Study of the C-reactive protein and tumor necrosis factor-α levels in the elderly before and after resistance exercise training

Noha M. El-Sabbagh[a], Enas M. Shahin[b], Nany H. Abo El Makarem[a], Rania S. Swelem[c], Shaymaa A. I. M. AbdElMoneim[d]

Departments of [a]Internal Medicine-Geriatric [b]Physical Medicine, Rheumatology and Rehabilitation, [c]Clinical and Chemical Pathology and [d]Internal Medicine, Health Insurance Hospitals, Faculty of Medicine, University of Alexandria, Alexandria, Egypt

Correspondence to Shaymaa A. I. M. AbdElMoneim, MS, Internal Medicine, Health Insurance Hospitals, Faculty of Medicine, University of Alexandria, Alexandria, Egypt
e-mail: shaymaaahmed1329@yahoo.com

Received 04 January 2015
Accepted 24 January 2015

Egyptian Journal of Obesity, Diabetes and Endocrinology
2015, 1:7–13

Introduction
Aging results in chronic low-grade inflammation that is associated with an increased risk for disease, poor physical functioning, and mortality. The biomarkers that are mostly related to inflammation such as tumor necrosis factor-α (TNF-α) and C-reactive protein (CRP) are created to stimulate and activate the immune system in response to inflammation. Strategies that reduce age-related inflammation may improve the quality of life in older adults. The benefits of regular exercise for the elderly are well established, whereas less is known on the impact of low-intensity resistance exercise on this chronic low-grade inflammation in the elderly.

Aim of the study
To study the level of TNF-α and CRP before and after programmed resistance exercise in Egyptian elderly individuals.

Patients and methods
Thirty healthy elderly individuals aged 60 years or older, of both sexes, participated in 4 weeks of resistance exercise training (RET). Circulating levels of TNF-α and CRP were measured before and after the exercise training.

Results
This study found that both inflammatory markers, TNF-α and CRP, were statistically significantly decreased (P = 0.036, 0.009), respectively, in comparison with the previous starting level measured before the exercise in the same individuals.

Conclusion
There was a negative correlation between TNF-α and CRP levels and the RET, which indicated that RET represents a low-cost strategy that may reduce age-related inflammation and may thus improve the quality of life in older adults.

Keywords:
biomarkers, C-reactive protein, resistance exercise training, strategies, tumor necrosis factor-α

Egyptian Journal of Obesity, Diabetes and Endocrinology 1:7–13

2356-8062

Introduction

Aging is the process of becoming older, a process that is genetically determined and environmentally modulated. Time modifies many biologic processes. Aging is characterized by progressive and broadly predictable changes that are associated with increased susceptibility to many diseases. Aging is not a homogenous process. Rather, organs in the same individual age at different rates influenced by multiple factors including genetic, lifestyle choices, and environmental exposures [1].

Aging theories

The traditional aging theories hold that aging is not an adaptation or genetically programmed. Modern biological theories of aging in humans fall into two main categories: the programmed theory has three subcategories: programmed longevity, endocrine theory, and immunological theory. The damage or error theory includes wear and tear theory, rate of living theory, cross-linking theory, free radicals theory, and somatic DNA damage theory [2].

Aging process

Musculoskeletal system

Skeletal muscle fibers become smaller in diameter and less elastic because of decreasing number of myofibrils associated with increasing amounts of fibrous connective tissue, a process called fibrosis.

Reduction in the number of muscle capillaries is a factor that can alter muscle strength as it reduces blood flow to active muscles and consequently decreases oxygen and nutrients supply and removal capacity for metabolites [3].

Age-related apoptotic motor neuron loss is proposed to directly attenuate strength, rate of force development, and muscular power, and eventually leads to a decrease in muscle fiber number [4].

The ability to recover from muscular injuries decreases as the number of satellite cells steadily decreases with age and the amount of fibrous tissue increases. As a result, when an injury occurs, repair capabilities are limited. Scar tissue formation is the usual result [5], all this resulting in decreased tolerance for exercise [6].

Muscle protein metabolism in the elderly

Net protein balance is defined as the difference between skeletal muscle protein synthesis (MPS) and breakdown (MPB). Thus, a significant increase in MPS (anabolism) and/or a reduction in MPB (catabolism), such that net protein balance remains positive, can result in the accretion of skeletal muscle proteins. Conversely, in the elderly, a negative net protein balance, arising from a reduction in MPS and/or an increase in MPB, will result in a loss of skeletal muscle protein [7].

Only overloading of muscle with weight-lifting exercise (resistance training) may prevent losses of muscle mass (and also strength) in older individuals depending on the individual's characteristics and intensity of the program [8].

Sarcopenia as a geriatric syndrome

What is sarcopenia?

Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength, with an impaired state of health, increased risk of falls and fractures, impaired ability to perform activities of daily living, disabilities, loss of independence, and increased risk of death. The European Working Group on Sarcopenia in Older People (EWGSOP) developed a practical clinical definition and consensus diagnostic criteria for age-related sarcopenia [9].

Criteria for the diagnosis of sarcopenia: [10]

Diagnosis is made on the basis of documentation of criterion 1 plus criterion 2 or criterion 3:

(1) Low muscle mass.
(2) Low muscle strength.
(3) Low physical performance.

Some have argued that the term dynapenia is better suited to describe age-associated loss of muscle strength and function. However, sarcopenia is already a widely recognized term; thus, replacing it might lead to further confusion [11].

Mechanisms of sarcopenia

Sarcopenia categories and stages

Sarcopenia can be considered 'Primary' (or age-related) when no other cause is evident but aging itself, whereas sarcopenia can be considered 'Secondary' when one or more other causes are evident (Fig. 1).

The 'presarcopenia' stage is characterized by low muscle mass without impact on muscle strength or physical performance. This stage can only be identified by techniques that measure muscle mass accurately.

The 'sarcopenia' stage is characterized by low muscle mass, and low muscle strength or low physical performance.

'Severe sarcopenia' is the stage identified when all three criteria of the definition are fulfilled (low muscle mass, low muscle strength, and low physical performance). Identification of stages of sarcopenia may help in selecting treatments and setting appropriate recovery goals [11].

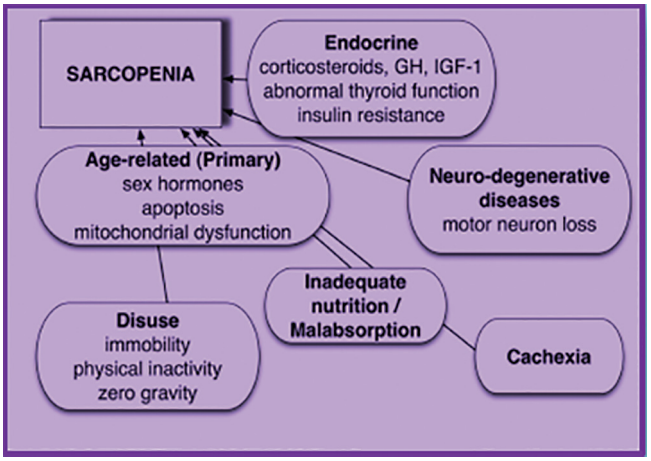
Immune system

Aging of the immune system, particularly the dysregulation of T-cell function, appears to be partly responsible for the comorbidities presented by the elderly population, although it is possible that exercise or lifestyle acts to prevent or treat immunosenescence [12] that results from the accumulation of molecular and cellular defects because of oxidative damage and thymic involution [13].

Oxidative stress and the molecular inflammatory theory of aging

The molecular inflammatory theory of aging has been proposed implicating reactive oxygen and nitrogen

Figure 1



Causes of sarcopenia[10].

species and proinflammatory molecules as key players in the aging process [14]. Increases in oxidative stress with aging may also contribute toward the development of chronic inflammation that is related to atherosclerosis and insulin resistance [13].

A low-level increase in circulating proinflammatory cytokines such as interleukin-6 and tumor necrosis factor-α (TNF-α), and acute-phase proteins such as C-reactive protein (CRP) and serum amyloid A is defined as low-grade inflammation, typically in the elderly, even in the absence of chronic disease [15].

Tumor necrosis factor-α

TNF-α is one of the main inducers of the acute-phase response, playing an important role in alterations of muscle protein metabolism [16]. TNF is produced predominantly by activated macrophages, mast cells, T and B lymphocytes, natural killer cells, neutrophils, endothelial cells, smooth and cardiac muscle cells, fibroblasts, and osteoclasts. As a regulatory cytokine, TNF orchestrates communication between immune cells and also controls their functions [17].

Many of the proinflammatory effects of TNF can be explained on the basis of TNF's effects on vascular endothelium and endothelial leukocyte interactions. In response to TNF, endothelial cells promote inflammation by displaying different combinations of adhesion molecules for leukocytes, including E-selectin, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1. TNF-induced expression of cyclo-oxygenase 2 can increase extracellular production of vasodilatory prostaglandins 2, resulting in vasodilatation and also TNF-induced expression of procoagulant proteins, such as tissue factor, and downregulation of anticoagulant protein, such as thrombomodulin; thus, TNF can cause intravascular thrombosis [18].

C-reactive protein

CRP is a very useful nonspecific biochemical marker of inflammation [19]. It has several functions associated with host defense. A major function of CRP is as a component of the innate immune system as it promotes agglutination, bacterial capsular swelling, phagocytosis, induction of inflammatory cytokines in monocytes, and complement fixation through its calcium-dependent binding to phosphorylcholine [20].

The amount of CRP produced by the body varies from individual to individual, and this is affected by an individual's genetic factors and lifestyle. Higher levels are found in late pregnant women, active inflammation, bacterial infection, tissue injury (postoperation), trauma, and burns. Smoking and obesity are correlated positively with CRP levels, whereas exercise [21], weight loss, cessation of smoking, and medications such as statins, niacin, and fibrates decrease CRP values [19].

The diurnal variation: CRP values show no diurnal variation and are unaffected by eating. Only liver failure impairs CRP production [22]. The half-life of CRP is constant under all conditions of health and disease. Therefore, the CRP level is mainly determined by the rate of production (and hence the severity of the precipitating cause) [23].

Lifestyle interventions such as exercise training and dietary modifications may provide a low-cost and long-term alternative to limit inflammation and slow declines in the elderly [24].

Physical activity

Sedentary living has assumed epidemic proportions in the industrialized world and therefore regular physical activity (PA) is one of the most main nonpharmaceutical important modifiable factors that determine the risk of chronic morbidity and mortality in the population in general [25]. The concept of successful aging is the first line of a preventive approach of care for older individuals. Moderate but regular PA is associated with a reduction in total morbidity among older individuals [26].

Categories of physical activity

Physical therapy for the elderly may be classified into three categories: first, prevention or restoration of the sequelae of disuse in healthy elderly individuals; second, prevention or restoration of the sequelae of disuse in the acute and chronically ill; and third, rehabilitation of functional losses caused by trauma and disease [27,28].

Resistance exercise

Resistance exercise is generally recommended as the preferred approach to elicit improvements in muscular hypertrophy and strength adaptations. Following even short-term resistance exercise interventions, aging adults may expect improvements in protein synthesis [29]. However, low-intensity treadmill walking seems to abolish the age-related insulin resistance of MPS. These data are promising because they show that the intensity of contraction required to improve skeletal muscle anabolic sensitivity may be relatively low. Thus, the strategy is to encourage the elderly to maintain daily habitual PA [30].

Current guidelines for PA in older adults have been developed by the American College of Sports Medicine

and American Heart Association. These 'minimum' recommendations call for 'muscle-strengthening activity' to be performed 2 or more nonconsecutive days per week using a single set of 8–10 resistance exercises for the entire body [31].

There is evidence that exercises can both cause and attenuate inflammation. Acute, unaccustomed exercise can cause muscle and connective tissue damage, especially if performed at high intensities and for prolonged durations. This typically manifests as delayed-onset muscle soreness that is preceded by microstructural skeletal muscle damage, inflammatory cell infiltration, and increase in muscle-specific creatine kinase isoforms. This damaging response is attenuated if exercise is performed repeatedly as the tissue adapts to the new overload stress [32].

Contraindications of exercise

Contraindications of exercise in older adults are not different from those applicable to younger healthier adults. In general, frailty or extreme age is not a contraindication to exercise, although the specific modalities may be altered to accommodate individual disabilities and acute illnesses, particularly febrile illnesses, undiagnosed or unstable chest pain, uncontrolled diabetes, and hypertension, irrespective of exercise status [33].

Regular PA is recommended, and generally considered to be an important strategy, for the reduction or prevention of functional decline with aging. In addition, PA reduces the risk of disease and has a beneficial effect on the impact of a large number of chronic diseases and the functional consequences and multimorbidity [34].

Aim of the study

The aim of this work is to study the level of TNF-α and CRP before and after programmed resistance exercise in Egyptian elderly individuals.

Participants and methods

This study was carried out on 30 elderly individuals ranging in age from 60 to 78 years and of both sexes with no history of any systemic metabolic diseases such as diabetes, hypertension, and hepatic or renal diseases. The participants were attending the Department of Physical Medicine, Rheumatology and Rehabilitation in El Hadara Alexandria University Hospital.

After an assessment of full medical history of the selected participants, complete clinical examination, ECG, and routine laboratory investigations (complete blood picture, random blood sugar, and renal functions tests) were performed. Other inflammatory markers (TNF-α and CRP) were measured twice before and after regular resistance exercise training (RET).

Tumor necrosis factor-α [35]

TNF-α was assessed by high-performance immunoassays 'Human TNF-alpha' using eBioscience Platinum ELISA (San Diego, California). Expected values: normally there were no detectable human TNF-α levels found.

Quantitative C-reactive protein [36]

CRP was assessed using the cardio phase 'hs-CRP'. BN Π/BN ProSpec System. Reference interval: expected values for healthy individuals are typically up to 3 mg/dl.

Resistance exercise training

Exercise protocol: The exercise sessions were performed three times per week for 4 weeks and involved low-intensity RET performed for both upper and lower limbs. RET sessions involved the following: a warm-up period (5 min) on a selective bicycle ergometer (Bike-Max) at low intensity; specific resistance training period: 30 min of exercises performed using elastic bands and dumbbells; and a cool-down period (5 min).

The exercise consisted of the following:

(1) Resistance training for dorsiflexors (a cable is attached to the foot from the floor and the thigh is raised).
(2) Front traction (a horizontally drawn cable is grasped and stretched forward).
(3) Vertical traction (a cable is grasped from above and stretched downward) [37].

Statistical analysis of the data: [38]

Data were fed to the computer and analyzed using the IBM SPSS software package, version 20.0 [39]. Comparison between the different periods was performed using the Wilcoxon signed ranks test. Correlations between two quantitative variables were assessed using the Spearman coefficient. The significance of the results obtained was determined at the 5% level.

Results

Demographic data

In our study, the 30 elderly subjects included 11 males (36.7%) and 19 females (63.3%), their age ranged from

60-78 years with mean age value 66.17 ± 5.57 as there are 17 subjects (56.7%) between 60-65 years; 7 subjects (23.3%) between 66-70 years;and 6 subjects (20%) above 70 years old. Among the elderly subjects, there were 17 worker (56.7%) and 13 non-workers (43.3%); also 24 subjects were non smokers (80%) and 6 only were smokers (20%).

Clinical assessment of the participants studied (diagnosis)

Among the 30 individuals selected in this study, 21 were diagnosed with postimmobilization stiffness (70%), six others were diagnosed to have knee osteoarthritis (20%), and only one individual had a previous medical history of medial leminescus tear (3.3%); another participant had been diagnosed with carpal tunnel syndrome (3.3%) and finally one participant complained of chronic low back pain because of old disc prolapse (3.3%) (Table 1).

Laboratory findings in the participants studied

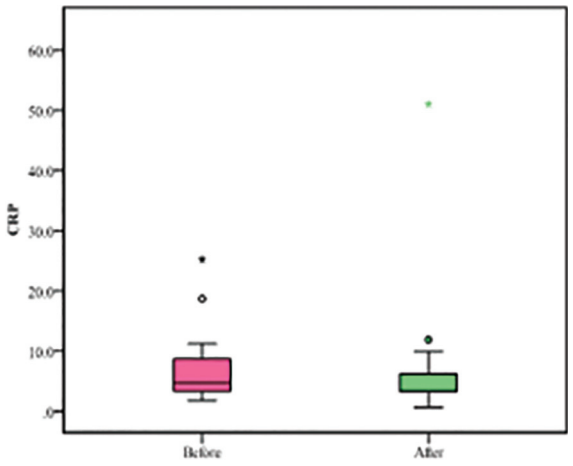
Complete blood picture, random blood sugar, and renal function tests were within the normal range.

Serum level of specific inflammatory markers

Tumor necrosis factor-α (n = 29)

After excluding one participant because of the extreme unexplained level of TNF-α, 26 pg/ml, the TNF-α level ranged between 0 and 10.4 pg/ml before exercise and between 0 and 8.6 pg/ml after the RET. The mean value was 3.07 ± 3.06 and 2.23 ± 2.37 pg/ml before and after exercise training, respectively. This difference was statistically significant (P = 0.036), P up to 0.05 (Table 2 and Fig. 2).

Figure 2



Levels of TNF-α before and after resistance exercise training. CRP, C-reactive protein; TNF-α, tumor necrosis factor-α.

C- reactive protein

The CRP level ranged between 1.83 and 25.2 mg/l before RET and between 0.6 and 51 mg/l after exercise training. In our selected individuals, the mean value was 6.57 ± 5 and 6.03 ± 8.84 mg/l before and after RET, respectively. This difference was statistically significant (P = 0.009), P up to 0.05 (Table 3 and Fig. 3).

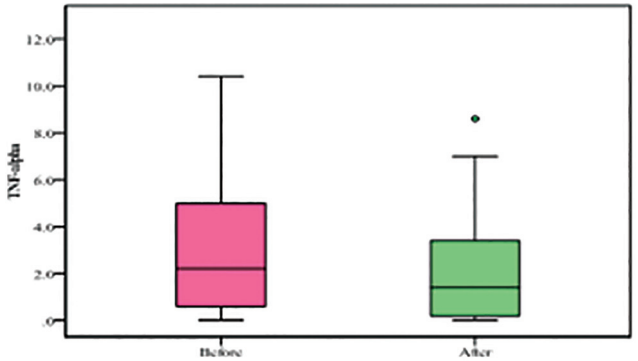
Discussion

We found in this study that, after exposure of the participants to 4 weeks of programmed RET, there was a significant decrease in both the TNF-α level and the serum CRP level (P = 0.036 and 0.009), respectively, compared with the previous starting level measured before the exercise in the same individuals. This indicates that RET represents a low-cost strategy that reduces age-related inflammation by decreasing the inflammatory markers and may thus improve the quality of life in older adults.

Table 1 Distribution of the participants studied according to demographic data

Demographic data	*N* (%)
Sex	
Male	11 (36.7)
Female	19 (63.3)
Age (years)	
60–65	17 (56.7)
66–70	7 (23.3)
>70	6 (20.0)
Minimum–maximum	60.0–78.0
Mean ± SD	66.17 ± 5.57
Median	65.0
Occupation	
Worker	17 (56.7)
Nonworker	13 (43.3)
Habits	
Nonsmoker	24 (80.0)
Smoker	6 (20.0)

Figure 3



Levels of CRP before and after resistance exercise training. CRP, C-reactive protein; TNF-α, tumor necrosis factor-α.

Table 2 Levels of TNF-α before and after resistance exercise training

TNF-α	Before exercise	After exercise
Minimum–maximum	0.0–10.40	0.0–8.60
Mean ± SD	3.07 ± 3.06	2.23 ± 2.37
Median	2.20	1.40
Z (*P*)	2.099* (0.036*)	

n = 29; TNF-α, tumor necrosis factor-α; Z, Z for Wilcoxon signed ranks test; *Statistically significant at $P \leq 0.05$.

Table 3 Levels of CRP before and after resistance exercise training

CRP	Before exercise	After exercise
Minimum–maximum	1.83–25.22	0.62–51.0
Mean ± SD	6.57 ± 5.0	6.03 ± 8.84
Median	4.70	3.36
Z (*P*)	2.597* (0.009*)	

CRP, C-reactive protein; Z, Z for Wilcoxon signed ranks test; *Statistically significant at $P \leq 0.05$.

In partial agreement with this study, Ogawa *et al*. [40] studied 21 elderly women, mean age 85 ± 4.5 years, who had participated in RET sessions at least once per week for 12 weeks. The exercise program involved low-intensity resistance exercise. The duration of each exercise session was ~40 min consisting of foot press, front traction, vertical traction, and shoulder press performed on Kinesis devices. Circulating levels of CRP and TNF-α were measured before and after the exercise training. Ogawaand colleagues found that RET led to a significant reduction in the CRP level ($P < 0.05$) and nonsignificant changes in the TNF-α level. These results suggest that even low-intensity exercise is beneficial for sedentary elderly individuals as it induced a reduction in inflammatory markers and cytokine levels.

This is consistent with the study of Griewe *et al*. [41], who studied the TNF-α level in muscles of eight elderly subjects (81±1 year old) underwent skeletal muscle biopsies before and after 12 weeks of resistance exercise program. They found that muscle TNF-α mRNA and protein levels decreased after RET and the MPS rate was inversely related to the levels of TNF-α protein. These data suggest that TNF-α contributes toward age-associated muscle wasting and that resistance exercise may attenuate this process by suppressing skeletal muscle TNF-α expression.

Similarly, Moreno *et al*. [42] studied the serum CRP level in a group of 120 sedentary older Latino adults, with high rates of sedentary lifestyle, before and after PA. They found that the increased PA was associated with improvements in inflammatory markers. Moreover, changes in self-reported PA level correlated inversely with decreases in the serum CRP level ($P = 0.03$).

Similarly, an increase in inflammatory cytokine levels in plasma is associated with a reduction in physical performance and independence in the elderly. This was the conclusion of the Pereira *et al*. [43] study, which included 451 elderly women aged 65 years or older. Participants were allocated to muscle-strengthening exercise (resistance) and aerobic exercise groups. Both protocols lasted 10 weeks and included 30 sessions performed three times per week. There was a significant correlation between TNF-α levels and the effect of exercise on physical performance in the elderly women irrespective of the exercise type as TNF-α was decreased significantly ($P = 0.001$).

Another study was carried out and reported results that were not in agreement with this study. Hammett *et al*. [44] recruited 30 healthy elderly individuals ranging in age from 60 to 85 years. After 6 months of regular resistance exercise, the level of CRP ($P = 0.3$) did not show any significant change despite a significant improvement in their cardiorespiratory fitness. Alternatively, the cumulative effect of exercise may influence serum CRP levels over the course of many years, although not by shorter term changes in exercise levels.

Conclusion

From the previous discussion, it can be concluded that:

(1) Increases in circulating levels of proinflammatory cytokines such as TNF-α and acute-phase proteins such as CRP were typical in the elderly, even in the absence of chronic disease.
(2) Exercise has a beneficial effect, as evidenced by a statistically significant decrease in CRP and TNF-α after 1 month of RET in participants of both sexes.
(3) Maintenance of moderate but regular PA is associated with a reduction in total morbidity among older individuals.

Recommendations

Long-term and regular but nonstrenuous PA, even 30 min of activity over the course of the day, is an important strategy for the reduction or prevention of functional decline with aging.

Acknowledgements

Conflicts of interest

None declared.

References

1 vB Hjelmborg J, Iachine I, Skytthe A, Vaupel JW, McGue M, Koskenvuo M, *et al*. Genetic influence on human lifespan and longevity. Hum Genet 2006; 119:312-321.

2 Davidovic M, Sevo G, Svorcan P, Milosevic DP, Despotovic N, Erceg P. Old age as a privilege of the 'selfish ones'. Aging Dis 2010; 1:139–146.

3 Kutsuzawa T, Shioya S, Kurita D, Haida M, Yamabayashi H. Effects of age on muscle energy metabolism and oxigenation in the forearm muscle. Med Sci Sports Exerc 2001; 33:901–906.

4 Aagaard P, Suetta C, Caserotti P, Magnusson SP, Kjaer M. Role of the nervous system in sarcopenia and muscle atrophy with aging: strength training as a countermeasure. Scand J Med Sci Sports 2010; 20:49–64.

5 Hartman JW, Tang JE, Wilkinson SB, Tarnopolsky MA, Lawrence RL, Fullerton AV, Phillips SM. Consumption of fat-free fluid milk after resistance exercise promotes greater lean mass accretion than does consumption of soy or carbohydrate in young, novice, male weightlifters. Am J Clin Nutr 2007; 86:373–381.

6 Krogh-Madsen R, Thyfault JP, Broholm C, Mortensen OH, Olsen RH, Mounier R, *et al.* Nutrient signalling in the regulation of human muscle protein synthesis. J Appl Physiol 2010; 108:1034–1040.

7 McKenzie D, Bua E, McKiernan S, Cao Z, Aiken JM. Mitochondrial DNA deletion mutations: a causal role in sarcopenia. Eur J Biochem 2002; 269: 2010–2015.

8 Sheffield-Moore M, Yeckel CW, Volpi E, Wolf SE, Morio B, Chinkes DL, *et al.* Postexercise protein metabolism in older and younger men following moderate-intensity aerobic exercise. Am J Physiol Endocrinol Metab 2004; 287:513–522.

9 Rolland Y, Czerwinski S, Abellan Van KanG, Morley JE, Cesari M, Onder G, *et al*. Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives. J Nutr Health Aging 2008; 12:433–450.

10 Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, *et al*. European Working Group on Sarcopenia in Older People Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on sarcopenia in older people. Age Ageing 2010; 39:412–423.

11 Clark BC, Manini TM. Sarcopenia =/= dynapenia. J Gerontol A Biol Sci Med Sci 2008; 63:829–834.

12 Timmerman KL, Flynn MG, Coen PM, Markofski MM, Pence BD Exercise training-induced lowering of inflammatory ($CD14^+CD16^+$) monocytes: a role in the anti-inflammatory influence of exercise? J Leukoc Biol 2008; 84:1271–1278.

13 Chung HY, Cesari M, Anton S, Marzetti E, Giovannini S, Seo AY, *et al*. Molecular inflammation: underpinnings of aging and age-related diseases. Ageing Res Rev 2009; 8:18–30.

14 Chung HY, Sung B, Jung KJ, Zou Y, Yu BP. The molecular inflammatory process in aging. Antioxid Redox Signal 2006; 8:572–581.

15 Ogawa K, Suzuki K, Okutsu M, Yamazaki K, Shinkai S. The association of elevated reactive oxygen species levels from neutrophils with low-grade inflammation in the elderly. Immun Ageing 2008; 5: 13.

16 Toth MJ, Matthews DE, Tracy RP, Previs MJ. Age-related differences in skeletal muscle protein synthesis: relation to markers of immune activation. Am J Physiol Endocrinol Metab 2005; 288:883–891.

17 Faustman D, Davis M. TNF receptor 2 pathway: drug target for autoimmune diseases. Nat Rev Drug Discov 2010; 9:482–493.

18 Mark KS, Trickler WJ, Miller DW. Tumor necrosis factor-alphainduces cyclooxygenase-2 expression and prostaglandin releasein brain microvessel endothelial cells. J Pharmacol Exp Ther 2001; 297:1051–1058.

19 Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest 2003; 111:1805–1812.

20 Slade GD, Ghezzi EM, Heiss G, Beck JD, Riche E, Offenbacher S. Relationship between periodontal disease and C-reactive protein among adults in the Atherosclerosis Risk in Communities study. Arch Intern Med 2003; 163:1172–1179.

21 Burris CA, Ash wood ER, Burns DE. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 4th ed. St. Louis: Elsevier Saunders 2006; 1633:962–967.

22 Sabet M, Lee SW, Nauman RK, Sims T, Um HS. The surface (s) layer is a virulence factor of *Bacteroides forsythus*. Microbiology 2003; 149: 3617–3627.

23 McPherson RA, Matthew R Pincus MR Henry's clinical diagnosis and management by laboratory methods. 22nd ed. Philadelphia: Elsevier Saunders; 2011. p. 254–255.

24 Forsythe LK, Wallace JM, Livingstone MB. Obesity and inflammation: the effects of weight loss. Nutr Res Rev 2008; 21:117–133.

25 Wen CP, Wai JP, Tsai MK, Yang YC, Cheng TY, Lee MC, *et al*. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. Lancet 2011; 378:1244–1253.

26 Tajiri Y, Kato T, Nakayama H, Yamada K. Reduction of skeletal muscle, especially in lower limbs, in Japanese type 2 diabetic patients with insulin resistance and cardiovascular risk factors. *Metab Syndr Relat Disord* 2010; 8:137–142.

27 Kumar V, Selby A, Rankin D, Patel R, Atherton P, Hildebrandt W, *et al.* Age-related differences in the dose-response relationship of muscle protein synthesis to resistance exercise in young and old men. *J Physiol* 2009; 587(Pt 1): 211–217.

28 American College of Sports Medicine. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. Med Sci Sports Exerc 2009; 41:687–708.

29 Burd NA, West DW, Moore DR, Atherton PJ, Staples AW, Prior T, *et al*. Enhanced amino acid sensitivity of myofibrillar protein synthesis persists for up to 24 h after resistance exercise in young men. J Nutr 2011; 141:568–573.

30 Pennings B, Koopman R, Beelen M, Senden JM, Saris WH, van Loon LJ. Exercising before protein intake allows for greater use of dietary proteinderived amino acids for de novo muscle protein synthesis in both young and elderly men. Am J Clin Nutr 2011; 93:322–331.

31 Nelson ME, Rejeski WJ, Blair SN, Duncan PW, Judge JO, King AC, *et al*. American College of Sports Medicine; American Heart Association Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. Circulation 2007; 116:1094–1105.

32 Woods JA, Vieira VJ, Keylock KT. Exercise, inflammation, and innate immunity. Immunol Allergy Clin North Am 2009; 29:381–393.

33 Chodzko-Zajko WJ, Proctor DN, Fiatarone Singh MA, Minson CT, Nigg CR, Salem GJ, Skinner JS. American College of Sports Medicine American College of Sports Medicine position stand. Exercise and physical activity for older adults. Med Sci Sports Exerc 2009; 41:1510–1530.

34 De Gonzalo-Calvo D, Fernández-García B, de Luxán-Delgado B, Rodríguez-González S, García-Macia M, Suárez FM, *et al*. Long-term training induces a healthy inflammatory and endocrine emergent biomarker profile in elderly men. Age (Dordr) 2012; 34:761–771.

35 Croft M. The role of TNF superfamily members in T-cell function and diseases. Nat Rev Immunol 2009; 9:271–285.

36 Chenillot O, Henny J, Steinmetz J, Herbeth B, Wagner C, Siest G. High sensitivity C-reactive protein: biological variations and reference limits.Clin Chem Lab Med 2000; 38:1003–1011.

37 Sanada K, Kearns CF, Midorikawa T, Abe T. Prediction and validation of total and regional skeletal muscle mass by ultrasound in Japanese adults. Eur J Appl Physiol 2006; 96:24–31.

38 Leslie E, Geoffrey J, James M. Interpretation and uses of medical statistics. 4th ed. Oxford, UK: Oxford Scientific Publications(pub); 1991. 411-416.

39 Kirkpatrick LA, Feeney BC. *A simple guide to IBM SPSS statistics for version 20.0*.. Belmont, CA: Wadsworth, Cengage Learning; 2013. 115.

40 Ogawa K, Sanada K, Machida S, Okutsu M, Suzuki K. Resistance exercise training-induced muscle hypertrophy was associated with reduction of inflammatory markers in elderly women. Mediators Inflamm 2010; 2010:171023.

41 Greiwe JS, Cheng B, Rubin DC, Yarasheski KE, Semenkovich CF. Resistance exercise decreases skeletal muscle tumor necrosis factor alpha in frail elderly humans. FASEB J 2001; 15:475–482.

42 Moreno G, Mangione CM, Wang PC, *et al.* Physical activity, physical performance, and biological markers of health among sedentary older latinos Curr Gerontol Geriatr Res 2014; 10:1155–1171.

43 Pereira DS, Mateo ECC, de Queiroz BZ, Assumpção AM, Miranda AS, Felício DC, *et al.* TNF-α, IL6, and IL10 polymorphisms and the effect of physical exercise on inflammatory parameters and physical performance in elderly women. Age (Omaha) 2013; 35:2455–2463.

44 Hammett CJK, Oxenham HC, Baldi JC, Doughty RN, Ameratunga R, French JK, *et al*. Effect of six months' exercise training on C-reactive protein levels in healthy elderly subjects. J Am Coll Cardiol 2004; 44:2411–2413.