Study on relationship between elderly sarcopenia and inflammatory cytokine IL-6, anti-inflammatory cytokine IL-10

Yu-Dong Rong1*, Ai-Lin Bian2, Hui-Ying Hu2, Yue Ma3 and Xin-Zi Zhou2

Abstract

Background and objectives: The pathophysiological mechanism of sarcopenia in the elderly has not yet been fully understood. Here, we aim to explore the relationship between sarcopenia and the inflammatory cytokine interleukin-6 (IL-6), and the anti-inflammatory cytokine interleukin-10 (IL-10) in an elderly population.

Methods: Our study comprised 118 males and 46 females aged between 61 and 90 who had received a general medical examination in Tianjin First Central Hospital. Subjects were divided into a sarcopenia group and a non-sarcopenia group, defined according to the criteria of the Asian Working Group for Sarcopenia (AWGS). We compared body composition, handgrip strength (HS), gait speed (GS), biochemical indexes, levels of IL-6 and IL-10, living habits, and disease status between these groups.

Results: Non-sarcopenia subjects undertook more regular physical exercise than sarcopenia patients. Sarcopenia subjects had higher nutrition risk but lower body mass index (BMI), serum albumin (ALB), triglyceride (TG), and creatinine (Cr) levels compared to non-sarcopenia subjects. Sarcopenia subjects were older and had higher visceral fat tissue (VFA) than non-sarcopenia subjects (P < 0.05), along with higher IL-6 and IL-10 levels. Furthermore, IL-6/IL-10 ratios were higher in subjects with sarcopenia (P < 0.05). Age, BMI, levels of physical activity, nutritional risk, VFA, IL-6, IL-10, IL-6/IL-10 ratio were independently associated with the presence of sarcopenia in univariate regression analyses. Following adjustment for confounding factors, the presence of sarcopenia was positively correlated with IL-6, IL-10, IL-6/IL-10 ratio and inversely correlated with BMI. Age is associated with increased presence of sarcopenia.

Conclusions: The levels of inflammation cytokine IL-6, anti-inflammatory IL-10 and IL-6/IL-10 ratio were increased in elderly sarcopenia subjects. Sarcopenia was associated with increased levels of inflammatory cytokine IL-6, anti-inflammatory cytokine IL-10, and IL-6/IL-10 ratios.

Keywords: Elderly, Sarcopenia, Interleukin-6, Interleukin-10

Background

The global elderly population is growing as a result of increasing life expectancies. Consequently, chronic age-related morbidities have become a societal burden. Among age-related diseases, sarcopenia is often overlooked. Many studies have reported associations between sarcopenia and adverse outcomes in elderly individuals including increased risk of fall and fracture, impaired ability to perform activities of daily living, disability, increased admission and re-admission rates, and mortality [1]. The consensus on the definition and diagnosis of sarcopenia was published by the European Working Group on Sarcopenia in Older People (EWGSOP) in 2010 and Asian Working Group for Sarcopenia (AWGS) in 2014. In light of this, sarcopenia has garnered increasing interest and attention. Currently, sarcopenia has been accepted as a new geriatric disorder characterised by progressive and generalised loss of skeletal muscle mass and function, along with low muscle strength and poor physical performance.

The pathophysiological mechanisms of the onset and progression of sarcopenia are complex with a variety of
causes and interactions. But it may include an age-associated state of low-degree systemic inflammation [2, 3] – inflammaging, which is characterised by increasing levels of pro-inflammatory cytokines (including tumor necrosis factor alpha-TNFα and interleukin 6 - IL-6), and decreasing levels of anti-inflammatory cytokines such as interleukin 10 (IL-10) [3].

Studies have reported increased levels of circulating pro-inflammatory cytokines such as IL-6 and TNFα in elderly sarcopenia cases [4, 5]. However, the role of anti-inflammatory cytokines in elderly sarcopenia patients is unknown. IL-10 is currently recognized as an inflammatory and immunosuppressive factor. As an anti-inflammatory cytokine, it suppresses human monocytes and macrophage ability, and the production of pro-inflammatory cytokines including IL-6. To the best of our knowledge, no studies have yet evaluated the potential role of IL-10 in sarcopenia patients. To investigate this question, we measured serum concentrations of the inflammatory cytokine IL-6 and the anti-inflammatory cytokine IL-10, and estimated the association between IL-6 levels, IL-10 levels, and IL-6/IL-10 ratios with sarcopenia in elderly individuals.

Methods
Research subjects
A total of 421 elderly subjects (306 male and 115 female) aged between 61 and 90 attended general medical examinations between May 2015 and September 2016 in the Health Management Centre of Tianjin First Central Hospital, China. Eighty-two participants were diagnosed with sarcopenia according to the criteria of AWGS [6]. These subjects included 58 males and 24 females between the ages of 61 and 90 (mean age 76.03 ± 4.33 years). Eighty-two individuals without sarcopenia included 60 males and 22 females between the ages of 61 and 88 (mean age 73.24 ± 5.32 years) were randomly selected from the remaining 339 participants for the non-sarcopenia group.

Inclusion criteria
All participants were aged over 60 years old and could stand and walk unaided. In the AWGS criteria for sarcopenia in older people [6], diagnosis is based on presentation of criterion 1 (low muscle mass), plus either criterion 2 (low muscle strength) or criterion 3 (poor physical performance) with recommended cutoff values for muscle mass measurements (7.0 kg/m² for men and 5.7 kg/m² for women based on bioimpedance analysis), handgrip strength-HS (< 26 kg for men and < 18 kg for women), and usual gait speed-GS (< 0.8 m/s).

Exclusion criteria
Exclusion criteria comprised individuals younger than 60 years of age, subjects with tumor, subjects who have been bedridden due to illness such as serious cerebral stroke, heart failure, renal failure, fracture, edema and massive ascites; subjects with severe endocrine diseases that are poorly-managed, subjects who were suffering from infectious diseases, subjects with autoimmune diseases, and subjects with a history of mental illness.

Medical history and lifestyle
Details on subjects’ medical history and lifestyle were obtained through a questionnaire including smoking and drinking behaviour, physical exercise and medical history. Physical exercise was defined as >30 min for each activity, >3 times a week and lasting for more than 6 months. Smoking was defined as people who have smoked for consecutively or cumulatively for six months. Drinking was defined as drinking >3 times a week over a period of at least 6 months.

Body measurements
Height, weight and blood pressure (mmHg) were measured by routine. Body mass index (BMI) was calculated using routine measures. Measurement of HS was obtained using a hand-muscle developer (WCS-II, Beijing). Physical performance was determined by usual GS < 0.8 m/s over a course of 4 m. According to the recommendation of AWGS, height-adjusted skeletal muscle mass (ASM) defined by appendicular skeletal muscle mass (ASM)/height (m)² was used to evaluate the muscle mass. ASM and visceral fat tissue (VFA) were measured by bioelectrical impedance analysis (BIA).

Nutritional risk
We evaluated the nutritional risk using the mini nutritional assessment short form (MNA-SF). Participants with scores less than or equal to 11 points were considered to be at a risk of malnutrition.

Laboratory indicators
5 ml of elbow venous blood was drawn in the morning for each subject after at least hours of fasting. Hemoglobin (Hb) and blood biochemistry indicators were tested immediately upon blood-draw. The remaining sera were stored at −80°C for later testing of IL-10 and IL-6 levels.

IL-6 and IL-10 quantification
IL-6 and IL-10 were quantified with competitive inhibition of enzyme-linked immunosorbent assay kits (ELISA; Rapid Bio RB, USA). The sensitivity of detectable concentrations were 0.4 pg/ml for IL-6 and 0.1 pg/ml for IL-10.

Statistical methods
Continuous variables were expressed by mean ± standard deviation (SD). Categorical variables were described as percentage (%). The differences in means and proportions between different groups were analyzed with t-test and
Chi-square tests, respectively. Multiple logistic regression analysis was performed to estimate the odds ratios (OR) and 95% confidence intervals (CIs) for sarcopenia in relation to inflammatory factors. To understand whether potential confounders could affect ORs, we used a multivariate model with adjustment for the following covariates: age, sex, BMI, VFA, hypertension, diabetes, cardiovascular disease, smoking behaviors, drinking behavior, physical activity, nutritional risk, triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), hemoglobin A1C (HbA1C), Hb, serum albumin (ALB), creatinine (Cr). All statistical analyses were performed using SPSS software version 19.0. A two-tailed value of less than 0.05 was considered to be statistically significant.

Results
Sample demographics are presented in Table 1. Compared to those without sarcopenia, participants with sarcopenia undertook less regular physical exercise, had lower BMI, ALB, TG and Cr, but higher nutritional risk. Patients with sarcopenia were older on average, and had higher VFA relative to those without sarcopenia.

Comparisons of IL-6 and IL-10 levels between sarcopenia and non-sarcopenia patients are summarized in Table 2. Higher levels of IL-6 and IL-10 were observed in participants with sarcopenia (< 0.05). Moreover, higher ratios of IL-6/IL-10 were observed in the sarcopenia group (< 0.05). Univariate analyses were performed investigating the relationship between sarcopenia and IL-6 levels, IL-10 levels and IL-6/IL-10 ratios are presented in Table 3. Independent associations were observed between sarcopenia and age, BMI, physical activity, nutritional risk, VFA, IL-6 levels, IL-10 levels and IL-6/IL-10 ratios. Finally, we performed multivariate analyses to assess the relationship between sarcopenia and IL-6 levels, IL-10 levels and IL-6/IL-10 ratios (Table 4). Following adjustment for potential confounders (age, sex, BMI, physical activity, nutritional risk, VFA), positive associations were present between sarcopenia and IL-6 levels, IL-10 levels, and IL-6/IL-10 ratios. Sarcopenia incidence was found to increase with advancing age whereas there was an

| Table 1 Basic characteristics of study sample |
| Variable | Sarcopenia n = 82 | Non-Sarcopenia n = 82 | p |
| Sex (male/female) | 58/24 | 60/22 | 0.728 |
| Age | 76.03 ± 4.33 | 73.24 ± 5.32 | < 0.001 |
| BMI | 23.13 ± 2.78 | 25.52 ± 2.23 | < 0.001 |
| VFA | 104.12 ± 18.21 | 96.01 ± 16.80 | 0.003 |
| ASMI | 6.60 ± 0.75 | 7.61 ± 0.80 | < 0.001 |
| Hypertension (%) | 25 (30.49) | 22 (26.83) | 0.604 |
| Diabetes (%) | 12 (14.63) | 10 (12.20) | 0.647 |
| Cardiac (%) | 27 (32.93) | 22 (26.83) | 0.394 |
| Smoke (%) | 13 (15.85) | 10 (12.20) | 0.500 |
| Drink (%) | 12 (14.63) | 9 (10.98) | 0.483 |
| Sport (%) | 9 (10.98) | 21 (25.61) | 0.015 |
| MNA-SF (%) | 32 (39.02) | 20 (24.39) | 0.044 |
| TG | 1.32 ± 0.45 | 1.56 ± 0.60 | 0.006 |
| LDL-C | 3.14 ± 0.62 | 3.09 ± 0.61 | 0.637 |
| HbA1C | 5.37 ± 0.95 | 5.24 ± 1.07 | 0.433 |
| Hb | 124.99 ± 12.05 | 123.80 ± 17.16 | 0.618 |
| ALB | 41.13 ± 4.55 | 44.71 ± 4.92 | < 0.001 |
| Cr | 66.68 ± 14.21 | 73.16 ± 11.73 | 0.002 |

BMI body mass index, VFA visceral fat tissue, ASMI appendicular skeletal muscle index, MNA-SF mini-nutritional assessment short-form, TG triglyceride, LDL-C low-density lipoprotein cholesterol, HbA1C hemoglobin A1C, Hb hemoglobin, ALB serum albumin, Cr creatinine

| Table 2 Comparison of levels of inflammatory cytokines |
| Variable | Sarcopenia | Non-Sarcopenia | p |
| IL-6 (pg/ml) | 43.80 ± 10.13 | 27.38 ± 9.53 | < 0.001 |
| IL-10 (pg/ml) | 4.13 ± 1.03 | 3.75 ± 1.21 | 0.032 |
| IL-6/IL-10 | 9.71 ± 1.43 | 9.09 ± 1.71 | 0.013 |

IL-6: interleukin-6, IL-10: interleukin-10

| Table 3 Univariate regression analysis for relationship between follow indexes and sarcopenia |
| Variable | OR (CI 95%) | p |
| Age | 1.09 (1.01–1.17) | 0.015 |
| sex | 0.96 (0.81–1.12) | 0.534 |
| BMI | 0.80 (0.67–0.96) | 0.021 |
| VFA | 1.12 (1.02–1.23) | 0.039 |
| Hypertension (%) | 1.25 (0.55–1.65) | 0.092 |
| Diabetes (%) | 0.98 (0.72–1.12) | 0.063 |
| Cardiac (%) | 0.97 (0.90–1.05) | 0.362 |
| Smoke (%) | 0.83 (0.59–1.05) | 0.342 |
| Drink (%) | 0.94 (0.79–1.08) | 0.128 |
| Sport (%) | 0.83 (0.65–0.98) | 0.041 |
| MNA-SF(n) | 1.05 (1.01–1.35) | 0.035 |
| TG | 0.92 (0.79–1.16) | 0.756 |
| LDL-C | 0.83 (0.53–1.14) | 0.665 |
| HbA1C | 0.94 (0.82–1.10) | 0.485 |
| Hb | 0.77 (0.65–1.03) | 0.086 |
| ALB | 0.84 (0.73–1.03) | 0.053 |
| Cr | 0.83 (0.65–1.14) | 0.058 |
| IL-10 | 1.42 (1.25–1.48) | 0.005 |
| IL-6 | 1.20 (1.06–1.40) | 0.056 |
| IL-6/IL-10 | 1.32 (1.12–1.58) | 0.023 |

OR: odds ratio, CI: confidence interval, BMI: body mass index, VFA: visceral fat tissue, MNA-SF: mini-nutritional assessment short-form, TG: triglyceride, LDL-C: low-density lipoprotein cholesterol, HbA1C: hemoglobin A1C, Hb: hemoglobin, ALB: serum albumin, Cr: creatinine, IL-6: interleukin-6, IL-10: interleukin-10
been shown to result in proteolysis and atrophy of α and in-vitro. Infusion of TNF and reduced muscle mass both in-vivo (rodent models) demonstrated a causal link between inflammatory cytokines and muscle catabolism induced by higher levels of inflammatory markers [12]. In adults suffering from rheumatoid arthritis, increased levels of IL-6 and CRP levels have been reported [8, 10, 11]. One possible mechanism for this relationship may relate to increased muscle catabolism in elderly individuals, and age-associated inflammation (i.e. inflammaging). Evidence exists for a relationship between sarcopenia and BMI.

Recent years have seen increased interest in the potential role of inflammatory mediators in sarcopenia. Evidence exists for a relationship between sarcopenia and age-associated inflammation (i.e. inflammaging). Others have observed elevated levels of circulating pro-inflammatory markers such as IL-6 and TNFα in elderly sarcopenia cases. Moreover, elevated levels of these proteins have been associated with reduced muscle mass and strength [4, 5, 7–9]. Increased levels of inflammatory cytokines have also been reported to play a role in the functional decline of muscle in elderly individuals. Our observation of increased IL-6 levels in sarcopenia is supported by several analyses, in which correlations between reduced physical performance and increased levels of IL-6 and C-reactive protein (CRP) levels have been reported [8, 10, 11]. One possible mechanism for this relationship may relate to increased muscle catabolism induced by higher levels of inflammatory markers [12]. In adults suffering from rheumatoid arthritis, increased levels of TNFα production coincides with higher rates of protein catabolism [13]. Others have demonstrated a causal link between inflammatory cytokines and reduced muscle mass both in-vivo (rodent models) and in-vitro. Infusion of TNFα and IL-6 in rats have been shown to result in proteolysis and atrophy of skeletal muscle [14, 15]. Moreover, negative correlations have been reported between the rate of protein synthesis in skeletal muscle, and levels of CRP, IL-6 and TNFα receptor-2 [16]. Taken together, these findings suggest a role for low-grade inflammation in the development of sarcopenia.

There are multiple reasons for the observed levels of inflammatory markers in our study, the main reason being an age-associated low-grade chronic inflammatory state (i.e. inflammaging), characterized by increased levels of pro-inflammatory cytokines including TNFα, IL-6 and CRP.

Additionally, it is increasingly recognized that skeletal muscle itself is an important source of inflammatory mediators, collectively known as ‘myokines’. These locally generated cytokines (e.g. IL-6, IL-1b, TNFα, IL-1ra) are expressed in skeletal muscle in elderly individuals, and may be linked to the inflamming process [17, 18].

Age-related changes in body composition, primarily more fat depositing in abdomen and muscles might also be involved in the observed increase of pro-inflammatory cytokines. The present cross-sectional study also showed sarcopenia subjects had higher VFA than non-sarcopenia subjects. As a major endocrine organ, visceral adipose tissue is responsible for insulin resistance and a chronic systemic inflammation. Visceral adipose tissue could release a wide range of inflammatory cytokines, including TNFα, CRP and IL-6 [19].

Additionally, evidence exists to suggest age-associated inflammation and sarcopenia may be related to the change of IL-10 during aging [20]. IL-10 is an anti-inflammatory cytokine, mainly produced by macrophages, T-helper 2 cells, B-cells and monocytes. IL-10 is responsible for suppressing the pro-inflammatory response in various tissues, including skeletal muscle [21], by suppressing the activation of macrophages and releasing and activating inflammatory cytokines such as IL-6, TNFα, and IL-1β [22, 23]. Hacham et al. (year) showed that IL-10 levels and signaling in skeletal muscle are reduced in aging mice [24] whereas Alvarez-Rodriguez et al. (2012) studies also showed decreasing serum levels of IL-10 in aging humans [25]. Furthermore, the IL-10 homozygous knockout mouse has been shown to display increased levels of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)-induced inflammatory mediators [26]. Furthermore, levels of IL-6 in the IL-10 homozygous knockout mice are significantly increased at 50 weeks. These mice display decreased skeletal muscle strength, skeletal muscle quality and muscle weakness with aging, rendering them attractive models for sarcopenia [27]. However, serum IL-10 levels are quite variable in elderly individuals. Previous studies have demonstrated a significant age-related increase in serum IL-10 [28]. So far, few studies have examined whether the association exists

### Table 4 Multivariate regression analysis for relationship between IL-6 levels, IL-10 levels, IL-6/IL-10 ratio and sarcopenia

| Variable | OR (CI 95%) | p     |
|----------|-------------|-------|
| IL-10    | 1.14 (1.03–1.29) | 0.047 |
| Age      | 1.11 (1.03–1.17) | 0.017 |
| sex      | 0.87 (0.67–1.14) | 0.483 |
| BMI      | 0.83 (0.69–1.03) | 0.032 |
| VFA      | 0.63 (0.51–1.12) | 0.271 |
| IL-6     | 1.32 (1.07–1.55) | 0.021 |
| IL-6/IL-10 | 1.76 (1.56–1.91) | 0.035 |
| MNA-SF   | 1.13 (0.82–1.45) | 0.312 |
| Sport    | 0.79 (0.64–1.19) | 0.376 |

OR: odds ratio, CI: confidence interval, IL-10: interleukin-10, BMI: body mass index, VFA: visceral fat tissue, IL-6: interleukin-6, MNA-SF: mini nutritional assessment short-form
between the antiinflammatory cytokine IL-10 and sarcopenia in elderly individuals. Dong et al. (year) evaluated the serum levels of inflammatory markers in disabled and non-disabled elderly Chinese individuals, and found patients with a disability displayed higher levels of IL-10 compared with the control group. Moreover, increased IL-10 was associated with poor physical performance [29]. In the current study, we observed significantly increased levels of IL-10 in elderly individuals with sarcopenia. Consistent with Dong et al.’s findings, we showed IL-10 levels increased with age [30]. Age-related changes in body composition in sarcopenia, primarily more fat depositing in the abdomen and muscles, may be associated with serum IL-10 levels. According to our results, we propose that IL-10 suppresses pro-inflammatory cytokine production by feedback [31]. The increased IL-10 levels observed in elderly sarcopenia patients might therefore be compensatory, in an attempt to suppress the chronic low level inflammatory state.

In recent years, the ratio of proinflammatory cytokine IL-6 to anti-inflammatory cytokine IL-10 (IL-6/IL-10 ratio) has been used as a reliable marker for measuring inflammatory status [32, 33]. In the present study, we showed that IL-6/IL-10 ratios were higher for elderly individuals with sarcopenia compared to controls. We speculate that the pro-inflammatory cytokine IL-6 increases with the compensatory increasing of the anti-inflammatory cytokine IL-10 to inhibit the continued pro-inflammatory status, but the compensatory increasing of IL-10 cannot completely counteract the increasing levels of IL-6. Ultimately, the pro-inflammatory status is predominant whereas the anti-inflammatory cytokine IL-10 is relatively insufficient in elderly individuals with sarcopenia. However, more studies are needed to better understand the mechanisms involved in this process.

There is a number of limitations to the current study. Firstly, the make-up of the sample comprised a greater proportion of males than females. There is therefore a risk of selection bias influencing the results and conclusions. Although we included sex as a variable in the univariate and multivariate analyses. The associations demonstrated may differ in a more representative population with an equal proportion of males and females. Secondly, the cross-sectional design limits us from identifying a cause-effect association between sarcopenia and IL-6 levels, IL-10 levels and IL-6/IL-10 ratios. Prospective studies are therefore required. The relatively small sample size of our study poses an additional limitation. To our knowledge, this is the first study to evaluate the relationship between sarcopenia and IL-6 levels, IL-10 levels and IL-6/IL-10 ratios. It is important to note that recombinant IL-10 in humans has been deemed safe in clinical trials for the treatment of autoimmune and neurodegenerative disorders. Thus, IL-10 may be a promising therapeutic candidate for preventing sarcopenia in elderly individuals.

Conclusion
In conclusion, we propose that elderly individuals with sarcopenia exhibit a compromised “inflammatory status” characterized by higher IL-6, IL-10 concentrations and IL-6/IL-10 ratios. Moreover, IL-10 may prove to be a promising therapeutic agent for the prevention of sarcopenia in the elderly.

Abbreviations
ALB: Serum albumin; ASM: Appendicular skeletal lean mass; ASMI: Appendicular skeletal muscle index; EWGSOP: The Asian Working Group for Sarcopenia; BIA: Bioelectrical impedance analysis; BMI: Body mass index; CI: Confidence interval; Cr: Creatinine; CRP: C-reactive protein; Hb: Hemoglobin; HbA1C: Hemoglobin A1C; HS: Handgrip strength; IL-6: Interleukin-6; IL-10: Interleukin-10; LDL-C: Low-density lipoprotein cholesterol; MNA-SF: Mini-nutritional assessment short-form; NF-KB: Nuclear factor kappa-light-chain-enhancer of activated B cells; OR: Odds ratio; SD: Standard deviation; TG: Triglyceride; TNFα: Tumor necrosis factor alpha; VFA: Visceral fat tissue

Acknowledgements
None.

Funding
This research was supported by the science and technology fund of Tianjin City Health and Family Planning Commission. These fund permitted the collection of data.

Availability of data and materials
The datasets generated and/or analyzed during the current study are not publicly available for reasons of patient privacy and a non-disclosure requirement from the funding body.

Authors contributions
Conception and design: RYD and BAL. Data acquisition, analysis and interpretation: HHY, HY, ZXZ. Drafting and revision of the manuscript: MY, ZXZ. Final approval of the manuscript: RYD. All authors have read and approved the final manuscript.

Ethics approval and consent to participate
This study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committee of Tianjin First Central Hospital. All participants were provided with details on the purpose of this study and how the collected data were used. Written informed consent was obtained from all participants prior to their inclusion in the study.

Consent for publication
Not applicable.

Competing interests
The authors have no competing interests to declare.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details
1 Health Management Centre, Tianjin First Central Hospital, No. 24 of Fukang Road, Nankai District, Tianjin 300192, China. 2 Department of Gerontology, Tianjin First Central Hospital, Tianjin, China. 3 Department of Gerontology, Yanda International Hospital, Hebei, China.
References

1. Wraland S, Guillett G, Salles J, Cano N, Borrie Y. Physiopathological mechanism of sarcopenia. Clin Geriatr Med. 2011;27(3):365–85.

2. Franceschi C, Bonafe M, Valentini S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G. Inflamm-aging: an evolutionary perspective on immunosenescence. Ann N Y Acad Sci. 2000;908:244–54.

3. Baylis D, Barrett DB, Patel HP, Roberts HC. Understanding how we age: insights into inflammaing. Longev Healspan. 2013;2(1).

4. Pedersen M, Brunsgaard H, Weis N, Hendel HW, Andreasen BU, Eldrup E, De la F, Pedersen BK. Circulating levels of TNF-alpha and IL-6-relation to truncal fat mass and muscle mass in healthy elderly individuals and in patients with type-2 diabetes. Mech Ageing Dev. 2005;126(4):495–502.

5. Visser M, Pahor M, Taaffe DR, Goodpaster BH, Simonsick EM, Newman AB, Nevitt M, Harris TB. Relationship of interleukin-6 and tumor necrosis factor-alpha with muscle mass and muscle strength in elderly men and women: the health ABC study. J Gerontol A Biol Sci Med Sci. 2002;57(5):M326–32.

6. Chen LN, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, Chou MY, Chen LY, Hsu PS, Kraitik O, Lee JS, Lee WJ, Lee Y, Liang CK, Limapawattana P, Lin CS, Peng LN, Satake S, Suzuki T, Won CW, Wu CH, Wu SN, Zhang T, Zeng P, Akishita M, Arai H. Sarcopenia in Asia: consensus report of the Asian working group for Sarcopenia. J Am Med Dir Assoc. 2014;15(2):95–101.

7. Schaa LP, Pluim JM, Deeg DJ, Visser M. Inflammatory markers and loss of muscle mass (sarcopenia) and strength. Am J Med. 2006;119(8):s26–9.

8. Taaffe DR, Harris TB, Ferrucci L, Rowe J, Seeman TE. Cross-sectional and prospective relationships of interleukin-6 and C-reactive protein with physical performance in elderly persons. MacArthur studies of successful aging. J Gerontol A Biol Sci Med Sci. 2000;55(12):M709–15.

9. Legrand D, Vaes B, Mathei C, Adriaensen W, Van Pottelbergh G, Degryse JM. Muscle strength and physical performance as predictors of mortality, hospitalization, and disability in the oldest old. J Am Geriatr Soc. 2014;62(6):1030–9.

10. Penninx BW, Kritchevsky SB, Newman AB, Nicklas BJ, Simonsick EM, Rubin S, Legrand D, Vaes B, Mathei C, Adriaensen W, Van Pottelbergh G, Degryse JM. Association of low interleukin-10 levels with the metabolic syndrome in obese women. J Clin Endocr Metab. 2003;88(3):1055–6.

11. Cesari M, Penninx BW, Lauretani F, Corsi AM, Rhys Williams G, Pahor M. Association of low interleukin-10 levels with the metabolic syndrome in older women. J Gerontol A Biol Sci Med Sci. 2004;59(12):M709–15.

12. Toth MJ, Matthews DE, Tracy RP, Pevins MJ. Age-related differences in muscle breakdown in rats. Am J Physiol. 1991;260(5 Pt 1):E727–30.

13. Haddad F, Zaldivar F, Cooper DM, Adams GR. IL-6-induced skeletal muscle atrophy. J Appl Physiol (1985). 2005;98(3):911–7.

14. Goodman MN. Tumor necrosis factor induces skeletal muscle protein synthesis: relation to markers of immune activation. J Appl Physiol. 2001;91:242–8.

15. Ferrucci L, Penninx BW, Volpato S, Harris TB, Bandeen-Roche K, Balfour J, Lee JS, Lee WJ, Lee Y, Liang CK, Limapawattana P, Lin CS, Peng LN, Satake S, Suzuki T, Won CW, Wu CH, Wu SN, Zhang T, Zeng P, Akishita M, Arai H. Sarcopenia in Asia: consensus report of the Asian working group for Sarcopenia. J Am Med Dir Assoc. 2014;15(2):95–101.

16. Toth MJ, Matthews DE, Tracy RP, Pevins MJ. Age-related differences in muscle protein synthesis: relation to markers of immune activation. Am J Physiol Endocrinol Metab. 2005;288(5):E883–91.

17. Scotchard D, Soper DE, Kiely DK, Withers PM. Inflammatory markers and loss of muscle mass (sarcopenia) and strength. Am J Med. 2006;119(8):s26–9.

18. Visser M, Pahor M, Taaffe DR, Goodpaster BH, Simonsick EM, Newman AB, Nevitt M, Harris TB. Relationship of interleukin-6 and tumor necrosis factor-alpha with muscle mass and muscle strength in elderly men and women: the health ABC study. J Gerontol A Biol Sci Med Sci. 2002;57(5):M326–32.

19. Chen LN, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, Chou MY, Chen LY, Hsu PS, Kraitik O, Lee JS, Lee WJ, Lee Y, Liang CK, Limapawattana P, Lin CS, Peng LN, Satake S, Suzuki T, Won CW, Wu CH, Wu SN, Zhang T, Zeng P, Akishita M, Arai H. Sarcopenia in Asia: consensus report of the Asian working group for Sarcopenia. J Am Med Dir Assoc. 2014;15(2):95–101.

20. Schaa LP, Pluim JM, Deeg DJ, Visser M. Inflammatory markers and loss of muscle mass (sarcopenia) and strength. Am J Med. 2006;119(8):s26–9.

21. Taaffe DR, Harris TB, Ferrucci L, Rowe J, Seeman TE. Cross-sectional and prospective relationships of interleukin-6 and C-reactive protein with physical performance in elderly persons: MacArthur studies of successful aging. J Gerontol A Biol Sci Med Sci. 2000;55(12):M709–15.

22. Legrand D, Vaes B, Mathei C, Adriaensen W, Van Pottelbergh G, Degryse JM. Muscle strength and physical performance as predictors of mortality, hospitalization, and disability in the oldest old. J Am Geriatr Soc. 2014;62(6):1030–9.

23. Mital SK, Roche PA. Suppression of antigen presentation by IL-10. Curr Opin Immunol. 2015;34:22–7.

24. Hacham M, White RM, Argov S, Segal S, Apte RN. Interleukin-6 and interleukin-10 are expressed in organs of normal young and old mice. Eur J Immunol. 2004;15(1):37–46.

25. Alvarez-Rodriguez L, Lopez-Hoyos M, Muñoz-Cacho P, Martínez-Taboada VM. Aging is associated with circulating cytokine dysregulation. Cell Immunol. 2012;273:124–32.

26. Rennick D, Davidson N, Beng D. Interleukin-10 gene knockout murine model of chronic inflammation. Clin Immunol Immunopathol. 1995;76(3 Pt 2):5174–8.

27. Walston J, Fedarko N, Yang H, Leng S, Beam R, Espinoza S, Lipton A, Zheng H, Becker K. The physical and biological characterization of a frail mouse model. J Gerontol A Biol Sci Med Sci. 2008;63(4):391–8.

28. Alvarez-Rodriguez L, Lopez-Hoyos M, Muñoz-Cacho P, Martínez-Taboada VM. Aging is associated with circulating cytokine dysregulation. Cell Immunol. 2012;273(2):124–32.

29. Dong B, Sun B. Inflammatory Markers and Disability in Chinese older adults. J Gerontol Geriatr Res. 2016;275.

30. Esposito K, Pompillo A, Giugliano F, Giugliano G, Marfella R, Nicosetti G, Giugliano D. Association of low interleukin-10 levels with the metabolic syndrome in obese women. J Clin Endocrinol Metab. 2003;88(3):1055–6.

31. Tedgui A, Mallat Z. Anti-inflammatory mechanisms in the vascular wall. Circ Res. 2001;88(9):877–87.

32. Sun J, Su J, Xie Y, Yin MT, Huang Y, Xu L, Zhou Q, Zhu B. Plasma IL-6/IL-10 ratio and IL-8 LDH, and HBDM level predict the severity and the risk of death in AIDS patients with pneumocystis pneumonia. J Immunol Res. 2016;2016:1583951.

33. HB Sapan I, Paturusi I, Jusuf IP, Massi MN, Pusponegoro AD, Arief SK, Labeda I, Islam AA, Randy L, Hatta M. Pattern of cytokine (IL-6 and IL-10) level as inflammation and anti-inflammation mediator of multiple organ dysfunction syndrome (MODS) in polytrauma. Int J Burns Trauma. 2016;6(2):37–43.