoff (SC score 366; sensitivity 74%, specificity 65%). AUC = 0.70 (bootstrap 95% CI 0.60–0.79). The dashed line is chance (AUC = 0.50).

3.4.3. Supplement Use

Within the AMD group, use of any supplement was associated with higher carotenoid scores although this did not reach statistical significance (median 350.5 vs. 318, r rank-biserial= 0.176, p = 0.055, FDR-adjusted p= 0.102). Among specific supplements, AREDS2 supplementation showed the strongest association, with a median score of 375 in users vs. 322 in non-users (r rank-biserial= 0.253, FDR-adjusted p = 0.006). In addition, the number of supplements taken was positively correlated with carotenoid score (Spearman ϱ = 0.211, FDR-adjusted p = 0.006). Vitamins and minerals alone were not associated with scores (FDR-adjusted p = 0.391 and 0.420, respectively).

3.4.4. Smoking

SC scores differed across smoking status (Kruskal–Wallis H(2) = 11.68, FDR-adjusted p = 0.006). Median scores were 361 in participants who never smoked (n = 129), 304.5 in past smokers (n = 56) and 283.5 in current smokers (n = 14). Post-hoc pairwise comparisons using Dunn's test with BH correction showed that never-smokers had significantly higher SC scores than both current smokers (FDR-adjusted p = 0.026) and past smokers (FDR-adjusted p = 0.014), while current and past smokers did not differ significantly from each other (adjusted p = 0.466).

3.4.5. Demographic, Socioeconomic and Geographical Characteristics

Age, sex, BMI, and SES were not significantly associated with SC scores in univariate analysis within the AMD group (Spearman ϱ = −0.078, FDR-adjusted-p = 0.387 for age; ϱ = −0.018, FDR-adjusted p = 0.797 for BMI; ϱ = 0.024, FDR-adjusted-p = 0.797 for SES; Mann–Whitney test, FDR-adjusted p = 0.384 for sex).

Two nominally significant associations that did not survive multiple-comparison correction are reported as exploratory findings. Any-supplement use was more common among women than men (79.8% vs. 63.2%; raw p = 0.014), but this did not survive correction for multiple comparisons. AREDS2 users had a higher SES, though not statistically significant (median 7 vs. 6, Mann–Whitney r rank-biserial = 0.161, p = 0.076). Another weak positive association was observed between SES and fruit intake (ϱ = 0.159,

$p = 0.07$), although this association did not reach statistical significance. Country-of-birth data were available for 191 patients with AMD (95.0%), of whom 50.8% were born in Israel, 22.0% in other Middle Eastern or North African countries, 17.8% in Europe or the former Soviet Union, and 9.4% elsewhere. SC scores did not differ across these groups ($p = 0.564$).

3.5. Adjusted and Multivariable Analyses

3.5.1. Age- and Sex-Adjusted Associations

After adjustment for age and sex, significant associations with SC scores were maintained for fruit intake, vegetable intake, adherence to both MEDAS produce targets, AREDS2 supplementation, number of supplements, and smoking status. Current versus never smoking showed an estimated difference of −73.98 points ($p = 0.006$), followed by vegetable intake ≥2 servings/day ($\beta = 69.88$, $p < 0.001$), adherence to both MEDAS targets ($\beta = 69.02$, $p < 0.001$), and fruit intake ≥3 servings/day ($\beta = 58.81$, $p < 0.001$). Full results are presented in Table 2.

Table 2. Age- and sex-adjusted associations with SC score in the AMD cohort.

Predictor	**N**	**β**	**95% CI**	***p*-Value**	**FDR *p* (BH)**
Dietary intake					
Fruit >= 3/day	164	+58.81	[25.85, 91.78]	<0.001	0.001
Vegetables >= 2/day	164	+69.88	[36.79, 102.97]	<0.001	<0.001
High total produce, MEDAS	164	+69.02	[35.17, 102.87]	<0.001	<0.001
Supplement use					
Any supplement	201	+34.43	[4.10, 64.76]	0.026	0.026
Number of supplements	201	+27.51	[12.81, 42.20]	<0.001	<0.001
AREDS2 supplement	201	+45.15	[18.89, 71.41]	<0.001	0.001
Smoking					
Current vs. never	199	−73.98	[−126.13, −21.83]	0.006	0.006
Past vs. never	199	−50.06	[−80.23, −19.89]	0.001	0.002

All models adjusted for age and sex. β = regression coefficient for the skin carotenoid score; CI = confidence interval; FDR = false discovery rate; BH = Benjamini–Hochberg; MEDAS = Mediterranean Diet Adherence Screener; AREDS2 = Age-Related Eye Disease Study 2 formulation.

3.5.2. Multivariable Model

A pre-specified multivariable model fitted within the AMD cohort (n= 162 with complete data on all variables) explained 31.3% of the variance in SC scores ($R^2 = 0.313$, adjusted R^2= 0.277). Fruit and vegetable intake, current and past smoking, AREDS2 supplementation, and BMI were all independently significant predictors of SC score, whereas age and sex were not. Full results are shown in Table 3. Model estimates are also shown in Figure 5. Adjusted GVIF values ranged from 1.017 to 1.052. The 39 excluded patients were older than the 162 included patients (median 81 vs. 78 years, $p = 0.005$), with no significant differences in the other assessed baseline characteristics. Missing data were predominantly related to dietary intake because the questionnaire was introduced after recruitment commenced.

Table 3. Multivariable model of SC score in the AMD cohort (n = 162 with complete data).

Predictor	β	95% CI	p-Value
Fruit intake (per category increase)	+30.99	[18.04, 43.95]	<0.001
Vegetable intake (≥2 servings/day)	+41.81	[10.77, 72.85]	0.009
Current smoking (vs. never, n = 9)	−61.05	[−117.09, −5.02]	0.033
Past smoking (vs. never, n = 47)	−29.82	[−58.38, −1.26]	0.041
AREDS2 (vs. no AREDS2) supplements	+32.39	[6.81, 57.97]	0.013
Age	−1.54	[−3.23, 0.15]	0.075
Sex (male vs. female)	+18.86	[−6.49, 44.21]	0.144
BMI	−3.04	[−5.44, −0.64]	0.013

Model n= 162 (participants with complete data on all variables). R^2 = 0.313, adjusted R^2 = 0.277. BMI = body mass index (kg/m²); AREDS2 = Age-Related Eye Disease Study 2 formulation supplementation. Reference categories are never smoking, female sex, and no AREDS2 use.

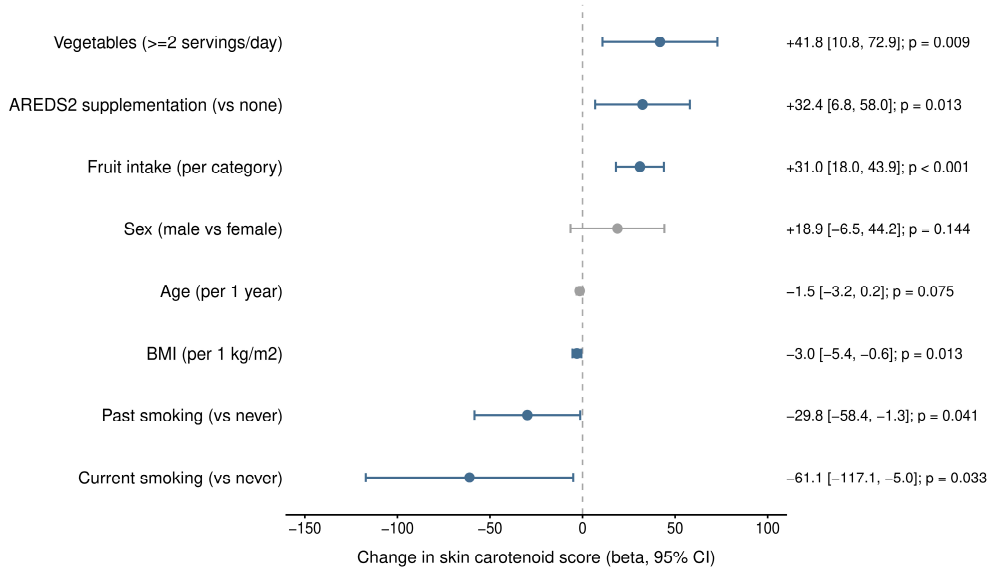

Figure 5. Multivariable linear regression model of SC score in the AMD cohort. Reference categories are never smoking, female sex and no AREDS2 use. BMI = body mass index (kg/m²); AREDS2 = Age-Related Eye Disease Study 2 formulation supplementation; β = multivariable regression coefficient; CI = confidence interval.

The model estimated a 31.0-point higher SC score per increase in fruit intake category and a 41.8-point higher score among participants consuming ≥2 servings of vegetables per day, a 61.1-point lower score for current versus never smokers, a 32.4-point higher score for AREDS2 users versus non-users, and a 16.7-point lower score across the BMI interquartile range of the modelled sample (23.9–29.4 kg/m²). Sensitivity analysis using multiple imputation (n = 201) yielded comparable regression estimates, with all significant associations identified in the complete-case analysis remaining statistically significant.

3.6. International Comparison

SC scores in the Israeli AMD cohort (mean 354.7 ± 96.3, n= 201) were compared with two published cohorts measured using the same Veggie Meter device used in the current study. Scores in our cohort were similar to those reported for AMD patients in a large Japanese ophthalmology clinic population (mean 346.2 ± 146.4, n = 435; p = 0.385). In contrast, scores in our cohort were significantly higher than those in a US cohort of low-income older adults enrolled in a federal food assistance program (mean 172.3 ± 77.2, n = 153, p < 0.001).

4. Discussion

This cross-sectional study measured SC levels in Israeli patients with AMD, DR and controls using non-invasive reflection spectroscopy, and examined factors associated with carotenoid scores within the AMD group, to assess the potential of SC as a non-invasive biomarker of fruit and vegetable intake and self-reported AREDS2 supplement use. Scores did not differ across the three clinical groups even after adjusting for age, sex, BMI, smoking status and supplement use. Within the AMD cohort, dietary produce intake showed a moderate-to-strong positive association with SC scores, and AREDS2 supplement use showed a more modest positive association. Smoking showed a strong negative association with scores, and higher BMI showed a more modest inverse association. Finally, SC scores in the Israeli AMD cohort were similar to those reported in a Japanese AMD population and higher than those observed in low-income older adults in the United States. While these comparisons provide context for SC levels in our cohort, they remain exploratory, as differences in demographic characteristics, smoking habits, supplement use, and measurement conditions between populations were not accounted for.

Our findings that dietary produce intake was associated with SC scores are consistent with the technique used to assess SC. Carotenoids are not endogenously synthesized and skin levels reflect cumulative dietary intake [26]. These results align with findings across diverse populations. In a large Italian cohort of 2078 university students, participants consuming at least 2 vegetables and 3 fruits daily had significantly higher scores than those who did not (391.7 ± 101.0 vs. 349.3 ± 90.9, $p < 0.001$) [31], a pattern mirrored in our AMD cohort, in which participants meeting the same cut-offs had higher scores (400 [360–457] vs. 328 [274–404]). Similar associations have been reported in other settings, including low-income older adults, in whom fruit and vegetable intake was positively correlated with SC scores (r = 0.192, $p = 0.018$) [29].

Among US racial and ethnic minority adolescents in Houston, vegetable intake significantly predicted carotenoid scores while fruit intake alone did not, an observation attributed to the lower carotenoid content of commonly consumed fruits such as apples and bananas compared with carotenoid-rich vegetables [32]. In our cohort, fruit intake was also significantly associated with higher carotenoid levels, although the effect size was smaller than that observed for meeting the vegetable intake recommendation in age- and sex-adjusted analyses (β= 58.81 vs. β= 69.88). This weaker association may also reflect limited precision, given that only 39 of 164 AMD patients (23.8%) reported meeting the fruit intake recommendation, as well as differences between the cohorts in age and specific fruits and vegetables consumed. Carotenoid composition varies by food source, with lutein particularly abundant in dark green leafy vegetables and β-carotene in orange and yellow produce [33]. Other plant-derived bioactive compounds, such as polyphenols, may also contribute to retinal protection through antioxidant and anti-inflammatory mechanisms [34].

To our knowledge, this is the first study to examine both skin carotenoid levels and dietary fruit and vegetable intake in patients with AMD. Overall, the associations between dietary produce intake and SC scores in our AMD cohort were moderate to strong and were larger than those reported in some prior studies. This may reflect a wider range of dietary intake in our AMD population, from patients with very low produce consumption to those adhering closely to a Mediterranean dietary pattern, as well as the additive contribution of AREDS2 supplementation in a subset of participants, which likely broadened the overall spread of scores and enhanced detectable associations.

AREDS2 supplementation was independently associated with higher scores after adjustment for age, sex, diet, BMI, and smoking in the multivariable model (β = +32.39, $p = 0.013$). The association between AREDS2 use and higher scores is consistent with the pharmacological rationale: AREDS2 formulations contain lutein and zeaxanthin,

carotenoids that are detected by RS. Similar results were previously reported in a large Japanese cohort, where lutein supplementation resulted in higher SC scores (415 vs. 325, $p < 0.001$), and remained a significant independent predictor of scores after multivariable adjustment [30]. These findings are further supported by a prospective supplementation study using RS in which scores increased during carotenoid supplementation and declined after supplementation ceased, demonstrating that the device is responsive to changes in supplement use [35]. Furthermore, SC levels have been shown to respond to changes in carotenoid intake over a period of weeks, suggesting that recent carotenoid exposure may be more relevant to current SC measurements than long-term supplementation history [36].

Among patients with AMD, SC scores differed significantly by smoking status, with lower median scores in past and current smokers compared to never smokers (361 in never smokers, 304.5 in past smokers, and 283.5 in current smokers). Post-hoc comparisons showed that past and current smokers did not differ significantly from one another, suggesting that the overall association was primarily driven by differences between never smokers and participants with a smoking history. Fruit and vegetable intake was similar across smoking groups ($p = 0.409$ and $p = 0.898$, respectively), so the measured dietary intake alone is unlikely to explain the difference in SC scores. AREDS2 use was less common among current smokers (14%) than among never (50%) or past smokers (45%; $p = 0.03$) and may have contributed in part. However, smoking remained independently associated with lower SC scores after adjustment for age, sex, BMI, diet, and AREDS2 use. Notably, current smokers showed a numerically larger deficit compared to past smokers ($\beta = -61.05$ vs. -29.82, both relative to never smokers), though this difference between past and current smoking was not significant, possibly because of the small number of participants in these groups. The persistence of lower scores among past smokers is notable because the SC measurement is thought to reflect carotenoid status over the preceding 2–4 weeks, whereas many past smokers had stopped smoking years earlier. These findings may reflect long-term effects of smoking on carotenoid metabolism or absorption, differences in dietary intake not fully captured in the study, or other confounding factors.

This pattern has been consistently replicated across populations. A Japanese cohort [30] and an Italian cohort [31] both found smoking to be a strong independent negative predictor of scores after multivariable adjustment. The proposed mechanism involves increased oxidative stress from smoking, which may deplete circulating and tissue carotenoids [37]. Cigarette smoke promotes oxidative stress and can induce oxidative DNA damage, lipid peroxidation and mitochondrial dysfunction, processes implicated in RPE dysfunction and AMD pathogenesis [38].

Higher BMI was independently associated with lower SC scores in the multivariable model ($\beta = -3.04$ per kg/m^2, $p = 0.013$), despite the absence of a significant univariate association (Spearman $\rho = -0.018$, $p = 0.797$). This may reflect confounding or a suppression effect, where a correlation between BMI and other predictors such as dietary intake or AREDS2 supplementation obscured the association in the unadjusted analysis. An inverse association between adiposity and skin carotenoid levels has been described in other populations although the effect here was mild.

Socioeconomic status, sex and age were not independently associated with SC scores. The association that approached significance before correction, between AREDS2 use and higher socioeconomic status, is unlikely to explain the AREDS2 and SC association reported above, since SES itself was unrelated to SC scores. Similarly, because SES and sex were not associated with SC scores in this cohort, they are less likely to account for the observed diet, supplement, and smoking associations. However, residual confounding cannot be excluded, and SES could not be formally entered into the multivariable model because of its high rate of missingness (19.4% of the AMD cohort). Participants with AMD had higher SES than those in the control and DR groups. Published data on socioeconomic

status and carotenoids are mixed. Higher SES has been associated with higher plasma carotenoid concentrations in some populations [39]. In contrast, RS studies have found either no income difference in skin carotenoid scores or fruit and vegetable intake, or even higher scores in children from lower-income schools [40,41]. In our AMD cohort, SES was not associated with SC scores, and the correlation with produce intake was only borderline. This may reflect the use of an area-based SES index rather than household income, the high rate of missing SES data, and a clinic sample in which produce intake did not vary strongly by SES.

The absence of significant differences in carotenoid scores across AMD, DR, and healthy controls (p = 0.24) is consistent with findings from a Japanese cohort in which scores similarly did not differ by macular disease status [30]. A possible explanation is that dietary fruit and vegetable intake did not differ significantly across the three groups (p = 0.121 for the four category fruit intake variable and p = 0.396 for binary vegetable intake), and dietary intake was the strongest independent predictor of carotenoid scores in this cohort. Therefore, similar dietary patterns would be expected to produce similar carotenoid scores regardless of clinical diagnosis. Although AREDS2 supplementation was more prevalent among patients with AMD than among controls, the two groups had similar SC scores, potentially reflecting the relatively modest association between AREDS2 supplementation and SC scores.

Despite the absence of significant differences across the three clinical groups, a secondary analysis revealed higher SC levels among patients with dry AMD compared with those with neovascular AMD. These findings suggest a potential relationship between SC levels and AMD phenotype, raising the possibility that carotenoid status may be associated with progression to neovascular disease. Adjustment for self-reported dietary intake attenuated the association, suggesting that dietary factors may contribute to the observed difference. This possibility is supported by evidence from the AREDS, which demonstrated that antioxidant and mineral supplementation can reduce progression to advanced AMD [42]. Furthermore, secondary analyses of AREDS2 demonstrated a reduced risk of neovascular AMD among participants receiving lutein and zeaxanthin compared with beta-carotene-containing formulations [43]. Given the cross-sectional design, longitudinal studies are needed to establish whether higher SC levels precede the development of neovascular AMD.

The mean SC score in our Israeli AMD cohort (354.7 ± 96.3) was closely similar to that reported for AMD patients in a large Japanese ophthalmology clinic (346.2 ± 146.4, n = 435; p = 0.385), despite differences in genetics and dietary culture. The similarity likely reflects shared characteristics of both samples: older patients with a high proportion taking nutritional supplementation. In contrast, scores were significantly higher than those of low-income older US adults enrolled in a federal food assistance program (172.3 ± 77.2). This cohort had a documented mean fruit and vegetable intake of only 2.5 cups per day and a 65.6% rate of food insecurity, suggesting that the lower scores likely reflect genuinely lower dietary carotenoid intake. Taken together, these findings further support the use of SC measurements as an objective marker of fruit and vegetable intake.

The relationship between skin and macular carotenoid levels is relevant to interpreting our findings in the AMD population. A clinic-based US study using resonance Raman spectroscopy found a moderately strong correlation between SC levels and macular pigment volume under the curve at 9° (r = 0.663) [19]. However, a more recent review highlights substantial biochemical and physiological differences between skin and retinal carotenoid accumulation and concludes that SC measurements should not be considered direct proxies for macular pigment levels [18]. Regardless, RS may be useful as a complementary tool for assessing dietary carotenoid status rather than retinal carotenoid concentrations, particularly given the established relevance of nutrition to AMD. Dietary produce intake may be beneficial to patients with AMD through

mechanisms other than carotenoid intake alone [44]. RS is then relevant as a marker of produce intake, rather than a substitute for measuring macular carotenoids.

The findings of this study have practical relevance for supporting the clinical management of AMD. RS provides a rapid, non-invasive, and visually intuitive assessment of skin carotenoid status that requires no invasive tests or laboratory work and can be administered immediately at the clinic. Unlike dietary questionnaires, it provides objective biological feedback that may motivate patients to improve both dietary quality and supplement adherence, both of which were independently associated with higher carotenoid scores in this cohort [45]. The SC score showed moderate accuracy for identifying AMD patients who met both MEDAS fruit and vegetable recommendations (AUC 0.70; 10-fold cross-validated AUC 0.70). A cutoff of 366 detected 74% of adherent patients and correctly classified 65% of those who did not meet the targets. This level of discrimination limits its applicability as a standalone screening tool. However, SC measurements may complement self-reported dietary assessment rather than replace it. This is particularly important in the AMD population, who is advised to adhere to a Mediterranean diet and take AREDS2 supplementation, yet adherence is often suboptimal and is currently monitored only through self-report [42,44,46].

This study has several limitations. First, the cross-sectional design shows associations rather than causation. Second, dietary data were available for only 81.6% of participants with AMD and were limited to two components of the MEDAS screener, rather than a validated full dietary assessment. This limitation restricts conclusions regarding overall Mediterranean diet adherence. Yet, higher vegetable and fruit intake was previously associated with slower GA progression, suggesting that these dietary components are clinically meaningful in the context of AMD treatment. Third, although participants were classified according to neovascular involvement, detailed stratification into early AMD, intermediate AMD and GA was not collected, limiting assessment of stage-specific associations. Additionally, the duration of AREDS2 supplementation was not systematically recorded, limiting our ability to assess whether supplementation duration influenced SC levels.

5. Conclusions

In this cross-sectional study of Israeli patients with AMD, SC levels measured by RS were most strongly associated with dietary fruit and vegetable intake, with additional independent contributions from AREDS2 supplementation and smoking status. Carotenoid scores did not differ across AMD, DR and control groups, likely reflecting similar dietary produce intake across these populations. However, SC levels were higher in patients with non-neovascular AMD than in those with neovascular AMD, supporting the existence of a potential protective role for factors associated with higher SC levels. Scores in this Israeli AMD cohort were similar to those reported in a Japanese AMD population and substantially higher than those observed in a low-income US cohort.

These findings support the potential utility of RS as a rapid, objective, and practical tool for assessing dietary carotenoid status and AREDS2 supplementation in AMD patients. Due to the insufficient diagnostic accuracy, it may be regarded as a recommendation support tool rather than an accurate measure of diet and supplement intake. Future studies should evaluate correlations between SC levels and clinical parameters in patients with AMD to further evaluate the role of SC measurement in research and management of AMD.

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