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Low serum carotenoids and development of severe walking disability among older women living in the community: the Women's Health and Aging Study I

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Abstract

Objective—to determine whether low serum carotenoid levels, an indicator of low intake of fruits and vegetables, are associated with the progression of disability in older women.

Design—longitudinal analysis in a population-based cohort.

Setting—moderately–severely disabled women, ≥65 years, living in the community in Baltimore, Maryland (the Women's Health and Aging Study I).

Participants—554 women without severe walking disability (inability to walk or walking speed <0.4 m/s) at baseline.

Main outcome measure—incidence of severe walking disability assessed every 6 months over 3 years.

Results—155 women (27.9%) developed severe walking disability during follow-up. Rates of development of severe walking disability per 100 person-years among women in the lowest and in the three upper quartiles of total carotenoids were, respectively, 13.8 versus 10.9 ($P = 0.0017$). Adjusting for confounders, women in the lowest quartile of total carotenoids were more likely to develop severe walking disability (hazards ratio 1.57, 95% confidence interval 1.24–2.00, $P = 0.0002$) compared with women in the three upper quartiles.

Conclusion—low serum carotenoid levels, an indicator of low intake of fruits and vegetables, are independent predictors of the progression towards severe walking disability among older women living in the community.

Keywords

ageing; carotenoids; disability; risk factors; women; elderly

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Conflict of interest
None declared.

Introduction

Disability is a serious problem for women in later life, as it threatens their independence and results in significant health care needs and associated expenditure. Women live longer than men and suffer disproportionately from disability and its consequences. An understanding of the processes that cause the progression of disability is essential in order to develop strategies to prevent or delay disability. Two recent epidemiological studies suggest that low serum levels of carotenoids or low β-carotene intake is associated with loss of muscle strength, impaired physical function, and severe limitation in walking in older adults. Among 669 women aged 70–79 years in the Women's Health and Aging Studies, (WHAS) I and II, low serum carotenoids were associated with poor muscle strength [1]. In the InCHIANTI study, a population-based study of ageing and disability in Italy, low β-carotene intake was also associated with impaired lower extremity performance [2]. Serum carotenoids are considered the most valid indicators of fruit and vegetable intake [3], and thus, carotenoids may be considered as biomarkers for dietary intake of fruits and vegetables.

There is growing scientific evidence that a relatively high fruit and vegetable intake [4–7] and a type of diet rich in fruits and vegetables, such as the Mediterranean diet [8–10], are beneficial for health and survival in older adults. The exact mechanisms by which a higher fruit and vegetable intake may improve health are not completely clear but may relate to the role of dietary antioxidants, such as carotenoids and plant polyphenols, in the protection against oxidative stress and inflammation [10]. It is not clear whether low circulating levels of antioxidant nutrients predict adverse functional outcomes such as severe walking disability, because the previous studies that specifically addressed antioxidant nutrients were cross-sectional [1,2]. To address the hypothesis that low serum carotenoid levels may predict the worsening of physical disability, we examined the relationship between serum total carotenoids at baseline and the development of severe walking disability over 36 months of follow-up among participants in WHAS I, a population-based study of moderately–severely disabled women living in the community. Severe walking disability was operationalised as extremely slow walking disability or the inability to walk. This condition is characteristic of an advanced stage in the disablement process.

Methods

Subjects in this study were women, aged 65 and older, who participated in WHAS I, a population-based study designed to evaluate the causes and course of physical disability in older women living in the community. WHAS I participants were recruited from an age-stratified random sample of women aged 65 years and older selected from Medicare enrollees residing in 12 contiguous zip code areas in Baltimore [11]. Women were screened to identify self-reported physical disability that was categorised into four domains. The domains of disability were ascertained in a 20–30 min home interview that included questions relating to: (i) mobility and exercise tolerance, i.e. walking for a quarter of a mile, walking up 10 steps without resting, getting in and out of bed or chairs; (ii) upper extremity function, i.e. raising your arms up over your head, using your fingers to grasp or handle, lifting or carrying something as heavy as 10 pounds; (iii) higher functioning tasks (a subset of instrumental activities of daily living (ADL), not including heavy housework, i.e. using the telephone, doing light housework, preparing your own meals, shopping for personal items); and (iv) basic self-care tasks (a subset of non-mobility-dependent ADL, i.e. bathing or showering, dressing, eating, using the toilet). WHAS I enrolled the one-third most disabled women aged 65 and older, those with disabilities in two or more domains. Of the 1,409 women who met the study eligibility criteria, 1,002 agreed to participate in the study in 1992. There were no major differences in sociodemographic or reported health characteristics between eligible participants and those who declined to participate [11].

Standardised questionnaires were administered in the participant's home by trained interviewers. The results of Mini-Mental Status Examination (MMSE) was recorded [11]. Race was assessed in a questionnaire as black, white, or other, current smoking as yes or no, and education as 0–8, 9–11, 12 years or >12 years as the highest level of formal education achieved. Two weeks later, a trained registered full-time study nurse conducted an examination of each study participant in her home, using a standardised protocol that included physical performance measures and a standardised physical examination. Approximately 75% of women also consented to phlebotomy performed during a separate visit by a trained phlebotomist who followed a standardised protocol. Further details on the methods and sampling design of the WHAS studies are published elsewhere [11].

Women were categorised as having severe walking disability based upon the inability to walk or having a walking speed of <0.4 m/s [12]. The 0.4 m/s cut-off point was approximately at the top of the lowest quartile in the WHAS population at baseline [13] and has been shown to predict functional dependence [14]. Participants were asked to walk over a 4-m course. They were instructed to stand with both feet at the starting line and to start walking after a specific verbal command. Timing began when the command was given. In this test, the subject could use a cane, a walker, or any other walking aid, but not take the help of another person. The time taken to complete the first metre and the entire path was recorded. The test was repeated three times: twice at the women's usual pace, and once at their fastest possible pace. The speed of the faster of the two usual-pace walks was used in the analyses. The length of the walk expressed in metres divided by the time in seconds was used to calculate the average walking speed [11]. Demographic characteristics, self-rated health, and information about appetite and eating were measured in the WHAS questionnaires. Chronic diseases were adjudicated by WHAS co-investigators based on the questionnaire, physical examination and physician contact [11].

There were 1,002 women enrolled in WHAS I, of whom 753 participated in the blood drawing and had serum nutrient measurements at baseline. Of the 753 women, 150 had severe walking disability at baseline, 554 of the 753 women did not have severe walking disability at baseline and had at least one follow-up visit, and 49 women did not have severe walking disability at baseline but did not have a follow-up visit (17 dropped out and 32 died). Women who were unable to walk had a greater severity of ADL disability [11]. There were no significant differences in race or body mass index between those who did and did not participate in the blood drawing, but women who did and did not participate in the blood drawing were different by age (77.4 versus 80.7 years, respectively, $P>0.0001$).

Non-fasting blood samples were obtained by venipuncture between 9 a.m. and 2 p.m. Processing, aliquoting, and freezing were carried out at the Core Genetics Laboratory of The Johns Hopkins University School of Medicine following a standardised protocol. Blood samples were delivered to Quest Diagnostics Laboratories (Teterboro, NJ) and, in part, stored continuously at −70°C until the time of analyses for carotenoids by high performance liquid chromatography (HPLC) [1]. Total carotenoids were calculated as the sum of α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin, and lycopene in μmol/l. Within-run and between-run coefficients of variation, respectively, were 10.7 and 23.9% for α-carotene, 7.0 and 19.1% for β-carotene, 4.7 and 8.5% for β-cryptoxanthin, 4.1 and 4.6% for lutein/zeaxanthin, and 10.0 and 14.0% for lycopene.

Descriptive statistics were used to characterise the study population and to describe biochemical measurements of micronutrients and other indicators of nutrition. The subjects were categorised into quartiles because conventional cut-offs to define deficient carotenoids have not been established. The cut-off for the lowest quartile of total carotenoids was 1.04 μmol/l. Body mass index was categorised as underweight (<18.5 kg/m^2), normal range (18.5–

24.9 kg/m^2), overweight (≥25–29.9 kg/m^2) and obese (≥30 kg/m^2) according to World Health Organization criteria [15].

Grouped-time Cox proportional hazards models [16] were used to examine the associations between carotenoids and the risk of developing severe walking disability because severe walking disability was determined at 6-month intervals. Women who did not have at least one follow-up visit after enrolment because of death, refusal, or loss to follow-up were excluded from the longitudinal analyses. The length of follow-up in longitudinal analyses was 36 months. Women who died, refused further participation, or were lost to follow-up after a follow-up visit were censored according to their severe walking disability status at their last visit in the study. The hazard ratio (HR) for developing severe walking disability was calculated for the lowest quartile of each nutrient's distribution, using all other quartiles combined as reference. Total carotenoids were used instead of individual carotenoids because the major dietary carotenoids are present in the same food group of fruits and vegetables. The statistical programmes used were SAS (SAS Institute, Cary, NC).

Results

There were 554 women who did not have severe walking disability at baseline, had serum carotenoid measurements available, and had at least one follow-up visit. One hundred and fifty-five (27.9%) of the women developed severe walking disability during follow-up with an overall rate of severe walking disability of 11.6 per 100 person-years. The rate of severe walking disability was 13.8 per 100 person-years for women in the lowest quartile of total carotenoids versus 10.9 per 100 person-years for women in the upper three quartiles (P = 0.0017).

Grouped-time Cox proportional hazards models were used to examine the relationship between demographic and health characteristics and the development of severe walking disability among 554 women who did not have severe walking disability at baseline and had at least one follow-up visit (Table 1). Age, race, body mass index <18.5, and the presence of morbid conditions including congestive heart failure, peripheral artery disease, and diabetes mellitus were significantly related to the development of severe walking disability. Education ≤12 years, current smoking, multivitamin use, and the presence of coronary artery disease, stroke, osteoarthritis, and chronic obstructive pulmonary disease were not significantly related to the development of severe walking disability.

In a final multivariate grouped-time Cox proportional hazards model that adjusted for age, race, and body mass index, women in the lowest quartile of serum carotenoids had an increased risk of developing severe walking disability (HR 1.57, 95% CI 1.24–2.00, P = 0.0002) (Table 2). Congestive heart failure, peripheral artery disease, and diabetes mellitus were not included as covariates because these are considered to be in the causal pathway of undernutrition, inflammation, and disability. However, when these three additional conditions were also included in the model with age, race, and body mass index, the findings were substantially unchanged (HR 1.58, 95% CI 1.24–2.00, P>0.0002). We also conducted tests of collinearity among variables, and collinearity was not significant.

Discussion

This study shows that older women with low serum carotenoid concentrations are at a higher risk of developing severe walking disability. To our knowledge, this is the first study to examine the relationship between carotenoids and the development of severe walking disability in a population of older adults living in the community. Previous cross-sectional studies suggested that low carotenoid intake and serum levels and low serum α-tocopherol concentrations were

associated with low skeletal muscle strength and impaired physical performance [1,2]. As noted previously, serum carotenoids reflect fruit and vegetable intake [3]. Fruits and vegetables are rich sources of antioxidants, including the carotenoids, vitamin C, flavonoids, and other polyphenols. The findings from the present study are consistent with findings from different large cohort studies that show a high fruit and vegetable intake is protective against inflammation, cardiovascular disease, and mortality [4–7]. Recent data from the Atherosclerosis Risk in Communities study also show that fruit and vegetable intake is inversely correlated with functional limitations and disability [17].

Sarcopenia, defined as loss of muscle mass and muscle strength, plays a central role in disability and contributes to frailty, mobility disability, difficulty with ADL, and increased risk of falls and hospitalisations [18]. Some limited evidence suggests that sarcopenia results from excessive oxidative stress [19]. Increased oxidative damage to DNA, protein, and lipids has been described in skeletal muscle with atrophy and loss of muscle fibres with ageing [20–22], but whether oxidative stress is the initiating event in the causal pathway leading to sarcopenia is unclear. Additionally, the relationship between sarcopenia and more general systemic indicators of oxidative stress, such as serum antioxidant, has not been adequately studied. Serum carotenoids play an important role in reducing oxidative stress through the quenching of hydroxyl radicals and reducing lipid peroxidation [23]. By reducing free radical concentrations, carotenoids may intersect one of the main pathways that lead to the expression of proinflammatory cytokines such as interleukin-6 (IL-6). Elevated serum IL-6 concentrations are associated with an increased risk of reduced physical function and sarcopenia [24,25] and the development of disability [12,26]. Low serum carotenoids were independently predictive of subsequent increases in serum IL-6 among older women living in the community [27]. The present study adds to the growing evidence that oxidative stress plays a role in the pathogenesis of sarcopenia [1,2,28].

The limitations of this study are that the WHAS population includes only women, and the findings cannot necessarily be extrapolated to men. The WHAS did not include dietary assessment, and there were no data on total caloric or protein intake. Thus, some caution should be taken in the interpretation of these findings. Serum carotenoids at baseline were used to predict subsequent severe walking disability, and the findings might be strengthened if it could be shown that women with a decline in serum total carotenoids over time did worse than women without a decline in these nutrients. Currently, serial measurements of carotenoids in this study are not available, and this approach could be utilised in future studies. Further studies are also needed to examine the relationship between serum carotenoids, balance performance, and falls.

The intake of energy and nutrients decreases with age [29]. The prevention of undernutrition may potentially reduce the risk of disability; however, such a hypothesis would need to be tested through controlled trials. Given that the carotenoids are biological markers for fruit and vegetable intake [3] and that fruits and vegetables contain a complex mix of antioxidants, fibre, and vitamins, it is likely that dietary modification may be the most compelling approach to be tested as an intervention to prevent disability. Such an approach has been taken with the Dietary Approaches to Stop Hypertension Studies [30].

Key points

- Low intake of fruits and vegetables is associated with inflammation, cardiovascular disease, impaired physical function, and higher mortality in older adults, but the relationship with disability has not been well characterised.
- Population-based study of older women living in the community examining risk factors for the progression of disability, as indicated by severe walking disability (inability to walk or walking speed <0.4 m/s).

- Low serum carotenoid levels, an indicator of low intake of fruits and vegetables, are independent predictors for severe walking disability among older women living in the community.

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Table 1

Characteristics of women who developed and did not develop severe walking disability in the Women's Health and Aging Study I

Characteristic	Incident severe walking disability (*n* = 155)	No incident severe walking disability (*n* = 399)	*P*
Age (years)	78.7 (7.8)	75.3 (6.8)	<0.0001
Race (white) (%)	70.3	75.9	0.17
Education ≤12 years (%)	78.6	80.6	0.58
Current smoking (%)	15.5	11.8	0.24
Multivitamin use (%)	17.1	19.4	0.54
Body mass index (kg/m^2)	—	—	—
<18.5	10.3	4.5	0.08
18.5–24.9	22.6	25.1	—
25.0–29.9	32.9	34.8	—
≥30	34.2	35.6	—
MMSE score <24 (%)	16.1	10.5	0.07
Chronic diseases	—	—	—
Coronary heart disease (%)	22.6	24.1	0.71
Congestive heart failure (%)	12.3	6.3	0.019
Peripheral artery disease (%)	25.8	17.8	0.03
Stroke (%)	1.3	3.0	0.25
Osteoarthritis (%)	51.6	53.9	0.63
Chronic obstructive pulmonary disease (%)	19.4	17.3	0.57
Diabetes mellitus (%)	20.0	12.5	0.025

Table 2

Grouped-time Cox proportional hazard models for demographic and health characteristics and incidence of severe walking disability in the Women's Health and Aging Study I (*N* = 554)

Characteristic	Univariate HR	95% CI	*P*
Age (years)	1.06	1.05–1.07	<0.0001
Race (white)	0.70	0.55–0.88	0.0028
Education ≤12 years	0.86	0.73–1.25	0.77
Current smoking	1.06	0.77–1.45	0.73
Multivitamin use	1.18	0.91–1.54	0.2
Body mass index[a]	—	—	—
<18.5	1.93	1.27–2.94	0.002
18.5–24.9	—	—	—
25.0–29.9	1.03	0.76–1.39	0.85
≥30	1.32	0.98–1.77	0.06
Coronary heart disease	0.81	0.62–1.06	0.13
Congestive heart failure	2.10	1.54–2.85	<0.0001
Peripheral artery disease	1.50	1.17–1.93	0.001
Stroke	0.52	0.19–1.39	0.94
Osteoarthritis	1.01	0.81–1.25	0.94
Chronic obstructive pulmonary disease	1.19	0.91–1.55	0.19
Diabetes mellitus	1.58	1.21–2.07	0.0007

[a]For body mass index, 18.5–24.9 kg/m^2 was used as the reference category.