SERUM ALBUMIN AND HEMOGLOBIN ARE ASSOCIATED WITH PHYSICAL FUNCTION IN COMMUNITY-LIVING OLDER PERSONS IN SINGAPORE

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Abstract: *Objectives:* Albumin and hemoglobin are viewed as markers of nutritional and inflammatory status. This study examined the associations of serum albumin and hemoglobin with physical function in community-living older adults. *Design:* Population-based cross-sectional and longitudinal study. *Setting:* The Singapore Longitudinal Aging Studies (SLAS), a community-based study in urban Singapore. *Participants:* 2762 older adults aged 55 and above assessed at baseline, and 1829 at follow up 1-2 years later. *Measurements:* Serum albumin and hemoglobin, Performance Oriented Mobility Assessment (POMA), knee extension strength at baseline, and Instrumental Activities of Daily Living (IADL) at baseline and follow up. *Results:* In cross-sectional multivariate analyses that adjusted for haemoglobin and other confounders, albumin showed a significant linear association (p<0.001) with POMA balance score (b=0.06, SE=0.02) and knee extension strength (b=0.70, SE=0.10). Independently of albumin, hemoglobin also showed a significant linear association with POMA balance score (b=0.09, SE=0.04). In longitudinal analyses, albumin was significantly associated with IADL decline (IADL total score drop>=1 during follow-up), OR= 0.92 (0.87 - 0.97), p=<0.01. *Conclusion:* The findings suggest that low levels of albumin and hemoglobin are potentially useful risk markers of physical functional decline in older adults. Further research should investigate whether improvements in the levels of albumin and hemoglobin alter the level of functional disability and risk of functional decline.

Key words: : Albumin, hemoglobin, physical function, elderly.

Introduction

In ageing societies, the health services and social care needs of physically disabled older persons are a cause of great societal concern and burden. To devise and implement effective strategies for preventing or delaying the onset of physical disability, it is important to identify modifiable risk factors of physical functional limitations and disability. While research over decades have established a large number of modifiable risk factors for functional status decline in the elderly, nutritional factors have not been adequately investigated thus far (1).

Albumin is a conventional marker of nutritional status. In community-living older persons, low albumin has been reported to be associated with impaired performance of activities of daily living (ADL) (2) and decline in muscle strength (3). However, other studies have also reported that albumin alone did not independently predict physical function decline measured by subjective questionnaires (4) or objective performance tests (5). The inconsistent results could possibly be attributed to the use of different instruments with varying sensitivity to assess physical functional performance.

Another nutritional marker is hemoglobin. A growing body of evidence has linked "mild" anemia or low-normal hemoglobin in the elderly to adverse events (6). Population-based studies have consistently reported an association between low hemoglobin and poor physical function (7-9) or greater decline in physical performance (10) among community-living elderly persons.

So far, the relationship of albumin and hemoglobin with physical function has been studied in isolation, and not in tandem. Hence, their independent and relative effects on physical function are unclear. Albumin and hemoglobin are associated with distinct physiological processes and biological mechanisms in human body. Low albumin concentration is associated with sarcopenia and muscle strength decline in the elderly (11). As such, albumin has been proposed to be a marker of inflammatory response and increased vascular permeability that underline various chronic diseases (12). Low haemoglobin is well known to occur in individuals with chronic disease as a result of suppressed erythropoiesis by systemic inflammation (13).

In the present study, we measured albumin and hemoglobin together, and physical function using both performance-based tests and self-reported questionnaires in a large sample of community dwelling elderly from the Singapore Longitudinal Ageing Study cohort. We tested the hypothesis of linear associations between serum albumin and hemoglobin with measures of physical function, and investigated whether albumin or hemoglobin exerted a more pronounced effect on physical function in relation to each other.

Methods

Study population

The Singapore Longitudinal Ageing Study (SLAS) is a prospective cohort observational study of ageing and health among community-dwelling elderly Singaporeans. During recruitment and baseline data collection between September 2003 and December 2005, all older adult residents aged ≥55 years (N=2,804, 78% response rate) were identified by door-to-door census in South East Singapore for participation in the study. Residents who were severely physically or mentally ill, and incapacitated to give informed consent or participate, were excluded. The study was approved by the National University of Singapore Institutional Review Board, and all participants gave signed informed consent. The details of the SLAS have been described in previous publications (14-16).

For the current study, we performed cross-sectional analyses of 2,762 respondents who had complete baseline data for albumin, hemoglobin and performance-based assessment of gait, balance and strength. Longitudinal analyses for instrumental ADL ability was performed for 1,829 participants with baseline and follow up assessments at 1-2 years (median=1.5 years) available for only instrumental ADL ability.

Measurements

Participants completed an extensive series of face-to-face interviews, assessments and tests which were performed by trained research nurses, in the preferred language (English or Chinese or Malay) or dialect.

Self-reported physical function

Self-reported physical functional status was assessed using items from the Lawton scale (17-19), which had been validated in previous studies. The subjects' ability to perform instrumental activities of daily living were categorized as follows: "unable to do at all" (score-0), "needed some assistance" (score-1), or "needed no help" (score-2). Higher summed IADL was scored across different items represent higher function levels. IADL change score was calculated by subtracting the follow up score from the baseline score and analyzed as a continuous variable. Subjects were defined as having suffered a decline in IADL function if their IADL score fell by 1 or more points during the follow up period, and analyzed as a dichotomous variable.

Physical Performance tests

Gait and balance were measured by the performance oriented mobility assessment (POMA) tool (20). Static sitting balance (rising from the sitting position without using hands) was assessed using graded scores by the need for assistance and the number of attempts; standing balance was assessed within the first five seconds after the subject's sternum was gently pushed by the examiner, and when stance was stabilized. Staggering or excessive sway of the subject was examined wth the subject standing and his eyes closed. Steadiness and continuity of steps were observed with the subject turning in a complete 360 degree circle. Gait assessment was performed with the subject walking 6 meters and returning quickly to the starting point, noting the ability to initiate walking and any hesitancy, step height and length, the lack of symmetry or inability to clear the floor, step continuity, deviation in the path and walking stance. The POMA scores for balance and gait were tallied separately using standard scoring criteria, and a combined total score was determined.

Testing of lower limb strength (knee extension muscle strength) was performed using a spring gauge attached to the subject's leg using a webbing strap with a Velcro fastener. The force of the knee extensor was measured with the subject sitting on a tall chair with a strap around the leg 10 cm above the ankle joint, and the hip and knee joint angles positioned at 90 degrees. In 3 trials per muscle group, the subject attempts to pull against the strap assembly with maximal force for 2 to 3 seconds, and the greatest force for each muscle group was recorded (21).

Laboratory measurements

Overnight fasting venous blood samples were analyzed for serum level of albumin (g/L) on an Advia 2400 auto-analyzer (Bayer HealthCare Diagnostics) using Bromcresol Green (BCG) dye binding method (CV ranging from 1%-3%). Measurements of hemoglobin level (g/dL) were performed on the same automated system.

Other variables

Other information collected included age, gender, education, housing type, cigarette smoking (current smokers, past-smokers, or non-smokers), alcohol consumption (at least 1 alcoholic drink daily versus nil), and any hospitalization in the past 12 months. Body Mass Index (BMI) was calculated as kg/m^2 with measured weight and height.

Respondents were asked to report whether in the 12 months prior to the interview they were diagnosed and treated by a doctor for any one or more of a list of specific medical conditions, which included asthma, chronic obstructive pulmonary disease (COPD), coronary artery disease, heart failure, hypertension, diabetes mellitus, stroke, hip fracture, arthritis, cataract, and other conditions specified by them. The total number of co-morbidities was used in the analysis.

Cognitive performance was assessed by the Mini-Mental State Examination (MMSE) (22), which has been externally validated for local use in another study population of Singaporean older adults (23). Poor cognitive performance was defined by MMSE total score of 23 or less.

The presence of depressive symptoms was assessed using the 15-item Geriatric Depression Scale (24, 25) which has been validated for use in local Chinese, Malay and Indian subjects (26, 27). The use of the GDS avoids the measurement artifact due to overlapping symptoms of the somatic illness and symptoms indicative of depression.

Statistical analysis

Group comparisons of categorical and continuous variables were performed using chi-squared test or analysis of variance, as appropriate. In multiple regression and logistic regression analyses, POMA gait, POMA balance, knee extension strength, baseline IADL score , IADL change score (continuous variable) and IADL decline (dichotomous variable) were analyzed as dependent variables. Regression coefficient (b) or odds ratio (OR) of association for albumin and hemoglobin (continuous variables) were estimated in base models (Model 1: unadjusted), and adjusted in hierarchical models that controlled for age, gender, education, housing type, number of co-morbidities, hospitalization in past year, GDS score, MMSE score, body mass index, creatinine level, history of arthritis and hip fracture (Model 2); and finally with hemoglobin and albumin together (Model 3). Baseline IADL score was significantly associated with serum albumin and hemoglobin and predicted future decline of physical function, however in some plausible situations, adjusting for baseline health status may inflate regression coefficient estimates for the effect (28). In longitudinal analyses, therefore, the multivariate models included models (Model 3) with and without (Model 2) baseline IADL scores as a baseline covariate. In further analyses, subjects with IADL disability (needing any help in IADL) at baseline were excluded (Model 5), to determine the effect of albumin and hemoglobin in well functioning individuals in predicting incident cases of IADL functional decline. A 2-sided p value of less than 0.05 was considered as statistically significant. All analyses were carried out with SPSS statistical software version 18.0 (SPSS, Inc., Chicago, Illinois).

Results

Table 1 displays characteristics of the study sample. The mean age of the study participants was 66 (SD=7.7), and 1430 (51.8%) had less than 6 years of schooling. Low albumin (<38 g/L) was present in 199 (7.2%) of the participants and low hemoglobin (<12g/dl in females and <13g/dl in males) was found in 397 (14.4%).

POMA scores, knee extension strength and IADL score were lower in anemic (versus non-anaemic) and hypoalbuminemic (versus normoalbuminaemic) respondents (p < 0.05) (Table-1). Anemic and hypoalbuminemic respondents were also noted to have lower MMSE score, GDS score, increased age, lower socio-economic status, more co-morbidities and hospitalizations. Mean BMI was lower and creatinine was higher in anaemic (versus non-anaemic) respondents.

Cross-sectional analyses (Table 2) showed that in the unadjusted base model (Model 1), albumin was significantly associated with POMA gait, POMA balance scores, knee extension strength and IADL scores (p<0.01). Controlling for

Table 1
Description of the study participants (n= 2762)

Variables	Low Albumin (<38 g/L)			Anemia [a]		
	Yes (N=199)	No (N=2563)	P[b]	Yes (397)	No (2365)	P[b]
Hemoglobin (g/dL),	12.6±1.6 (6.5-16.9)	13.6±1.3 (8.5-18.6)	<0.01	11.5±0.9 (6.5-12.9)	13.8±1.1 (12-18.6)	<0.01
Anemia, N (%)	74(37.2)	323(12.6)	<0.01	-	-	-
Albumin (g/L)	35.9±1.5 (30-37)	42.7±2.8 (38-54)	<0.01	40.7±3.6 (30-52)	42.4±3.1 (31-54)	<0.01
Low Albumin (<38 g/L), N (%)	-	-	-	74(18.6)	125 (5.3)	<0.01
Age	70.7±9.3 (55.1-95.7)	65.6±7.4 (55-97.6)	<0.01	69.6±9.1 (55.1-97.1)	65.4±7.2 (55-97.6)	<0.01
Gender (female), N (%)	125(62.8)	1619 (63.2)	0.9	257(64.7)	1487 (62.9)	0.47
Education (primary and below), N (%)	130 (65.3)	1300 (50.7)	<0.01	246 (62)	1184(50.1)	<0.01
Housing (≤3 rooms), N (%)	117 (58.8)	738 (28.8)	<0.01	163 (41.1)	692 (29.3)	<0.01
Number of co morbidities	2.4±1.7 (0-6)	2.3±1.5 (0-9)	0.36	2.6±1.6 (0-9)	2.3±1.4 (0-9)	<0.01
Hospitalized in past year, N (%)	14 (7.0)	96 (3.7)	0.02	28 (7.1)	82 (3.5)	<0.01
Current and Ex smoker, N (%)	14 (7.0)	449 (17.5)	<0.01	65 (16.4)	398(16.9)	0.8
Alcohol Drinker, N (%)	24 (12.1)	271 (10.6)	0.5	44(11.1)	251(10.6)	0.76
BMI (kg/m²)	23.6±4.9 (13.1-44.9)	23.8±3.7 (12.5-43.9)	0.5	22.5±3.8 (13.6-44.7)	23.9±3.7 (12.5-44.9)	<0.01
Creatinine(umol/L)	80.9±23.8 (38-166)	80.6±25.9 (34-468)	0.8	86.4±39.7 (38-468)	79.6±22.4 (34-388)	<0.01
History of arthritis, hip fracture, N (%)	32 (16.1)	447 (17.4)	0.7	68 (17.1)	411 (17.4)	0.9
MMSE total score	24.7±5.7 (4-30)	27.1±3.3 (3-30)	<0.01	25.6±4.6 (5-30)	27.1±3.4 (3-30)	<0.01
MMSE <24, N (%)	52 (26.5)	295 (11.5)	<0.01	92 (23.4)	255(10.8)	<0.01
GDS total score	2.6±3.5 (0-15)	1.8±2.7 (0-15)	<0.01	2.4±3 (0-15)	1.8±2.7 (0-15)	<0.01
GDS>=5, N (%)	40 (20.2)	321 (12.6)	<0.01	73 (18.5)	288(12.2)	<0.01
POMA total score at baseline	30.4±5.7 (1-35)	32.6±3.2 (5-35)	<0.01	31.1±4.7 (5-35)	32.7±3.2 (1-35)	<0.01
POMA Gait score	8.7±1.2 (0-9)	8.9±0.5 (0-9)	<0.01	8.8±0.9 (0-9)	8.9±0.5 (0-9)	<0.01
POMA Balance score	21.5±5.2 (0-26)	23.7±2.9 (4-26)	<0.01	22.3±4.2 (1-26)	23.7±2.9 (0-26)	<0.01
Knee extension strength (kg)	21.9±8.3 (8-37)	27.4±12.1 (6-212)	0.01	23±8.5 (8-46)	27.7±12.3 (6-212)	<0.01
IADL score	12.3±3.6 (0-14)	13.4±1.8 (0-14)	<0.01	12.97±2.8 (0-14)	13.4±1.8 (0-14)	<0.01

Figures shown are mean±SD (range) or N (%); a. WHO criteria: <12g/dl for women and <13 g/dl for men; b. Independent sample t test for continuous variables, chi-square test for categorical variables; BMI= Body Mass Index, MMSE= Mini-mental state examination, GDS= Geriatric Depression Score, POMA=Performance oriented mobility assessment, IADL= Instrumental Activity of Daily Living, SD= Standard deviation

Table 2
Cross-sectional analysis: associations of albumin and hemoglobin with physical performance measures

	POMA gait			POMA balance			Knee Extension Strength		
	b ± SE	Beta	p	b ± SE	beta	p	b ± SE	beta	P
Albumin									
Model 1	0.02 ± 0.003	0.09	<0.01	0.18 ± 0.02	0.19	<0.01	1.1 ± 0.2	0.3	<0.01
Model 2	0.003 ± 0.003	0.02	0.3	0.07 ± 0.02	0.07	<0.01	0.8 ± 0.1	0.2	<0.01
Model 3	0.003 ± 0.003	0.02	0.4	0.06 ± 0.02	0.06	<0.01	0.7 ± 0.1	0.2	<0.01
Hemoglobin									
Model 1	0.05±0.008	0.1	<0.01	0.4±0.04	0.16	<0.01	3±0.3	0.3	<0.01
Model 2	0.01±0.008	0.03	0.2	0.13±0.04	0.06	<0.01	1.03±0.3	0.12	<0.01
Model 3	0.009 ± 0.009	0.02	0.3	0.09±0.04	0.04	0.03	0.6±0.3	0.08	0.06

MMSE= Mini-mental state examination, GDS= Geriatric Depression Score, POMA=Performance oriented mobility assessment, IADL= Instrumental Activity of Daily Living, b= unstandardized coefficients, SE= standard error, beta= standardized coefficients. Model 1: Unadjusted. Model 2: Adjusted for age, gender, education, housing type, number of co morbidities, hospitalization in past year; GDS score, MMSE score, body mass index(BMI), creatinine level, and history of arthritis and hip fracture; Model 3: Adjusted for variables in Model 2 plus hemoglobin (for albumin) or albumin (for hemoglobin)

Table 3
Longitudinal analysis: association of baseline albumin and hemoglobin level with IADL decline (N=1829)

	IADL change			IADL decline*		
	b± SE	beta	p	OR	95% CI	P
Albumin						
Model 1	-0.03 ± 0.01	-0.06	<0.01	0.87	0.83 - 0.92	<0.01
Model 2	-0.02 ± 0.007	-0.05	<0.01	0.92	0.87 – 0.97	<0.01
Model 3	-0.03 ± 0.01	-0.06	<0.01	0.92	0.87 – 0.97	<0.01
Model 4	-0.02 ± 0.007	-0.05	0.01	0.92	0.87 – 0.97	<0.01
Model 5	-0.02 ± 0.008	-0.07	0.01	0.91	0.85 – 0.98	0.01
Hemoglobin						
Model 1	-0.02 ± 0.02	-0.02	0.5	0.94	0.84 – 1.11	0.3
Model 2	-0.02 ± 0.03	-0.02	0.6	0.95	0.83 – 1.11	0.5
Model 3	-0.02 ± 0.03	-0.02	0.4	0.95	0.83 – 1.11	0.5
Model 4	-0.001 ± 0.03	-0.001	0.9	0.99	0.86 – 1.15	0.9
Model 5	-0.02 ± 0.02	-0.03	0.4	0.94	0.79 – 1.13	0.5

* Defined as ≥1 point decline on IADL score during follow-up period; MMSE= Mini-mental state examination, GDS= Geriatric Depression Score, POMA=Performance oriented mobility assessment, IADL= Instrumental Activity of Daily Living, b= unstandardized coefficients, SE= standard error, beta= standardized coefficients, CI= confidence interval. Model 1: Unadjusted. Model 2: Adjusted for age, gender, education, housing type, number of co morbidities, hospitalization in past year; GDS score, MMSE score, body mass index(BMI), creatinine level, and history of arthritis and hip fracture. Model 3: Adjusted for age, gender, education, housing type, number of co morbidities, hospitalization in past year; GDS score, MMSE score, body mass index(BMI), creatinine level, and history of arthritis and hip fracture, plus IADL score at baseline. Model 4: Adjusted for variables in Model 2 plus haemoglobin (or albumin). Model 5: Excluded subjects with IADL disability at baseline (N=1435), adjusted for variables in Model 4. (Baseline IADL score not included).

gender, age, education, housing type, number of co-morbidities, hospitalization, GDS score, MMSE score, body mass index creatinine level and history of arthritis and hip fracture (Model 2), albumin was positively associated with POMA balance score and knee extension strength (p<0.01). With further adjustments for hemoglobin (Model 3), albumin remained significantly associated with POMA balance score (b=0.06, p<0.01) and knee extension strength (b=0.70, p<0.01).

Hemoglobin was significantly associated with all objective physical function measures in the unadjusted model (p<0.01), but only the association with POMA balance score (b=0.09, p=0.04) remained statistical significant when all potential confounder variables and albumin were adjusted for in model 3 (Table 2).

From follow up, 10% of participants (n=182) showed IADL decline. Longitudinal analyses (Table 3) showed that albumin was significantly associated with IADL decline (OR= 0.87, 95% CI = 0.83-0.92) in the unadjusted base model (Model 1). Controlling for gender, age, education, housing type, number of co-morbidities, hospitalization, GDS score, MMSE score, body mass index, creatinine level and history of arthritis and hip fracture (Model 2), albumin was significantly associated with IADL decline (OR= 0.92, 95% CI = 0.87-0.97). Further adjustments for baseline IADL score (Model 3) and hemoglobin (Model 4) showed that albumin remained significantly associated with IADL decline (OR= 0.92, 95% CI = 0.87-0.97). In further analyses that excluded subjects with IADL disability at baseline, we obtained similar results (Model

5. OR= 0.91, 95% CI = 0.85-0.98). Similar results were obtained when IADL change score (continuous variable) was used as the dependent variable (regression coefficient was -0.02 (SE= 0.008, P=0.01 in the final model).

Hemoglobin was not found to be significantly associated with IADL change score and IADL decline. Interaction between albumin and hemoglobin was explored, and no statistically significant interactions were found.

Discussion

In this community-based sample of older persons in Singapore, we found that serum albumin was linearly associated with POMA balance score, knee extension strength, IADL change score and IADL decline at follow-up. Serum hemoglobin was significantly associated with POMA balance score only.

Our findings are in line with previous studies that reported an association between albumin or hemoglobin with physical function in the elderly (2, 3, 7-10). The associations we observed remained statistically significant after adjusting for co-morbidities, cognitive function, depressive symptoms and other variables, suggesting that the relationships were not due to other health variables. The linear trend associations of albumin and hemoglobin with physical function, which suggest effects across the whole range of values of these continuous variables, are in line with previous findings (3, 7). Both low and low normal values of albumin or hemoglobin were associated with decreased physical function in healthy community dwelling older adults, and the use of conventional clinical cutoff values for albumin or hemoglobin may therefore not be applicable in healthy community dwelling older adults who are at risk of functional decline. Among well-functioning individuals, low and low normal values of albumin in particular were found to predict future risks of functional decline, suggesting that they are potentially useful risk markers of physical functional decline in older adults.

Furthermore, our results in regression models that controlled simultaneously for both albumin and hemoglobin suggest that albumin had clearly more pronounced effect on physical function as compared with hemoglobin. This was clearly most evident in longitudinal analyses in which albumin but not hemoglobin, was found to be significantly associated with IADL decline.

This is the first study that has examined the independent associations of albumin and hemoglobin with physical function in community-living older adults. Previous studies (7-10) had not adjusted for albumin when they examined the association between hemoglobin and physical function. Consequently, the actual effect size of the association between hemoglobin and physical function could be smaller than reported in those studies.

Given the reasonably good baseline BMI status and albumin and hemoglobin values in this cohort of well functioning community dwelling older adults, lower albumin values are less likely to be attributable to malnutrition. The association between serum albumin and physical function may be explained by two inter-related biological mechanisms. Firstly, albumin concentration is associated with age-associated skeletal muscle loss (sarcopenia) in older persons (11). Increased muscle breakdown and muscle depletion lead to decline in muscle strength, which could mediate the observed albumin-physical function associations. Secondly, albumin is a negative acute phase protein that decreases with systemic inflammation and is conventionally viewed as a marker of chronic inflammation. Since pro-inflammatory cytokines may cause muscle atrophy and has been associated with physical disability (29) or function decline (4), the observed association between albumin and physical function is also partly explained by chronic inflammation.

Since pro-inflammatory cytokines affect hematopoiesis, anemia in old age due to chronic inflammation may arguably explain the association of hemoglobin with physical limitations (6). Our analysis based on adjusted albumin (as a surrogate marker of inflammation) suggests that the observed association between hemoglobin and physical limitations was mediated by other non-inflammatory mechanisms. More likely, the relationship between hemoglobin and physical function is secondary to the effects of fatigue, weakness, poor muscle oxygenation, and low level of physical activity that are associated with anemia (9, 30, 31).

The strengths of this study included a large population-based sample and the use of both objective and subjective measures to assess physical function limitations and ADL disability. The multivariate analysis controlled for a wide range of potential confounders hence the results appear robust and reliable. A limitation of the study was that physical performance tests were not repeated at follow up; hence we were only able to demonstrate longitudinal relationship for albumin with IADL decline. Also, pro-inflammatory cytokines (such as IL-6, C-reactive protein, TNF-a, and others) were not measured, therefore we were not able to examine the specific mediating roles of those cytokines in physical functional status and decline. Furthermore, we did not include upper extremity measures of physical function or lean body mass and other anthropometric measures of nutrition and sarcopenia.

Conclusion

The significant associations of serum albumin and hemoglobin with physical function in community living older adults have practical implications for the prevention of physical disability in old age. The findings of the study suggest that low levels of albumin and hemoglobin are potentially useful risk markers of physical functional decline in older adults. Further research should investigate whether increases in the levels of albumin and hemoglobin alter the level of functional disability and risk of functional decline.

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