Malnutrition and Retinal Vascular Caliber in the Elderly: The POLA Study

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See the appendix for the members of the POLA Study Group.

Submitted: December 6, 2013
Accepted: April 27, 2014

PURPOSE. The pathway linking late-life malnutrition to greater risk of cardiovascular disease is unclear. Microcirculatory changes assessed by retinal vascular caliber have been linked with increased risk of stroke and coronary heart disease. The purpose of this study was to examine whether retinal vascular calibers are associated with malnutrition in elderly subjects free of cardiovascular diseases.

METHODS. This was a cross-sectional analysis of a community-dwelling cohort comprising 1145 individuals aged 60 years and older. Retinal vascular caliber was measured from fundus photographs using a semiautomated, standardized imaging software. Malnutrition was assessed using body mass index (BMI) < 18.5 kg/m² and biomarkers of protein malnutrition: plasma albumin and transthyretin.

RESULTS. In a multivariate model controlling for cardiovascular risk factors, retinal venular caliber was related to BMI ($P = 0.0002$) with an increased mean caliber for individuals with obesity and for those with low BMI. After multivariate adjustment for age, sex, hypertension, smoking, high-density lipoprotein (HDL) cholesterol, glomerular filtration rate and BMI, lower levels of albumin or transthyretin were associated with larger retinal venular caliber ($P = 0.026$ and $P = 0.0018$, respectively), that remain significant when adjusting for CRP ($P = 0.040$ and $P = 0.0060$, respectively) or orosomucoid ($P = 0.054$ and $P = 0.0020$, respectively). The relationships between retinal arteriolar caliber and BMI, albumin and transthyretin did not reach significance ($P = 0.14$, $P = 0.12$, and $P = 0.15$, respectively).

CONCLUSIONS. Protein malnutrition was identified as an additional factor associated with retinal venular dilatation beyond inflammation. This suggests that early microvascular changes may be one of the underlying mechanisms of increased risk of cardiovascular disease observed in elderly subjects suffering from malnutrition.

Keywords: risk factors, malnutrition, retinal vessels, microcirculation, albumin, transthyretin, elderly

According to the 2010 US population census, the proportion of elderly in the general population is increasing and presently constitutes 13% of the total population older than 65 years and 1.8% older than 85 years.1 Elderly people are at increased risk of malnutrition as compared with other adult populations2 with 5% to 10% of elderly subjects living in the community and 60% hospitalized being considered malnourished.3

Over the past decade, the importance of nutritional status has been increasingly recognized in a variety of morbid conditions in elderly people.4 Although there is no uniformly accepted definition of malnutrition in the elderly, some common indicators include involuntary weight loss and low body mass index (BMI) and biomarkers such as albumin and transthyretin.5 Hypoalbuminemia may be caused by malnutrition but also in response to inflammation thus requiring inflammatory markers to be simultaneously considered. Transthyretin, a serum and cerebrospinal fluid carrier of the thyroid hormone thyroxine and retinol-binding protein, is commonly used to assess protein status malnutrition. A meta-analysis of eight prospective population-based studies found an inverse association between serum albumin concentration and coronary heart disease risk.6

While obesity is known to be associated with increasing risk of cardiovascular disease (CVD),7 low BMI was also found to be associated with risk of cardiovascular mortality,8 notably in elderly subjects9 supporting the hypothesis of a link with malnutrition and increased risk of CVD. In a recent meta-
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analysis, an increased risk of cardiovascular mortality was observed both at higher and lower ranges of BMI.10

Previous studies have further suggested that microcirculatory changes are closely linked to cardiovascular modifications in humans.11,12 Changes in the caliber of retinal vessels have been shown to reflect the cumulative effects of birth weight,13,14 the aging process,15 cardiovascular risk factors,16,17 renal function,18 inflammation,19 oxidative stress,20 and genetic factors.21 In meta-analyses from epidemiological studies, wider retinal venules and narrower arterioles have been associated with an increased risk of coronary heart disease in women22 and an increased risk of global cardiovascular mortality,23 while wider retinal venular caliber predicted stroke.24 Retinal vascular caliber thus provides a practical indicator to test for the first time the hypothesis that malnutrition leads to cardiovascular disease throughout microcirculation changes. While malnutrition has already been associated with greater cardiovascular mortality,8-10 and with arteriolar stiffness,25 we hypothesize that this condition could be associated with human microcirculation as assessed from retinal vascular caliber.

The aim of our present study was to examine the relationship between retinal vascular calibers and body mass index or malnutrition plasma biomarkers taking into account inflammation biomarkers as they may reduce albumin concentration by decreasing its rate of synthesis.26 In order to assess the early stages of vascular remodeling, we focused our analyses on an elderly population with no history of diabetes, coronary heart disease, peripheral artery disease, or stroke.

METHODS

Study Population

The present study is a cross-sectional analysis from the Pathologies Oculaires Liées à l’Age (POLA) Study, a prospective study aimed at identifying the risk factors of age-related eye diseases. The study design has been published elsewhere.27 For inclusion in the study, participants were required to be residents of Sète (South of France) and aged 60 years or older. According to the 1990 population census, there were almost 12,000 eligible residents. The population was informed of the study through local media and the study organizers also contacted 4543 residents individually by mail and telephone, using the electoral roll. The baseline examinations took place in a mobile unit equipped with ophthalmologic instruments. Between June 1995 and July 1997, a total of 2584 participants were recruited.

From this sample, 471 (18.2%) individuals were excluded due to diabetes or clinical evidence of atherosclerosis if the subject also declared a history of complications of atherosclerosis whether related to stroke or coronary and peripheral artery disease. This was assessed with a standardized questionnaire on medical antecedents. From the remaining 2113 persons, 119 individuals were excluded due to missing data (10 for interview data, 109 for biochemical data). For 81 persons, retinal photographs were not performed and for 307, the photographs were not available because of technical failure or opacities. In addition, for 461 participants, the photographs were of insufficient quality for retinal vascular caliber measurement with semiautomated standardized software (rejection mainly due to default of centering on the optic disc and inability to identify major vessels). Statistical analyses are thus based on 1145 subjects, among the 2113 (54%) subjects free of diabetes or clinical atherosclerosis. This research was approved by the ethics committee of the University Hospital of Montpellier, France, and written informed consent was obtained from each participant.28,29

Retinal Photography and Measurement of Retinal Vascular Caliber

After pupil dilation, one 50° color retinal photograph (KodakGold 100 ASA; Eastman Kodak Company; Rochester, NY, USA) was taken of each eye. After film processing, retinal photographs were converted to digital images by a high-resolution scanner (Nikon LS2000; Nikon, Inc., Tokyo, Japan) using standard settings for all photographs.

Diameters of all vessels coursing through a specified area (0.5-1 disc diameter surrounding the optic disc) were measured by one of the authors (VD), blinded from other data and using image analysis software (IVAN, Department of Ophthalmology Visual Science, University of Wisconsin, Madison, WI, USA). The calibers of the central retinal artery and vein were estimated using the “Big-6 formula” and summarized as the central retinal artery and vein equivalents (central retinal artery [CRAE] and central retinal vein equivalent [CRVE]) representing the average diameter of respectively the arterioles and venules of the eye. The reproducibility of retinal vascular measurements was high, with intragrader correlation coefficients of 0.97 (95% confidence interval [CI]: 0.96–0.98) for CRAE and 0.95 (95% CI: 0.94–0.96) for CRVE. Due to the high intereye correlation reported in previous studies,32 we analyzed only one eye per subject (the right eye or, if unavailable or ungradable, the left eye).

Assessment of Indicators

Body mass index was defined as weight/height² in kg/m². Underweight was defined as a BMI below 18.5 kg/m². A BMI between 18.5 and 25 kg/m² was considered normal, between 25.1 and 30 kg/m² as overweight, and greater than 30 kg/m² as obese. Biological measurements were made from fasting blood samples taken at the participant’s home on the morning of the examination. Plasma albumin, transthyretin, and orosomucoid concentrations were determined by immunoturbidimetric methods, while hs-C-reactive protein (CRP) concentration was determined by latex-enhanced immunoturbidimetric method using reagents from Olympus (Rungis, France) on an biochemistry analyzer (Olympus AU2700; Olympus).34

The prognostic inflammatory and nutritional index (PINI) assessing the severity of inflammation/malnutrition status was defined as (C-reactive protein × orosomucoid)/[albumin × transthyretin].35 A PINI greater than 1, previously associated with the prediction of short-term mortality in hospitalized elderly patients with a sensitivity of 74% and a specificity of 72%, was used as a cutoff value.36

Covariates

Blood pressure was measured once, in a seated position, after at least 5 minutes of rest. Hypertension was defined as known treated hypertension confirmed by current use of antihypertensive medications and/or a systolic blood pressure (BP) of ≥140 mm Hg and/or diastolic blood pressure of ≥90 mm Hg. Fasting blood samples were obtained for the measurement of serum creatinine and plasma glucose. Plasma triglycerides and total cholesterol levels were measured by routine enzymatic methods with a reagent purchased from Boehringer Ingelheim Laboratories (Ingelheim, Germany). Renal function was assessed from estimates of glomerular filtration rate (eGFR) using the modification of diet in renal disease (MDRD) formula, based on plasma creatinine.37
Characteristics of the Participants in the POLA Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 1145 Included</th>
<th>n = 968 Not Included*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (interquartile range)</td>
<td>69.3 [64.4–72.6]</td>
<td>71.7 [66.2–75.9]</td>
<td>0.001</td>
</tr>
<tr>
<td>Male, %</td>
<td>39.8</td>
<td>41.9</td>
<td>0.42</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>58.6</td>
<td>62.0</td>
<td>0.15</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never, %</td>
<td>60.7</td>
<td>60.2%</td>
<td>0.25</td>
</tr>
<tr>
<td>Current, %</td>
<td>9.9</td>
<td>11.2%</td>
<td></td>
</tr>
<tr>
<td>Past, %</td>
<td>29.4</td>
<td>28.7%</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>26.4 (4.1)</td>
<td>26.1 (4.1)</td>
<td>0.12</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/L), mean (SD)</td>
<td>5.55 (1.0)</td>
<td>5.75 (1.45)</td>
<td>0.18</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L), mean (SD)</td>
<td>5.81 (1.11)</td>
<td>5.74 (1.03)</td>
<td>0.42</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L), mean (SD)</td>
<td>1.42 (0.37)</td>
<td>1.38 (0.37)</td>
<td>0.16</td>
</tr>
<tr>
<td>Triglycerides (mmol/L), mean (SD)</td>
<td>1.25 (0.73)</td>
<td>1.28 (1.04)</td>
<td>0.55</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²), mean (SD)</td>
<td>72.8 (18.4)</td>
<td>75.3 (39.2)</td>
<td>0.23</td>
</tr>
<tr>
<td>Albumin (g/L), mean (SD)</td>
<td>41.87 (3.71)</td>
<td>40.53 (4.98)</td>
<td>0.25</td>
</tr>
<tr>
<td>Transferrin (g/L), mean (SD)</td>
<td>0.26 (0.05)</td>
<td>0.25 (0.18)</td>
<td>0.35</td>
</tr>
<tr>
<td>HsCRP (mg/L), mean (SD)</td>
<td>3.62 (0.53)</td>
<td>3.64 (0.41)</td>
<td>0.93</td>
</tr>
<tr>
<td>Orosomucoid (g/L), mean (SD)</td>
<td>0.82 (0.21)</td>
<td>0.81 (0.22)</td>
<td>0.16</td>
</tr>
<tr>
<td>Central retinal arteriolar caliber (µm), mean (SD)</td>
<td>141.5 (16.7)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Central retinal venular caliber (µm), mean (SD)</td>
<td>202.8 (21.4)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

eGFR, estimated glomerular filtration rate from MDRD formula.

* A total of 119 individuals were excluded due to missing data (10 for interview data, 109 for biochemical data). For 81 persons, photographs were not performed and for 307, the photographs were not available because of technical failure or opacities. For 461 participants, photographs were of insufficient quality for retinal vascular caliber measurement with semiautomated standardized software (rejection mainly due to default of centering on the optic disc).

Statistical Analysis

Comparisons between included and excluded participants were performed using χ² and Student’s t-test or Wilcoxon test depending on data distribution. Retinal vascular calibers (CRAE and CRVE) were normally distributed in our sample.

Potential confounders retained in the multivariate models were covariates significantly associated with CRAE and CRVE assessed in a previous analysis on the same POLA population: age (years); sex (male versus female); hypertension status (hypertensive versus normotensive); current smoking status (current versus never/past); high-density-lipoprotein cholesterol (normal versus high); estimated glomerular filtration rate (normal versus renal insufficiency); and BMI.20

Retinal venular dilatation was defined from the highest quartile of retinal venular caliber. Multi adjusted odds ratios (ORs) were obtained by logistic regression, with retinal venular dilatation as the dependent variable. This model was used to assess the associations between BMI category (overweight, obese, and underweight), and retinal venular dilatation.

Analyses of covariance (ANCOVA) were used to determine the association of malnutrition biomarkers with retinal vascular calibers adjusted for age and sex and potential confounders in model 1, adding inflammation parameters in models 2 (CRP) and 3 (orosomucoid). Post hoc pairwise comparisons were corrected for multiple testing using the Tukey-Kramer method.

Retinal vascular calibers were assessed in two groups according to albumin levels (lowest tertile [≤40.6 g/L] versus middle and highest tertile) and transthyretin (lowest tertile [≤0.23 g/L] versus middle and highest tertile). A variable including subjects who were in the lower tertile of both albumin and transthyretin versus those in the middle or high tertile was also created. As inflammation and malnutrition both reduce albumin concentration by decreasing its rate of synthesis, 4-category variables were generated combining a biomarker of malnutrition (albumin or transthyretin) and a biomarker of inflammation (CRP or orosomucoid). Those in the low and middle tertiles of CRP (5.86 mg/L) or orosomucoid (0.93 g/L) were considered as having low inflammation.

Retinal venular caliber was the study outcome analyzed as the dependent variable in multi adjusted ANCOVA and logistic regression. All analyses were performed using statistical software (SAS version 9.2; SAS Institute, Cary, NC, USA).

RESULTS

Characteristics of the study sample are shown in Table 1. Median age (interquartile range) of the study sample was 69.3 (64.4–72.6) years, with 39.8% males, and 58.6% hypertensive individuals. In the total cohort, mean (±SD) central retinal arteriolar caliber was 141.5 µm (±16.7) and venular caliber 202.8 µm (±21.4). Participants included in the analysis were younger than persons eliminated due to missing data (P = 0.001), but no differences were found in relation to other characteristics, including cardiovascular risk factors and malnutrition indicators.

As shown in Figure 1, retinal venular caliber was related to BMI (P = 0.0002) with a probable “U-shaped curve” for venular dilatation. In post hoc comparisons, obese persons (P = 0.002) and those with low BMI (P = 0.05), differed from “normal” BMI even after adjustment for potential confounding factors. The relationships between BMI and retinal arteriolar caliber did not reach statistical significance (P = 0.14).

The adjusted associations of BMI and retinal venular dilatation are given in Table 2. Obese and underweight participants were more likely to have a retinal venular dilatation (OR = 1.56; 95% CI = 1.02, 2.38 and OR = 2.23; 95% CI = 1.01, 4.94, respectively).

Table 3 shows retinal venular calibers according to malnutrition biomarkers. After multivariate adjustment for age, sex, hypertension, smoking, HDL cholesterol, glomerular filtration rate and BMI, larger retinal venular caliber (mean ± standard error) was related to lower albumin (208.53 ± 1.48 vs. 205.56 ± 1.19 µm, P = 0.026); lower transthyretin (209.35 ± 1.46 vs. 205.09 ± 1.20 µm, P = 0.0018); lower albumin and...
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We detected no significant interactions between high sensitivity CRP or orosomucoid and biomarkers of malnutrition.

**Discussion**

The POLA cohort, with its extensive clinical phenotyping and elimination of diabetes and cardiovascular diseases, has permitted the examination of the relationship between retinal vascular caliber and malnutrition. Greater retinal venular caliber was related to low levels of malnutrition biomarkers (albumin and transthyretin) and an increase in PINI index.

Our results confirm previous reports of a relationship between obesity and retinal venular dilatation and revealed a possible “U-shaped curve” with the occurrence of specific venular dilatation in subjects with low levels of BMI. We thus explored the potential reasons for such an effect alongside the malnutrition biomarkers albumin and transthyretin. Regarding the relationship between CRAE and BMI, previous studies have given inconclusive results; CRAE being reported to both decrease and remain unchanged in patients with obesity. In the present elderly population, we observed that only retinal venular diameters correlated to BMI and malnutrition biomarkers (albumin and transthyretin).

One of the strengths of the present study was the use of multiple biomarkers of malnutrition. Indeed, age-related changes in body composition could be attributed to excess weight but also reduced muscle mass, recently defined as sarcopenic obesity. Body mass index alone may thus be an insufficient indicator of nutritional risk. Instruments for identifying malnourished persons are thus of particular importance. Weight loss or questionnaires such as the mini nutritional assessment are applicable to both community dwelling and hospitalized elderly; however, screening questionnaires may miss or delay identification of malnourished patients. In the present study, retinal venular dilatation was associated with low BMI, and also with low albumin and/or low transthyretin that permit earlier recognition of malnutrition. Hypoalbuminemia has been associated with long-term deterioration in nutritional status. Transthyretin is a marker of recent protein malnutrition and may also be of potential utility in the monitoring of short-term refeeding.

Indicators of inflammation such as CRP (acute phase protein) and orosomucoid (chronic inflammation) may aid in the determination of an etiologically based diagnosis. Together biological parameters of inflammation and malnutrition can provide an objective measure of nutritional status in order to characterize the type of malnutrition, the intensity (level of biomarkers), and also as prognostic indicators using, for example, PINI. Where there is no inflammation, malnutrition appears to be an additional risk factor for retinal venular dilatation independently of inflammation.

**Table 2. Association Between BMI and Retinal Venular Caliber**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
<th>Participants With Retinal Venular Dilatation, n (%)</th>
<th>Multi-Adjusted ORs*</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td></td>
<td>(n = 286 [25.0%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (18.5–25 kg/m²)</td>
<td>405 (35.37)</td>
<td>90 (22.22)</td>
<td>1</td>
<td></td>
<td>0.0002</td>
</tr>
<tr>
<td>Overweight (25–30 kg/m²)</td>
<td>533 (46.55)</td>
<td>129 (45.10)</td>
<td>1.07</td>
<td>0.77, 1.48</td>
<td></td>
</tr>
<tr>
<td>Obese (&gt;30 kg/m²)</td>
<td>177 (15.46)</td>
<td>54 (18.88)</td>
<td>1.56</td>
<td>1.02, 2.38</td>
<td></td>
</tr>
<tr>
<td>Malnourished (&lt;18.5 kg/m²)</td>
<td>30 (2.62)</td>
<td>13 (4.55)</td>
<td>2.23</td>
<td>1.01, 4.94</td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for age (years); sex (male versus female); hypertension status (hypertensive versus normotensive); current smoking status (current versus never/past); HDL cholesterol (normal versus high); eGFR (normal versus renal insufficiency); and logarithmic of high-sensitivity C-reactive protein.
<table>
<thead>
<tr>
<th>Retinal Venular Caliber*</th>
<th>Univariate</th>
<th>Multivariate Model 1†</th>
<th>Multivariate Model 2‡</th>
<th>Multivariate Model 3§</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Albumin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle and high tertile (&gt;40.6 g/L)</td>
<td>766 (66.90)</td>
<td>202.01 (0.77)</td>
<td>0.024</td>
<td>205.56 (1.19)</td>
</tr>
<tr>
<td>Lowest tertile (≤40.6 g/L)</td>
<td>579 (33.10)</td>
<td>205.04 (1.12)</td>
<td></td>
<td>208.53 (1.46)</td>
</tr>
<tr>
<td><strong>Transthyretin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle and high tertile (&gt;0.23 g/L)</td>
<td>746 (65.15)</td>
<td>201.46 (0.77)</td>
<td>0.005</td>
<td>205.09 (1.20)</td>
</tr>
<tr>
<td>Lowest tertile (≤0.23 g/L)</td>
<td>599 (34.85)</td>
<td>206.17 (1.12)</td>
<td></td>
<td>209.35 (1.46)</td>
</tr>
<tr>
<td><strong>Albumin and transthyretin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle or high tertile of albumin or transthyretin</td>
<td>942 (82.27)</td>
<td>201.81 (0.69)</td>
<td>&lt;0.0001</td>
<td>205.45 (1.15)</td>
</tr>
<tr>
<td>Lower tertile of albumin and transthyretin</td>
<td>203 (17.73)</td>
<td>209.01 (1.54)</td>
<td>&lt;0.0001</td>
<td>212.26 (1.82)</td>
</tr>
<tr>
<td><strong>PINI</strong>††</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal ≤1</td>
<td>986 (86.11)</td>
<td>201.88 (0.68)</td>
<td>&lt;0.0001</td>
<td>205.21 (1.17)</td>
</tr>
<tr>
<td>Risk of demutrition &gt;1</td>
<td>159 (13.89)</td>
<td>209.89 (1.68)</td>
<td></td>
<td>211.83 (1.87)</td>
</tr>
</tbody>
</table>

* Retinal vascular calibers in microns.
† Model 1: Multivariate association of retinal vascular caliber adjusted for age (years); sex (male versus female); hypertension status (hypertensive versus normotensive); current smoking status (current versus never/past); HDL cholesterol (normal versus high), eGFR (normal versus renal insufficiency); BMI (kg/m²).
‡ Model 2: model 1 with logeCRP (logarithm of high-sensitivity C-reactive protein).
§ Model 3: model 1 with orosomucoid.
†† PINI defined as (C-reactive protein × orosomucoid)/(albumin × transthyretin).
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Figure 2. Retinal venular caliber means (SE) according to protein malnutrition and orosomucoid levels adjusted for age, sex, hypertension status, current smoking status; HDL cholesterol, estimated glomerular filtration rate, BMI (kg/m²). Protein malnutrition defined as albumin ≤ 40.6 g/L and transthyretin ≤ 0.23 g/L. Normal protein nutrition defined as albumin > 40.6 g/L or transthyretin > 0.23. Orosomucoid normal defined as orosomucoid ≤ 0.93 g/L. Orosomucoid high defined as orosomucoid > 0.93. *Value for ANCOVA = 0.0001. P value for differences between groups: 1 vs. 2 = 0.009, 1 vs. 4 = 0.0003, 3 vs. 4 = 0.02.

may be as assumed to be exogenous; being related to low energy intake. Where there is mild to moderate inflammation, malnutrition may also be endogenous and related to chronic disease (e.g., rheumatoid arthritis, pancreatic cancer, etc.). If there is a marked inflammatory response, malnutrition could be related to acute disease or injury (e.g., infection, burns, trauma). Several studies have demonstrated that inflammatory biomarkers remain predictive of mortality even after adjustment for malnutrition parameters or, inversely, that malnutrition parameters remain significant after adjustment for inflammation biomarkers. However, the concomitant effect of a high level in an inflammation marker and a low level in a malnutrition marker has seldom been explored. Retinal vascular caliber may potentially be used as a tool for estimating risk of cardiovascular disease; the present analysis offers values for different degrees of retinal venular dilatation, depending on malnutrition and inflammation. Combined analyses for malnutrition biomarkers by orosomucoid level are presented in Figure 2. There is a clear dose effect in the relationship between biomarkers reflecting malnutrition and retinal venular caliber, which further supports the probability of a causal effect. From this, we observed that subjects suffering from malnutrition were at a higher risk of venular dilation with inflammation constituting an additional risk factor.

In a previous analysis of the POLA population, biomarkers of inflammation and malnutrition together were predictive of mortality and subjects with high orosomucoid and low transthyretin were at the highest risk of early death. In the present analysis, these two biomarkers appear strongly associated with retinal venular dilatation. The PINI is often used to jointly evaluate inflammatory and nutritional status in geriatric medicine to predict short-term mortality. The present study reveals the presence of retinal venular dilatation in individuals with a PINI becomes greater than 1. On the one hand, larger venules appear to be associated with higher cardiovascular risk when linked with greater BMI and current cigarette smoking. However, retinal venular caliber decreased with older age and poorer renal function. We thus hypothesize that retinal venular caliber decreases with chronological age and concomitant degradation of intrarenal vasculature. When exposed to metabolic risk factors such as obesity, inflammation, and in the present study protein malnutrition, venules may undergo a pathologic dilatation that is associated with an increased risk of stroke. Mechanisms involved in retinal venular dilatation remain unclear. They may be related to endothelial dysfunction, as shown in studies using flicker light. Endothelial dysfunction plays a central role in the pathogenesis of obesity, probably also in malnutrition as observed in experimental studies, as well as in dialysis patients. The relationship between malnutrition and orosomucoid high defined as orosomucoid > 0.93. Folate deficiency and hyperhomocysteinemia, a suggested risk factor for vascular disease, was associated with aging and poor nutritional status. This could explain the U-shaped curve with the occurrence of specific venular dilatation in subjects with low and high BMI levels. These findings should be further validated by reference to cellular and molecular biological investigations providing further information on changes in human microcirculation.

The strengths of this study include the precise measurement of retinal vascular caliber, the availability of a cohort free of cardiovascular events and the measurement of a wide range of cardiovascular risk factors as well as biomarkers of inflammation and malnutrition. However, several limitations of this study should be noted. The cross-sectional nature of the analyses precluded observation of the temporal sequence of the reported associations among the BMI, biomarkers of malnutrition, and retinal vascular caliber. Further longitudinal analyses are required to assess the determinants of microvascular remodeling as evaluated by retinal vessels. Apart from diabetic status/blood glucose, the main established associations between retinal vascular calibers and cardiovascular risk factors were confirmed in this elderly cohort. Ethnicity and axial length were not available in the POLA study. They were associated with retinal vascular caliber in previous studies and we could not adjust for their potential confounding effects.

In conclusion, retinal venular dilatation appears to be strongly associated with malnutrition biomarkers (albumin and transthyretin). This suggests that early microvascular changes may be one of the mechanisms associated with the increased risk of cardiovascular mortality among elderly subjects with malnutrition. Our data also suggest that an assessment of retinal vascular calibers may offer new insights into the pathophysiology of subclinical vascular processes and thus contribute to research and clinical investigations. The natural history of microvascular remodeling and its determinants remain to be investigated in biological and longitudinal clinical investigations.

Acknowledgments

The authors alone are responsible for the content and writing of the paper.

Disclosure: V. Daifen, None; I. Carriere, None; R. Kawasaki, None; J.-P. Cristol, None; M. Villain, None; P. Fesler, None; K. Ritchie, None; C. Delcourt, None

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APPENDIX

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