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Muscle strength but not functional capacity is associated with plasma interleukin-6 levels of community-dwelling elderly women

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The association of plasma interleukin-6 (IL-6) levels, muscle strength and functional capacity was investigated in a cross-sectional study of community-dwelling elderly women from Belo Horizonte, Brazil. Elderly people who present controlled chronic diseases with no negative impact on physical, psychosocial and mental functionality are considered to be community-dwelling. Psychological and social stress due to unsuccessfully aging can represent a risk for immune system disfunctions. IL-6 levels, isokinetic muscle strength of knee flexion/extension, and functional tests to determine time required to rise from a chair and gait velocity were measured in 57 participants (71.21 ± 7.38 years). Serum levels of IL-6 were measured in duplicate and were performed within one single assay (mouse monoclonal antibody against IL-6; High-Sensitivity, Quantikine®, R & D Systems, USA; intra-assay coefficient of variance = 6.9-7.4%; interassay coefficient of variance = 9.6-6.5%; sensitivity = 0.016-0.110 pg/mL; mean = 0.039 pg/mL). Muscle strength was assessed with the isokinetic dynamometer Biodex System 3 Pro®. After the Shapiro-Wilk normality test was applied, correlations were investigated using Spearman and Kruskal-Wallis tests. *Post hoc* analysis was performed using the Dunn test. A significant negative correlation was observed between plasma IL-6 levels (1.95 ± 1.77 pg/mL) and muscle strength for knee flexion (70.70 ± 21.14%; r = -0.265; P = 0.047) and extension (271.84 ± 67.85%; r = -0.315; P = 0.017). No significant correlation was observed between IL-6 levels and the functional tests (time to rise from a chair = 14.65 ± 2.82 s and gait velocity = 0.95 ± 0.14 m/s). These results suggest that IL-6 is associated with reduced muscle strength.

Key words: Muscle strength; Interleukin-6; Elderly women; Sarcopenia; Aging; IL-6

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Introduction

Extended lifespan is one of the greatest triumphs of humanity. It is also, however, accompanied by tremendous challenges. In developing countries, socioeconomic development often does not keep pace with the aging of the population (1). Between 1970 and 2025, it is expected that the world's elderly population will have grown by 223% (1). Since physical incapacity often occurs in the elderly, it is estimated that from 20 to 30% of individuals over 70 years of age experience incapacity in the performance of tasks that require mobility and locomotion, the activities of daily living (ADLs) and instrumental activities of daily living (IADLs) (2,3).

Sarcopenia, which is defined as the loss of muscle mass related to old age, contributes to the loss of functional mobility and independence (4-7). Due to the feminization of aging (i.e., more elderly women than men), sarcopenia occurs mainly among women (5). In the final stages of life, absolute maximum strength in women can be the minimum strength necessary for performing ADLs (8,9).

Biological aging is associated with a series of alterations specific to individual organs and systems. The group of immune system changes related to old age is called immunosenescence. This dysfunction increases the plasma levels of inflammatory mediators, such as cytokines and proteins of the acute phase, to two to four times the levels in young adults (10,11).

Interleukin-6 (IL-6), a biological marker, has been called a cytokine for gerontologists (12). A number of epidemiological studies have reported an association between high levels of IL-6 and the loss of functional capacity, as well as an increase in mortality rates for elderly people (10,13-16). Other studies have demonstrated an association between high levels of IL-6 and reduced muscle strength in the elderly (13,17,18). Haddad et al. (19) found atrophy in the tibialis anterior muscle of mice injected locally with relatively low doses of IL-6. It has been suggested that IL-6 causes functional decline by means of a catabolic effect on muscle tissue (13,18). Nevertheless, no study was found in the literature, which measured the muscle performance of elderly women using an isokinetic dynamometer, an instrument considered the gold standard for measuring muscle strength, and plasma IL-6 levels.

The aim of the present study was to determine the association between plasma IL-6 levels and muscle strength and functional capacity measured in elderly women residing in the general community from the city of Belo Horizonte, Brazil.

Subjects and Methods

This was an observational, cross-sectional study that included women from the general community of the city of Belo Horizonte, MG, Brazil. The sample selection was achieved by convenience, with the elderly women being recruited by an active search and contacted in person or by telephone from social groups and health centers in Belo Horizonte. Participants were included if they were 60 years of age or older (according to the World Health Organization definition of "elderly" for people living in developing countries) (5,20), had a body mass index that classified them as neither malnourished (below 18.49 kg/m^2) nor overweight (over 30 kg/m^2) (21), and were capable of walking with or without the use of an assistive device. The exclusion criteria were: acute unstable disease or illness; amputation or fracture of the upper or lower limbs in the previous 6 months; presence of any neurological disease; use of anti-inflammatory immunosuppressant drugs; cognitive disturbance detected by the mini-mental state examination adapted for the use with the Brazilian population (22), and a positive result obtained on the Geriatric Depression Scale (23).

A socio-demographic questionnaire was administered to all participants by the same group of researchers. The initial sample size of 62 participants was defined based on hypothetical tests for the significance of a correlation coefficient, taking into account an effect size of 0.35, significance level of 0.05, non-directional test, and a discriminatory power of 0.8 (24).

Procedures

Sample characterization was made by the application of a socio-demographic questionnaire, containing items about participant health conditions, habits and life style.

In order to measure plasma IL-6 levels, 5 mL blood was withdrawn from the participants and immediately centrifuged at 1500 *g* to obtain plasma. Aliquots were removed under a laminar flow hood and stored at -70°C for 2 months.

IL-6 was measured in duplicate by enzyme-linked immunosorbent assay of the previously frozen specimens (microplates coated with a mouse monoclonal antibody against IL-6; High-Sensitivity Quantikine® HS Kits, R & D Systems, USA). Results are reported as the mean of the duplicate samples in pg/mL ± SD, following the guidelines established by the manufacturer (intra-assay coefficient of variance = 6.9-7.4%; interassay coefficient of variance = 9.6-6.5%; sensitivity = 0.016-0.110 pg/mL; mean = 0.039 pg/mL). All determinations were performed within one single assay.

Functional capacity was assessed using the Five-Times-Sit-to-Stand test (45 cm in height), and by Habitual and Maximal Gait Velocities. Participants were instructed to rise from and sit down on the chair with their arms crossed in front of their chests for five times. The results are reported as the time in seconds spent on the task. For the walking velocity at both normal and fast paces, participants were instructed to walk a distance of 10 m, initially at a comfortable pace and then at the maximum possible velocity (25). Two trials for each walking velocity were conducted. A chronometer (Q & Q Japan CBM Corp., Japan) was used to measure the time spent on each of the four trials. In order to avoid interference from the acceleration and deceleration phases of the gait trials (25), only the data obtained from 3 to 8 m were considered for statistical analysis. Results are reported as the mean of the two trials for each gait velocity in m/s ± SD. These tests were used because they have shown high reliability (intraclass correlation coefficient = 0.84-0.92) and are commonly used to assess function in elderly people (26). During the tests, all participants received the same instructions from the same examiner for all trials.

A Biodex Systems 3 Pro (Biodex Medical Systems, USA) isokinetic dynamometer was used to assess the muscle strength of the quadriceps and hamstring groups. The procedure was carried out according to manufacturer instructions. A 10-min walk was completed, as a lower-limb muscle warm-up, prior to assessment with the isokinetic dynamometer.

The back of the chair was positioned at 85°, with a knee range of motion of 85°, starting at a 90° knee flexion. Muscle performance was assessed on the dominant leg at the angular velocity of 60°/s, with a single series of 5 repetitions. Participants initially familiarized themselves with the instrument by practicing an average of three times at sub-maximum force. The torque produced by the leg was then measured to correct for the effect of gravity. Five trials were then conducted, during which the participants were verbally encouraged to move the arm of the dynamometer "as fast and with as much force as possible". These results are reported in newtons/meter (Nm) for peak torque and percentage in work per body weight for both knee movements.

Procedures were approved by the Ethics Committee of the Universidade Federal de Minas Gerais (ETIC 186/05). Informed written consent was obtained from all subjects prior to their participation and subjects' rights were protected at all times (World Medical Association Declaration of Helsinki).

Statistical analysis

Descriptive analysis was performed in order to characterize the sample according to the following variables: age, weight, height, body mass index, plasma IL-6. The normality hypothesis of the response variable (IL-6) was verified by means of the Shapiro-Wilk test and rejected at the significance level of 5%. Spearman's correlation coefficient was used to determine the association of IL-6 levels with muscle strength and functional performance. Age was categorized in decades, and the Kruskal-Wallis test was used to determine the relationship between IL-6 and age.

The response variable (IL-6) was categorized by distribution of the sample into tertiles. The Kruskal-Wallis test was used to assess the relationship between the categorized IL-6 and age and the quantitative variables (strength and functional capacity). A *post hoc* analysis was performed with the Dunn test for the significant Kruskal-Wallis tests. The level of significance was set at 0.05 and all analyses were performed using the statistical package SPSS, version 13.0.

Results

Of the 62 participants initially recruited, 5 were excluded after IL-6 measurement, 2 no longer wished to participate in the study and 3 had health problems (fracture of the femur, uterine cancer and hepatic cirrhosis). Therefore, 57 elderly women (71.21 ± 7.38 years old) completed the study. IL-6 levels did not follow normal distribution (1.95 ± 1.77 pg/mL). Sample characteristics are reported in Table 1.

The sample was subdivided into tertiles of IL-6 distribution for the analysis of the relationship between IL-6 levels and the variables described above. Tertiles included IL-6 values ranging from 0.00 to 1.00, from 1.01 to 2.25, and from 2.26 to 8.89 pg/mL.

There was no statistically significant difference (P = 0.330) in the distribution of IL-6 levels by age either for the overall sample (Table 2) or for the IL-6 subdivided into tertiles (P = 0.101; Table 3). A statistically significant difference was found among the IL-6 plasma concentrations divided in tertiles by the Kruskal-Wallis test (Table 3). In order to locate and identify intergroup difference, the Dunn test was performed to compare two independent groups and a statistical difference was shown between the first and third tertiles in the variable work for body weight in knee extensors.

Generally, there was a negative correlation between IL-6 plasma levels and muscle strength, indicating that greater muscle strength was associated with lower levels of IL-6. Statistically significant correlations were observed

Table 1. Characteristics of 57 elderly women who participated in this study.

	Mean ± SD	Median	Minimum	Maximum
Age (years)	71.2 ± 7.4	70.0	60.0	88.0
Weight (kg)	63.0 ± 10.5	61.7	39.6	85.1
Height (m)	1.5 ± 0.06	1.5	1.4	1.6
BMI (kg/m^2)	27.0 ± 4.2	27.0	18.3	38.0
IL-6 (pg/mL)	2.0 ± 1.8	1.4	0.0	8.9

BMI = body mass index; IL-6 = plasma interleukin-6.

Table 2. Comparison of plasma IL-6 levels among subjects of different ages.

Age group	N	Mean ± SD	Median	Kruskal-Wallis
60 to 69 years	26	1.9243 ± 2.0084	1.5690	0.330
70 to 79 years	22	1.6330 ± 1.1547	1.2655	
80 years or older	9	2.7940 ± 2.1914	2.2500	
Total	57	1.9491 ± 1.7723	1.3655	

Plasma interleukin-6 (IL-6) levels are reported as pg/mL.

Table 3. Plasma interleukin-6 (IL-6) levels classified in terms of tertile, age and muscle strength.

Independent variable	Tertile of IL-6 (pg/mL)						Kruskal-Wallis
	0.00 |–| 1.00	Median	1.00 –| 2.25	Median	2.25 –| 8.89	Median	
Age (years)	68.63 ± 7.11	67.0	71.16 ± 6.37	70.0	73.84 ± 8.00	74.0	0.1010
Work per body weight (%) 60°/s extension (J)	150.64 ± 31.36	141.5	146.82 ± 35.35	150.2	129.19 ± 28.56	120.5	0.0390*
Work per body weight (%) 60°/s flexion (J)	78.53 ± 27.22	77.7	70.14 ± 15.92	72.7	63.42 ± 16.59	61.9	0.2020

Data are reported as means ± SD and median. *P < 0.05 (Kruskal-Wallis test).

only between the work per body weight and IL-6 for both knee flexion (P = 0.047) and extension (P = 0.017; Table 4).

There was no significant correlation of plasma IL-6 with the performance of the Five-Times-Sit-to-Stand functional tests (r_s = 0.061; P = 0.658), habitual gait velocity (r_s = 0.241; P = 0.072) and maximal gait speed (r_s = 0.128; P = 0.343).

Discussion

In the present study, the increase in the levels of IL-6 showed a significant inverse correlation with muscle strength, as assessed using an isokinetic dynamometer in community-dwelling health elderly women.

A number of studies have demonstrated that chronically high IL-6 plasma levels in the elderly reduce muscle mass and strength (13,17,18,27) but not in community-dwelling health elderly women. This is the first Brazilian study to investigate whether IL-6 levels are associated with muscle performance and functional capacity in community-dwelling elderly women.

Psychological and social stress related to unsuccessful aging is a risk factor for immune system alterations (28). It has been demonstrated that depression, chronic stress, socioeconomic factors, hopelessness, hostility, and other factors are associated with elevation of circulating cytokine levels in adults and elderly people (29-31).

High IL-6 plasma levels have also been associated with a decline in maximum isometric force of the knee extensors in elderly women (13) as well as with a reduction in the strength of the lower limbs and manual grip strength (17).

After completion of the *post hoc* analysis using the Dunn test, it was noted that within the study sample there was a statistically significant difference in the association between the IL-6 plasma levels and muscular strength only between the first and third tertiles. This suggests that the levels of IL-6 show a stronger association with the decrease of strength when IL-6 is present in higher concentrations as reported in the literature (10,13).

Table 4. Associations between muscle strength indices and plasma IL-6 levels.

Muscle strength	IL-6 correlation	
	Spearman's coefficient	P
Peak torque		
Extension (N/m)	-0.188	0.162
Flexion (N/m)	-0.167	0.214
Total effort		
Extension (J)	-0.183	0.174
Flexion (J)	-0.142	0.291
Work per body weight		
Extension (%)	-0.315	0.017*
Flexion (%)	-0.265	0.047*

IL-6 = interleukin-6. *P < 0.05 (Spearman's correlation coefficient).

The muscular strength for the extension and flexion knee movements variable was represented by work by body weight. In older individuals, this parameter is extremely important because it is a measure of the individual's capacity to maintain muscular contraction during the entire excursion of the handle of the arm of the isokinetic dynamometer; this is represented in the graph as the area below the torque curve. The work by body weight corresponds to the actual force produced by the muscle during muscle contraction.

Barbieri et al. (17) observed that an increase in IL-6 concentration above the 1.73 pg/mL threshold was an independent predictor of decreased muscle strength. In the present study, the average value of IL-6 plasma concentration of the global sample was 1.95 pg/mL. The muscular strength of the knee extensors and flexors assessed by isokinetic analysis inversely correlated with this index, demonstrating that it is a sensitive parameter in detecting IL-6 plasma alterations. Use of the isokinetic dynamometer, an instrument considered the gold standard for such analyses, may have contributed to the greater sensitivity of the measurements.

No significant correlation was observed between the functional tests and IL-6 plasma levels. In a longitudinal study, alterations only occurred when IL-6 plasma levels surpassed 2.5 pg/mL (10). In another study, Ferrucci et al. (13) observed that an increase in IL-6 was predictive of severe limitation in walking and other mobility activities in elderly individuals who had IL-6 levels above 3.1 pg/mL. Because the mean IL-6 value for the sample in the present study was 1.95 pg/mL, it is possible that the plasma levels did not reach a sufficient threshold to influence the functional capacity of the participants. It is also possible that other functional tests with a greater degree of difficulty would be more sensitive in detecting potential functional problems.

There is evidence that plasma IL-6 levels and their harmful effects increase with age (10,11). Although the participants of the present study were of an average age of 71.21 ± 7.38 years, this phenomenon was not observed in the present study for either the overall sample or when the statistical analysis considered the IL-6 values subdivided into tertiles (N = 19 in each tertile). The participants of the present cross-sectional study had normal aging, shown by their good state of health, the fact that they were independent in the performance of ADLs and IADLs, and the fact that many of the participants (63%) performed regular and adequate, non-strenuous physical exercise (such as walking), besides house-work activity, and leisure activities. In normal aging, controlled chronic diseases with no negative impact in physical, psychosocial and mental functionality may coexist.

The literature reports that physically active elderly individuals exhibit low IL-6 levels. Physical exercise reduces IL-6 levels (32-39), and it is suggested as a strategy for the prevention and treatment of sarcopenia (4-6,8,9). Physical exercise performed with adequate parameters favors the release of IL-6 by the muscle (myokine) through an independent tumor necrosis factor alpha (TNF-α) pathway, as observed in a normal inflammatory cascade (32,33,35, 37,40). The IL-6 released by the muscle stimulates the appearance of other anti-inflammatory cytokines, such as IL-1 receptor antagonist (IL-1-RA) and IL-10, and inhibits the production of pro-inflammatory cytokines, such as TNF-α, and the entire cascade it triggers (35,37,40).

The present study has some limitations. First, a cross-sectional study only allows us to state the existence of an association between measures. Second, because 5 participants dropped out of the study, the final sample size of 57 elderly women may not have been sufficiently large to demonstrate other significant associations that have been described previously in the literature, such as the association of IL-6 levels with age, associations demonstrated using other functional tests, and other variables assessed using the isokinetic dynamometer test. Therefore, it is possible that a type II error may have occurred. Finally, because the present sample is composed of healthy elderly women who, for the most part, are functionally independent and without significant limitations or restrictions of their ADLs and IADLs, the possibility of generalizing these data to the general elderly female population is potentially reduced.

This study identified a significant negative correlation between strength of the quadriceps and hamstring muscles and IL-6 plasma levels in healthy elderly women residing in the general community. However, functional capacity, as assessed by tests measuring gait velocity and Five-Times-Sit-to-Stand test, was not correlated with IL-6 plasma levels. These results, together with previous research, emphasize the need for health professionals to recognize the silent, chronic action of inflammatory mediators on muscle tissue in the elderly and its impact on the function of this population.

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References

1. Gontijo B. Envelhecimento global: trinfo e desafio. In: Anonimous, *Envelhecimento ativo: uma política de saúde*. Brasília: Organização Pan-Americana de Saúde; 2005. p 8-12.
2. Jette AM. Assessing disability in studies on physical activity. *Am J Prev Med* 2003; 25: 122-128.
3. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci* 2004; 59A: 255-263.
4. Frontera WR, Bigard X. The benefits of strength training in the elderly. *Sci Sports* 2002; 17: 109-116.
5. Doherty TJ. Invited review: aging and sarcopenia. *J Appl*

Physiol 2003; 95: 1717-1727.
6. Macaluso A, De Vito G. Muscle strength, power and adaptations to resistance training in older people. *Eur J Appl Physiol* 2004; 91: 450-472.
7. Reeves ND, Narici MV, Maganaris CN. Myotendinous plasticity to ageing and resistance exercise in humans. *Exp Physiol* 2006; 91: 483-498.
8. Skelton DA, Greig CA, Davies JM, Young A. Strength, power and related functional ability of healthy people aged 65-89 years. *Age Ageing* 1994; 23: 371-377.
9. Pereira LS, Narciso FM, Oliveira DM, Coelho FM, Souza DD, Dias RC. Correlation between manual muscle strength and interleukin-6 (IL-6) plasma levels in elderly community-dwelling women. *Arch Gerontol Geriatr* 2008 (in press).
10. Ferrucci L, Harris TB, Guralnik JM, Tracy RP, Corti M-C, Cohen HJ, et al. Serum IL-6 level and the development of disability in older persons. *J Am Geriatr Soc* 1999; 47: 639-646.
11. Krabbe KS, Perdersen M, Bruunsgaard H. Inflammatory mediators in the elderly. *Exp Gerontol* 2004; 39: 687-699.
12. Ershler WB. Interleukin-6: a cytokine for gerontologists. *J Am Geriatr Soc* 1993; 41: 176-181.
13. Ferrucci L, Pennix BWJH, Volpato S, Harris TB, Banden-Roche K, Balfour J, et al. Change in muscle strength explains accelerated decline of physical function in older women with high interleukin-6 serum levels. *J Am Geriatr Soc* 2002; 50: 1947-1954.
14. Cappola AR, Xué QL, Ferrucci L, Guralnik JM, Volpato S, Fried LP. Insulin-like growth factor I and interleukin-6 contribute synergistically to disability and mortality in older women. *J Clin Endocrinol Metab* 2003; 88: 2019-2025.
15. Roubenoff R, Parise H, Payette HA, Abad LW, D'Agostino R, Jacques PF, et al. Cytokines, insulin-like growth factor 1, sarcopenia, and mortality in very old community-dwelling men and women: The Framingham Heart Study. *Am J Med* 2003; 115: 429-435.
16. Pennix BWJH, Kritchevsky SB, Newman AB, Nicklas BJ, Simonsick EM, Rubin S, et al. Inflammatory markers and incident mobility limitation in the elderly. *J Am Geriatr Soc* 2004; 52: 1105-1113.
17. Barbieri M, Ferrucci LR, Ragno E, Corsi A, Bandinelli S, Bonafè M, et al. Chronic inflammation and the effect of IGF-I on muscle strength and power in older persons. *Am J Physiol Endocrinol Metab* 2003; 284: E481-E487.
18. Schaap LA, Pluijm SMF, Deeg DJH, Visser M. Inflammatory markers and loss of muscle mass (sarcopenia) and strength. *Am J Med* 2006; 119: 526e9-526e17.
19. Haddad F, Zaldivar F, Cooper DM, Adanis GR. IL-6-induced skeletal muscle atrophy. *J Appl Physiol* 2005; 98: 911-917.
20. United Nations. Problems of the elderly and the aged. Draft programme and arrangements for the World Assembly on the elderly: Report of the Secretary General. New York: United Nations; 1980.
21. World Health Organization Physical Status. *The use and interpretation of antropometry*. Geneve: WHO; 1995.
22. Bertolucci M. O mini-exame do estado mental em uma população geral. *Arq Neuropsiquiatr* 1994; 52: 1-7.
23. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* 1982; 17: 37-49.
24. Cohen J. *Statistical power analysis for the behavioral sciences*. 2nd edn. New York: Psychology Press Publication; 1988.
25. Bean JF, Kiely DK, Herman S, Leveille SG, Mizer K, Frontera WR. The relationship between leg power and physical performance in mobility-limited older people. *J Am Geriatr Soc* 2002; 50: 461-467.
26. VanSwearingen JM, Brach JS. Making geriatric assessment work: selecting useful measures. *Phys Ther* 2001; 81: 1233-1252.
27. Schrager MA, Metter EJ, Simonsick E, Ble A, Bandinelli S, Lauretani F, et al. Sarcopenic obesity and inflammation in the InCHIANTI study. *J Appl Physiol* 2007; 102: 919-925.
28. Luz C, Dornelles F, Preissler T, Collaziol D, da Cruz IM, Bauer ME. Impact of psychological and endocrine factors on cytokine production of healthy elderly people. *Mech Ageing Dev* 2003; 124: 887-895.
29. Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, Atkinson C, Malarkey WB, Glaser R. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proc Natl Acad Sci U S A* 2003; 100: 9090-9095.
30. Miller GE, Freedland KE, Carney RM, Stetler CA, Banks WA. Cynical hostility, depressive symptoms, and the expression of inflammatory risk markers for coronary heart disease. *J Behav Med* 2003; 26: 501-515.
31. Sjogren E, Leanderson P, Kristenson M, Ernerudh J. Interleukin-6 levels in relation to psychosocial factors: studies on serum, saliva, and *in vitro* production by blood mononuclear cells. *Brain Behav Immun* 2006; 20: 270-278.
32. Pedersen BK, Steensberg A, Schjerling P. Muscle-derived interleukin-6: possible biological effects. *J Physiol* 2001; 536: 329-337.
33. Febbraio MA, Pedersen BK. Muscle-derived interleukin-6: mechanisms for activation and possible biological roles. *FASEB J* 2002; 16: 1335-1347.
34. Reuben DB, Judd-Hamilton L, Harris TB, Seeman TE. The associations between physical activity and inflammatory markers in high-functioning older persons: MacArthur studies of successful aging. *J Am Geriatr Soc* 2003; 51: 1125-1130.
35. Pedersen BK, Steensberg A, Fischer C, Keller C, Keller P, Plomgaard P, et al. Searching for the exercise factor: is IL-6 a candidate? *J Muscle Res Cell Motil* 2003; 24: 113-119.
36. Steinacker JM, Lormes W, Reissnecker S, Liu Y. New aspects of the hormone and cytokine response to training. *Eur J Appl Physiol* 2004; 91: 382-391.
37. Kohut ML, McCann DA, Russell DW, Konopka DN, Cunnick JE, Franke WD, et al. Aerobic exercise, but not flexibility/resistance exercise, reduces serum IL-18, CRP, and IL-6 independent of beta-blockers, BMI, and psychosocial factors in older adults. *Brain Behav Immun* 2006; 20: 201-209.
38. Fischer CP, Bernsten A, Perstrup B, Eskildsen P, Pedersen BK. Plama levels of interleukin-6 and C-reative protein are associated with physical inactivity independent of obesity. *Scand J Med Sci Sports* 2007; 17: 580-587.
39. Portegijs E, Rantanen T, Sipila S, Laukkanen P, Heikkinen E. Physical activity compensates for increased mortality risk among older people with poor muscle strength. *Scand J Med Sci Sports* 2007; 17: 473-479.
40. Petersen AMW, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol* 2005; 98: 1154-1162.