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Better satisfaction with life is associated with normal immune profile (CD4/CD8 ratio) – and dependent on the successful aging status – in older Brazilian individuals

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ABSTRACT

Introduction: The immune system is an important determinant of longevity and has also contributed to the way individuals feel as they reach older ages. The inverted CD4/CD8 ratio is a parameter of the immune risk phenotype, and its prevalence increases with age. Association between immunological function, cognition and mood has been supported by studies with clinical and aging populations. **Objective:** We explored the relationship between the CD4/CD8 ratio and life satisfaction in a small sample of elderly people from Southern Brazil with good general health. **Method:** The sample consisted of 44 elderly individuals, who participated in an aging study in Southern Brazil (the PALA Study), and accepted to continue in the investigation collecting additional blood sample for the CD4/CD8 analysis. From this sample, 52% (N = 23) presented successful aging according to Rowe and Kahn's criteria. No participant was HIV positive or presented any autoimmune diseases. A questionnaire was applied for sociodemographic and clinical data, lifestyle, and occupational activity. Cognitive function, basic and instrumental activities of daily living, and depressive symptoms were evaluated with specific instruments. Life satisfaction was evaluated with the Life Satisfaction Scale from Diener et al. (1985). **Results:** Forty-two individuals (95%) showed CD4/CD8 ratio > 1. CD4/CD8 ratio correlated significantly with life satisfaction ($\rho = -0.35$) and with age ($\rho = -0.42$) for the whole sample and among the successful aging sub-group only. **Conclusion:** This is an exploratory analysis with a small sample of elderly participants from a cohort started in 1996 in Southern Brazil (the PALA study). Their level of satisfaction with life was high, and correlated significantly, and inversely, with the CD4/CD8 ratio. It was also dependent on the successful aging status.

Keywords: Life Satisfaction, Well-being, Immunosenescence, Health Ageing, CD4/CD8 ratio

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Introduction

The immune system is an important determinant of longevity and has also contributed to the way individuals feel as they reach older ages. As a result of the immunosenescence with the advance of human age, morbidity and mortality by infection increase, response to vaccination declines and the incidence of inflammatory diseases and cancer also rises (1, 2, 3).

The molecular and biochemical changes observed during aging influence CD4⁺ T and CD8⁺ T cells, regardless of their phenotype or their differentiation condition (4). Older individuals showed more marked changes in CD8⁺ T cells than younger ones (5). The inverted CD4/CD8 ratio is a parameter of the immune risk phenotype (6, 7), and its prevalence increases with age (8, 9, 10, 11). It is linked to altered immune function, and chronic inflammation, and has been correlated with survival rates in elderly people (12). Although the normal CD4/CD8 ratio in healthy subjects is poorly defined (13), the ratio is inverted when the value is less than 1 (9) and most likely to do so among men (6, 14). Values between 1.5 and 2.5 are generally considered within normality (15).

Studies on the effect of lifestyle upon T cells in healthy people showed that impoverished lifestyle increases the number of T cells (16) while better overall health care is protective (17, 18). The CD4⁺ T and CD8⁺ T lymphocyte levels of elderly people who practice continued physical activity are similar to those of younger individuals. These elderly individuals also do not present common lymphocyte recruitment defects to the sites of infection as showed by sedentary elderly individuals (19).

Association between immunological function, cognition and mood has been supported by studies with clinical and aging populations (20). Better cognitive performance was associated with lower numbers of effector memory CD4⁺ T cells and higher numbers of naive CD8⁺ T cells

and B cells. In addition, CD4⁺ T could predict general and executive function and memory, even considering factors that influence cognitive performance in older individuals (e.g., age, gender, education, and mood) (20). Furthermore, chronic psychosocial stress and emotional stress are associated with decline and/or impaired immune function (21). Psychological stress and depressive symptoms are considered predictors of suppression of natural killer immune cells (22, 23), which are linked to the onset of some age-related health problems (24, 25).

The relationship between life satisfaction and mortality (26, 27), work disability (28), and healthy behavior (29, 30) has been reported. Subjective well-being is beneficial to general health, while dissatisfaction with life is of risk for health problems. For this reason, in the present study we explore the relationship between the CD4/CD8 ratio and life satisfaction in a small sample of elderly people from Southern Brazil with good general health. Therefore, our hypothesis was that those participants who were satisfied with their lives and showed better cognitive and functional performances would present CD4/CD8 ratio values within normality.

Methods

The sub-sample consisted of 44 elderly individuals, who participated in an aging study in Southern Brazil (the PALA Study) during 16 years (31). At the baseline, 345 elderly people were enrolled for the study, from whom 152 died during the follow-up (deaths were certified at the official registry from Porto Alegre Health Department), 57 were alive, and 40 were not found (moved away without noticing the research group or invalid phone numbers) (32). Of the 57 living participants, 44 accepted to continue in the investigation collecting additional blood sample for the present analysis, from whom 52% (N = 23) presented successful aging according to Rowe and Kahn's criteria (33).

No participant was HIV positive or presented any autoimmune diseases. All individuals

signed the informed consent term before starting interviews. The study was approved by the Ethics Committee of the Institution and attributed the number 10-0347. We use Strobe Statement to support writing this article.

A questionnaire was applied for sociodemographic and clinical data (diagnoses, current diseases, medications, and hospital admissions), lifestyle, and occupational activity. Cognitive function, basic and instrumental activities of daily living, mobility (gait and balance), and depressive symptoms were evaluated with specific instruments. Functional status (basic and instrumental) was evaluated with bADL and IADL scales (34). Charlson comorbidity index was used to assess clinical severity and comorbidities (35). Cognitive and depressive screenings were performed with the MMSE and GDS-15 (36; 37). Cognitive tests were the clock drawing test (38), the Boston Naming Test: 15-item version (39), the Trail Making Test – B (39), the CERAD word list (39), the WAIS-III digit span (40), the semantic verbal fluency (41), and the phonemic verbal fluency (F.A.S.) (42).

Life satisfaction and well-being were evaluated with the Life Satisfaction Scale from Diener and co-workers (43). Scores are classified as: a) 35 to 31, extremely satisfied; b) 26-30 satisfied; c) 21 to 25, moderately satisfied; d) 20, neutral; e) 15 to 19, moderately dissatisfied; f) 10 to 14, dissatisfied; and g) 5 to 9, extremely dissatisfied.

Blood collection for immune markers was performed at the end of the interview by a nursing technician. The application of the complete protocol took 90 minutes on average.

Laboratory Measures

Cytometric Analysis

Lymphocyte characterization usually includes quantification of the CD4⁺ subpopulations, commonly referred to as T helper and CD8⁺, which exhibits cytotoxic properties. The most widely used method for lymphocyte phenotyping is flow cytometry, a technique to

measure the properties of cells in suspension, oriented in a laminar flow and intercepted one by one by a beam of light. The quantification of the positive cells for the respective CD is processed by flow cytometry, which has the advantage of rapid analysis (100-5000 cells/s), and the evaluation of multiple cellular parameters individually. Peripheral blood samples were analyzed on a flow cytometer according to the manufacturer's instructions.

CD8⁺ T and CD4⁺ T Cells Analyses

A suspension of isolated T cells was incubated with 5 microliters of CD8 FITC (for CD8⁺ T cells) monoclonal antibody and 5 microliters of CD4 FITC (for CD4⁺ T cells). 5 microliters of the corresponding FITC isotypic reagent IgG2a control R-PE-conjugated were added to labeled control tubes, and was mixed gently. Afterwards, all tubes were incubated for 15 minutes, in the dark, at room temperature (22 ± 3 °C). Lysis solution was added to all tubes according to the manufacturer's instructions. Then all tubes were centrifuged at 400 xg for 3 minutes at room temperature, and fixation solution was added to all tubes according to the manufacturer's instructions. Cells from all tubes were washed twice with 4 ml PBS, and centrifuged at 400 xg for 3 minutes after each washing procedure. The cells were re-suspended from the final wash in 1 ml PBS and stored in tubes at 2-8 °C in the dark until the time of analysis on the flow cytometer.

Statistical Analysis

The statistical analysis was based on data collected at baseline and the last follow-up visit in 2012, during which participants underwent a thorough evaluation. The statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS for Windows 18.0) software. Descriptive data (mean, SD and frequency) were calculated for demographic and clinical data. Parametric and non-parametric data were analyzed with the Student's *t*-test or Mann-Whitney test, respectively. Correlation analysis for the variables of interest was performed with

Spearman correlation (ρ). Significant correlations were those with values of $p < 0.05$.

Results

Table 1 shows the socio-demographic and clinical data of the sample. Most participants were women ($N = 36$, 81.8%). The median age was 84.00 years, and the median education was 8.00 years. The average score in the MMSE was 26.77 out of a total of 30 points.

The mean score for depressive symptoms was 2.84. The mean score on the Life Satisfaction scale was 29.11. The scores of the instrumental and basic activities of daily living scales (bADL/iADL) were 0.18 ± 0.58 and 0.48 ± 0.97 respectively. The most frequent health problem reported by participants was cardiac (43.2%; $N = 19$), followed by blood sugar (20.5%; $N = 9$), cancer (15.9%; $N = 7$), and lung (6.8%; $N = 3$).

Table 1. Socio-demographic and clinical data of the sample

Variable	N (%)	Mean \pm SD	Median (percentile 25%-75%)
Gender			
Male	8 (18,2)		
Female	36 (81,8)		
Marital status			
Single/Divorced	07 (15.5%)		
Married	10 (22.7%)		
Widow/widower	27 (61.4%)		
Age			84 (82 – 87)
Education (years)			8 (5 – 9)
Successful Aging (yes)	23 (52%)		
bADL		0.18 \pm 0.58 (0-3)	
iADL		0.48 \pm 0.97 (0-4)	
GDS-15		2.84 \pm 3.13	
MMSE		26.77 \pm 2.99	
Life Satisfaction scale		29.11 \pm 5.76 (10-35)	
CD4/CD8 ratio			2.1 (1.36-2.79)
Charlson comorbidity index			1.00 (0-2)

MMSE (Mini-Mental State Examination), GDS-15 (Geriatric Depression scale - 15 items), SD (Standard Deviation)

Table 2. Spearman (rho) correlation analysis for the variables of interest (N = 44)

Variables	Age	Life Satisfaction	MMSE	CD4/CD8 ratio	Charlson index
Age	1.00				
Life Satisfaction	0.35*	1.00			
MMSE	-0.36*	0.08	1.00		
CD4/CD8 ratio	-0.42*	-0.35*	0.11	1.00	
Charlson index	0.30	-0.09	-0.09	-0.21	1.00
bADL	0.055	0.044	-0.079	-0.182	0.103
iADL	0.35*	-0.211	-0.300*	-0.155	0.336*

*p<=0.05

The CD4/CD8 ratio showed the following distribution in the sample: 95% (N = 42) had a value > 1, from whom 29.5% (N = 13) remained in the interval between 1.5 and 2.5, and the others got values between >2.5 and <5. Only 5% (N = 2) of the participants were <1.

Spearman's correlation with the variables of interest showed the following statistically significant correlations (Table 2): a. positive: life satisfaction with age (rho = 0.35), iADL with age (rho = 0.35) and iADL with Charlson index (rho = 0.34); and b. negative: CD4/CD8 ratio with life satisfaction (rho = -0.35) and with age (rho = -0.42); and age with MMSE (rho = -0.36). The Charlson comorbidity index did not present significant correlation with the CD4/CD8 ratio (rho = -0.21). Additionally and to better understand these results, we removed the two subjects (females) from the sample who presented CD4/CD8 ratio <1, but the results were the same (data not shown).

We also performed these correlations among the groups successful aging and not successful separately to understand whether the findings could be related to this status. A similar pattern of results was observed for the successful aging group: a. positive: age with Charlson index (rho = 0.47); age with iADL (rho = 0.54), iADL with Charlson index (rho = 0.50), and

bADL with Charlson index (rho = 0.43); and b. negative: CD4/CD8 ratio with life satisfaction (r = -0.60), age with MMSE (rho = -0.73). The Charlson comorbidity index did not present significant correlation with the CD4/CD8 ratio (rho = -0.28). The other group showed significant correlations between age and CD4/CD8 ratios (rho = -0.47) and age and life satisfaction (rho = 0.44), but no correlation between CD4/CD8 ratio and life satisfaction (rho = -0.22).

Discussion

This is an exploratory analysis with a small sample of elderly participants from a cohort started in 1996 in Southern Brazil (the PALA study). These elderly individuals present good general health and no infectious disease. We hypothesized that higher levels of life satisfaction and better cognitive and functional performance would be related to CD4/CD8 ratio values within normal parameters (i.e., outside the immunological risk profile). From the present sample, 52% had a successful aging profile according to the Rowe and Kahn criteria, which have been applied at each cohort assessment since the baseline in 1996 (for a review, see reference 33). At the baseline the successful aging rate was 60%, declining to 52% over the 16 years but has still remained

high (44). As a consequence, the participants of this assessment showed good cognitive and functional performance (MMSE and bADL/iADL), and lower levels of depressive symptoms. Furthermore, the evaluation of comorbidities by the Charlson comorbidity index, which can be used as an estimate of general health conditions, showed low values (between 0 and 2), reinforcing the good health status of these participants. Therefore, the positive aging parameters confirm that the biological, cognitive, functional and emotional aging process of these elderly individuals remained with no significant loss.

The level of satisfaction with life was high (average of 29 for a maximum of 35), corroborating the positive profile of these older individuals, and correlated positively with age. Our older participants were more satisfied with their lives, which probably was related to the favorable profile of aging. Subjective well-being, especially life satisfaction, has been shown to remain relatively stable over time (45, 46), and correlates positively with age (47, 48).

The scores of life satisfaction correlated significantly, and inversely, with the CD4/CD8 ratio – i.e. the higher the satisfaction with life, the lower the ratio –, and were dependent on the successful aging status. In a previous study carried out in Porto Alegre, the authors found that satisfaction with family relations and friendships, as well as functional independence, was predictive of successful aging (49). However, it is important to emphasize that, in our analysis, we found mostly CD4+/CD8+ values within the normal intervals, with a higher CD4 + cell count and a lower number of CD8 + cells (ratios were mostly higher than 1). T lymphocytes, CD4 + and CD8 + subpopulations with cytotoxic properties have been identified as important markers of the immune system's aging (50). This finding of the CD4/CD8 ratio within the normal range also corroborates the already commented good general health status of these participants. The CD4/CD8 ratio with values below 1 was identified in numerous

studies as an important marker of immunological risk profile (51, 52, 14), and as a predictor of mortality (53). In this category, we found only two females among our participants. However, when we removed them from the analysis, the results did not modify and the magnitude of the correlations was maintained.

The CD4/CD8 ratio also negatively correlated with age, i.e., the older the individual, the lower the CD4/CD8 values, but these low scores did not reach the values of an inverted ratio, as mentioned above. The prevalence of the inverted ratio increases with age (8, 9, 10, 11), and has been demonstrated to correlate with survival rates in elderly people (12). Studies on the effect of lifestyle upon T cells in healthy people showed that impoverished lifestyle increases the number of T cells (16) while better overall health care is protective (17, 18). The CD4+ T and CD8+ T lymphocyte levels of elderly people who practice continued physical activity are similar to those of younger individuals. These elderly individuals also do not present common lymphocyte recruitment defects to the sites of infection as showed by sedentary elderly individuals (19).

Contrary to our a priori hypothesis, cognitive and functional performances (MMSE, bADL/iADL) did not correlate with CD4/CD8 ratio. Better cognitive performance has been associated with lower numbers of effector memory CD4+ T cells and with higher numbers of naive CD8+ T cells and B cells. In addition, CD4+ T could predict general and executive function and memory, even considering factors that influence cognitive performance in older individuals (eg, age, gender, education, and mood) (20). Older participants of this sample presented lower MMSE scores since age and MMSE negatively correlated. However, the average score of this cognitive screening test was above the cutoff point of 24. The correlation was present but the values were mostly in the normal range.

It is important to consider some limitations of the study. The sample is small and the majority

is women. Life satisfaction estimates and CD4/CD8 ratio were performed only once, which does not allow establishing cause/effect relationship. On the other hand, the study's strength is the long follow-up (16 years) of elderly individuals in a geographical area that has few studies of this nature. Finally, the main result of our exploratory study is that seniors with a positive aging profile that show subjective well-being (life satisfaction) have a normal immune response profile. We can neither say that being satisfied with life helps other mechanisms that influence the immune response by improving the immune profile, nor the opposite. Other studies with Brazilian samples exposed to the diversity of this region of the world are needed to advance this knowledge.

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