The Journal of Physical Therapy Science

S P T S

Original Article

# Effect of exercise therapy on cytokine secretion in the saliva of bedridden patients

Hidemasa Iki, RPT, MS[1], Shunji Sawa, OTR, PhD[1], Toshio Teranishi, RPT, PhD[1], Masao Tomita, RPT[1], Kazuhiro Nishii, MT, PhD[1], Kouji Yamada, MT, PhD[1]*

[1] Graduate School of Health Sciences, Fujita Health University: 1-98 Kutsukake-cho, Toyoake, Aichi 470-1192, Japan

**Abstract.** [Purpose] The number of bedridden patients requiring nursing care in Japan has increased sharply in recent years because of its aging population and advances in medical care and has become a major social issue. Because bedridden patients are susceptible to nursing and healthcare-associated pneumonia, it is very important to improve their immunocompetence. Therefore, the effect of exercise therapy on stimulation of cytokine secretion in the saliva of bedridden patients was investigated. [Subjects and Methods] The subjects of this study were bedridden patients admitted to nursing care facilities. They were instructed to perform active assistive movement in the supine and sitting positions, with vital signs used as an index of the exercise load. Thirty-five patients fulfilled the inclusion criteria, which included cerebrovascular disease as the main cause of being bedridden and at least 6 months since onset. Interleukins were measured by enzyme-linked immunosorbent assay as immune mediators. [Results] Vital signs improved significantly after therapeutic exercise intervention, and the IL-6, IL-8, IL-15, and IL-17 levels also increased significantly after the intervention. [Conclusion] The results demonstrated that measurement of saliva samples may offer a safe minimally invasive method of measuring immune response in bedridden patients. This study suggests that exercise therapy may hold promise as an effective means of improving immunity in bedridden patients and may contribute to preventing aspiration pneumonia and promoting spontaneous recovery.
**Key words:** Bedridden patients, Interleukin, Nursing and healthcare-associated pneumonia (NHCAP)

*(This article was submitted Apr. 22, 2016, and was accepted Jun. 27, 2016)*

## INTRODUCTION

The Japanese government is endeavoring to reduce the gap between the average lifespan and healthy life expectancy. Every year, however, the number of people certified as requiring the highest level of care under the public long-term care insurance program continues to increase. In particular, a large number of residents of institutions are bed-confined. A survey of the causes of death of bedridden patients found that 68.1% died of pneumonia[1]. As a consequence, pneumonia overtook cerebrovascular disease in 2011 to become the third most common cause of death in Japan. Guidelines on nursing and healthcare-associated pneumonia (NHCAP) were formulated in 2011 by the Japanese Respiratory Society[2]. According to these guidelines, bedridden patients are defined as "individuals in convalescent wards of general hospitals or residents of long-term care facilities" or "elderly individuals requiring long-term care." In many cases, the mechanism whereby NHCAP develops is aspiration pneumonia[3]. Preventing aspiration pneumonia in bedridden patients and promoting their recovery from this condition is thus an important challenge.

Aspiration pneumonia mainly develops as a result of infection with oral bacteria[4], and preventive measures include three important factors: eliminating sources of infection, blocking routes of infection, and improving host immunocompetence[5]. Oral care is the main method of eliminating sources of infection, while eating and swallowing rehabilitation is the major

means of blocking the route of infection; both of these have been shown to be effective[5]. With regard to improving host immunocompetence, however, pneumococcus vaccination is effective, but the benefit only lasts about five years. Side effects from revaccination have also been reported, and vaccination alone may be inadequate to prevent infection[6, 7].

We focused on exercise therapy as one strategy for dealing with this issue. Studies have shown that exercise generates an immune response[8–10], and there are many reports indicating that a moderate exercise load improves immunity in healthy individuals. Among the changes improving immunity, the cytokines produced by muscle cells as a result of the contraction of hypertrophic skeletal muscle, known as myokines, are attracting particular attention[11]. The cytokines expressed as myokines include several interleukins (ILs), such as IL-6, IL-8, IL-10, and IL-15[12–15]. IL-6 stimulates the production of anti-inflammatory cytokines, such as IL-1ra and IL-10, and suppresses tumor necrosis factor alpha (TNF-α) production in humans[16, 17].

In this study, it was hypothesized that exercise therapy may improve immune function in bedridden patients, which would help prevent aspiration pneumonia and promote spontaneous recovery. In addition to the previously reported myokines IL-6, IL-8, IL-10, and IL-15, we also investigated changes in the expression of the cytokines IL-17 and IL-22 in saliva; although there have been no reports of expression of the latter two as myokines, they have been implicated in the prevention of aspiration pneumonia and the promotion of recovery[18, 19].

## SUBJECTS AND METHODS

The study subjects were bed-confined residents of a long-term care facility. They met the following conditions: (1) The main cause of being bed-confined was cerebrovascular disease, and at least six months had passed since onset. (2) Their score on the Functional Independence Measure for the need for assistance with activities of daily living was 1 point for all motor dimensions. (3) Nutritional management was via tube feeding. (4) They were out of bed for less than 14 hours a week.

This study was approved by the Ethical Review Board for Epidemiological and Clinical Studies of Fujita Health University (approval no. 13-206). In implementation of the study, it was difficult to obtain informed consent from the study subjects owing to their physical and cognitive functional states. Informed consent in accordance with the regulations of the Ethical Review Board was therefore obtained from a representative of the subject (such as a family member, relative, or guarantor) and the facility's medical director and nursing director, who signed the consent form.

The exercise therapy intervention method used comprised active assistive movement, consisting of flexion and extension of the arms and legs to the greatest extent possible in the sitting and supine positions. The joint range of motion for each limb was measured, and active assistive movement up to the limit of the range of motion was performed. Each limb was flexed and extended 100 times; this exercise program was carried out for 10 minutes in the supine position followed by 10 minutes in the sitting position, for a total of approximately 20 minutes. The time at which the exercise therapy was carried out was set at around 9 a.m., which is when the measurements would be least affected by care activities.

Exercise load was measured in terms of variations in vital signs, with measurements covering blood pressure (systolic), pulse rate, and respiration rate. Measurements were made before the start of exercise, after 5 minutes of exercise while sitting, after 5 minutes of exercise while supine, and 5 minutes after the end of exercise.

Saliva samples were collected by inserting a cotton swab under the tongue (Salimetrics Children's Swab, Salimetrics LLC), with a thread attached to prevent aspiration, and retrieving it after at least 1 minute. After having gathered it, entered the freezer of −30 °C, and the sample froze up and saved it. When measurements were made, the samples were allowed to thaw naturally at room temperature, they were centrifuged at 3,000 rpm for 5 minutes, and the supernatant was then used for measurements. Saliva was sampled before the intervention (0 h) and 30 minutes, 1 hour, and 3 hours after the end of the intervention (0.5 h, 1 h, and 3 h).

The previously reported myokines IL-6, IL-8, and IL-10 were measured by using R&D Systems Quantikine enzyme-linked immunosorbent assay (ELISA) kits (Quantikine Human IL-6 D6050, CXCL8/IL-8 D8000C, and IL-10 D1000B, R&D Systems, Inc., Minneapolis, MN, USA), and IL-15 was measured using an abcam (Human ELISA kit ab100554, abcam Inc., Cambridge, MN, USA). IL-17 and IL-22 have not previously been reported as myokines but are cytokines that have been implicated in activity against *Klebsiella pneumoniae*, one of the causative pathogens of aspiration pneumonia[18, 20]. They were also measured by using abcam ELISA kits (Human ELISA kits ab119535 and ab119543), with all measurements performed according to the specified method for the kit concerned.

Statistical comparisons of three or more variables were carried out by performing repeated measures analysis of variance of a single factor. Mauchly's test of sphericity was carried out in the case of a normal distribution; if analysis of variance indicated a significant difference, a paired t-test was carried out by using Bonferroni's method. If the distribution was not normal, Friedman's test was used; if a significant difference was found, a Wilcoxon test was carried out by using Bonferroni's method. For comparisons of two variables, a t-test was used in the case of a normal distribution; if the distribution was not normal, Wilcoxon's signed rank test was used. The statistical software used was IBM SPSS Statistics 22.0 (IBM Japan, Ltd.), and $p < 0.05$ was regarded as significant. Values more than two standard deviations from the mean were excluded.

# RESULTS

The following cytokines known to be myokines were measured: IL-6, IL-8, IL-10, and IL-15. There were 21 subjects, and their mean age was $87.2 \pm 6.5$ years; the main reason for becoming bed-confined was cerebral infarction in 15 cases, cerebral haemorrhage in 4 cases, and hydrocephalus in 2 cases. The mean time since onset was $31.2 \pm 16.7$ months, and the mean time spent out of bed was $3.9 \pm 3.9$ hours per week (Table 1).

In terms of variation in vital signs, systolic blood pressure was $116.0 \pm 21.4$ mmHg before the start of exercise, $131.2 \pm 19.5$ mmHg after 5 minutes of exercise while sitting, $123.5 \pm 21.8$ mmHg after 5 minutes of exercise while supine, and $115.4 \pm 19.3$ mmHg 5 minutes after the end of exercise. There were significant differences between the values after 5 minutes of exercise while sitting and those before and after exercise and also between the values after 5 minutes of exercise while supine and after exercise ($p<0.05$). The pulse rate was $72.6 \pm 10.8$ bpm before exercise, $81.1 \pm 14.3$ bpm after 5 minutes of exercise while sitting, $74.8 \pm 9.5$ bpm after 5 minutes of exercise while supine, and $71.5 \pm 10.0$ bpm 5 minutes after the end of exercise. There was a significant difference between the values after 5 minutes of exercise while sitting and before and after exercise ($p<0.05$). The respiration rate was $18.9 \pm 4.8$ bpm before exercise, $23.4 \pm 6.4$ bpm after 5 minutes of exercise while sitting, $21.3 \pm 5.1$ bpm after 5 minutes of exercise while supine, and $19.1 \pm 4.6$ bpm 5 minutes after the end of exercise (Table 2). There were significant differences between the values after 5 minutes of exercise while sitting and after 5 minutes of exercise while supine compared with those before and after exercise ($p<0.05$, $p<0.001$, respectively).

The levels of IL-6, IL-8, and IL-15 in saliva were all changed at each time point after exercise (0.5 h, 1 h, and 3 h) compared with before exercise. The concentrations varied between individuals; however, a comparison of mean relative values was done with the value at 0 h taken as 1 (Table 3). As the value after exercise tended to increase compared with the value at 0 h, the frequency with which the value peaked at each time point was compared to investigate differences in the timing of IL expression (Table 4). The maximum values of IL-6, IL-8, and IL-15 were apparent at 0 h in four patients each. There was variation in the frequency with which the maximum values appeared before exercise and at 0.5 h, 1 h, and 3 h after exercise. A comparison of maximum values and values at 0 h showed that the maximum value was significantly higher after exercise compared with that at 0 h for IL-6, IL-8, and IL-15 ($p<0.05$) (Table 5). IL-10 was not detected (N.D.) at all.

The cytokines IL-17 and IL-22, which have been implicated in the prevention of pneumonia, were also measured. There were 14 subjects (mean age $86.8 \pm 7.3$ years); the main reason for becoming bed-confined was cerebral infarction in 9 cases, cerebral haemorrhage in 3 cases, and hydrocephalus in 2 cases. The mean time since onset was $29.9 \pm 11.9$ months, and the mean time spent out of bed was $3.5 \pm 3.5$ hours per week (Table 6).

The concentration of IL-17 changed after exercise compared with that at 0 h. A comparison of relative values, with the value at 0 h taken as 1, showed that the concentration was $3.1 \pm 2.4$ at 0.5 h after exercise, $4.1 \pm 3.4$ at 1 h after exercise, and

**Table 1.** Demographics of subjects for known myokines

| Demographics | |
|---|---|
| Total subjects (n) | 21 |
| Age (years) | $87.2 \pm 6.5$ |
| Etiology (n) | Cerebral infarction, 15 |
| | Cerebral haemorrhage, 4 |
| | Hydrocephalus, 2 |
| Time since onset (months) | $31.2 \pm 16.7$ |
| Time out of bed (hours/week) | $3.9 \pm 3.9$ |

**Table 3.** Changes in the relative levels of three kinds of IL

| | IL-6 | IL-8 | IL-15 |
|---|---|---|---|
| 0 h | 1.0 | 1.0 | 1.0 |
| 0.5 h | $1.5 \pm 0.9$ | $1.1 \pm 0.4$ | $1.5 \pm 1.2$ |
| 1 h | $1.3 \pm 0.9$ | $1.2 \pm 0.9$ | $1.3 \pm 1.0$ |
| 3 h | $1.7 \pm 1.3$ | $1.2 \pm 0.6$ | $1.5 \pm 1.1$ |

0 h, before the start of exercise; 0.5 h, 0.5 h after the end of exercise; 1 h after the end of exercise; 3 h after the end of exercise

**Table 2.** Changes in vital signs

| | Blood pressure (mmHg) | Pulse rate (bpm) | Respiration rate (bpm) |
|---|---|---|---|
| BE | $116.0 \pm 21.4$ | $72.6 \pm 10.8$ | $18.9 \pm 4.8$ |
| AEsi | $131.2 \pm 19.5^{*,\,**}$ | $81.1 \pm 14.3^{*,\,**}$ | $23.4 \pm 6.4^{***,\,****}$ |
| AEsu | $123.5 \pm 21.8^{**}$ | $74.8 \pm 9.5$ | $21.3 \pm 5.1^{*,\,****}$ |
| AE | $115.4 \pm 19.3$ | $71.5 \pm 10.0$ | $19.1 \pm 4.6$ |

BE: before the start of exercise therapy; AE: after the end of exercise; AEsi: after 5 minutes of exercise therapy while sitting; AEsu: after 5 minutes of exercise therapy while supine
*Significant ($p<0.05$) difference between BE and Aesi or Aesu
**Significant ($p<0.05$) difference between AE and Aesi or Aesu
***Significant ($p<0.001$) difference between BE and Aesi or Aesu
****Significant ($p<0.001$) difference between AE and Aesi or Aesu

2.6 ± 2.5 at 3 h after exercise showing a tendency to increase after exercise (Table 7). A comparison of the maximum value relative to the value at 0 h showed that the maximum value after exercise was significantly elevated at (5.2 ± 2.9; p<0.001; Table 8). IL-22 was not detected (N.D.) at all.

## DISCUSSION

Vital signs changed during exercise, becoming significantly more improved than when subjects were at rest before and after exercise. This improvement due to exercise therapy was particularly marked when the subjects were sitting. The subjects in this study passed almost their entire time lying down in bed, spending an average of only 3.9 ± 3.9 hours per week out of bed. Patients whose capacity for cardiopulmonary endurance had declined owing to disuse syndrome may have experienced exercise stress as a result of being placed in the sitting position.

Numerous studies have investigated the immune response generated by exercise in humans by using serum, plasma, or muscle biopsy[8, 13, 21]. The samples required for these methods, however, cannot be collected by a physiotherapist, and the invasive nature of sample collection also entails ethical issues. In this study, we used saliva samples, which are easy to collect noninvasively and safely. Byrne et al. compared measurements of IL-2 and IL-12 in serum and saliva from young people, and reported that measurement in saliva is feasible[22]. As this is safe for the patient and samples can be collected noninvasively, this method could potentially be used by a wide range of healthcare professionals to evaluate response to treatment, and this is a highly significant finding.

With respect to myokines[11], which are produced in response to skeletal muscle stimulation, Pedersen et al. found that the IL response was influenced by the intensity of exercise and that the contraction of skeletal muscle itself is an important source of supply of IL in blood[23]. Most of the subjects of our study, however, were bedridden patients who had difficulty in communication, and it was difficult to ask them to engage in muscle contraction by means of continuous active exercise. Active assistive movement was therefore used as the stimulus in exercise therapy. Myoelectric activity in passive movement is believed to occur because of the contraction of the shortening muscle in the stretch reflex of the antagonist muscle, which causes muscle activity in active assistive movement[24, 25]. Petersen et al. carried out in vitro experiments and found that cytokine expression was evident when muscle cells were stimulated with negative pressure[26]. This suggests that even when little voluntary contraction can be expected, as in the case for bedridden patients, stimulating muscles by extending them may

**Table 4.** Comparison of frequency of appearance of maximum IL values

|  | IL-6 | IL-8 | IL-15 |
|---|---|---|---|
| 0 h (n) | 4 | 4 | 4 |
| 0.5 h (n) | 6 | 2 | 5 |
| 1 h (n) | 3 | 5 | 5 |
| 3 h (n) | 8 | 3 | 5 |

**Table 5.** Comparison of maximum values and values at 0 h

|  | IL-6 | IL-8 | IL-15 |
|---|---|---|---|
| 0 h | 1 | 1 | 1 |
| Maximum values | 2.7 ± 2.4* | 1.2 ± 0.3* | 2.1 ± 1.4* |

*p<0.05

**Table 6.** Demographics of subjects for IL-17 and IL-22

| Demographics | |
|---|---|
| Total subjects (n) | 14 |
| Age (years) | 86.8 ± 7.3 |
| Etiology (n) | Cerebral infarction, 9 Cerebral haemorrhage, 3 Hydrocephalus, 2 |
| Time since onset (months) | 29.9 ± 11.9 |
| Time out of bed (hours/week) | 3.5 ± 3.5 |

**Table 7.** Changes in the relative levels of IL-17

|  | IL-17 |
|---|---|
| 0 h | 1.0 |
| 0.5 h | 3.1 ± 2.4 |
| 1 h | 4.1 ± 3.4 |
| 3 h | 2.6 ± 2.5 |

0 h, before the start of exercise; 0.5 h, 0.5 h after the end of exercise; 1 h after the end of exercise; 3 h after the end of exercise

**Table 8.** Comparison of maximum values and values at 0 h

|  | IL-17 |
|---|---|
| 0 h | 1 |
| Maximum values | 5.2 ± 2.9* |

*p<0.001

induce cytokine expression. This suggests that it may be important to carry out active assistive movements up to the limit of the range of motion in order to induce cytokine expression in bedridden patients by means of exercise therapy.

Comparatively large amounts of IL-6 and IL-15 mRNA are reportedly produced in skeletal muscles[27]. In the serum, IL-6 expression was found to persist for several hours after exercise during a month of strenuous exercise[28]. Additionally, while serum IL-8 levels did not change following mild exercise, increases were observed following highly stressful full-body exercise, such as long-distance or treadmill running[29]. The hypothesis that muscular damage is involved in IL production was based on these reports. Moreover, a study reported no change in serum IL-15 levels immediately after exercise[30], while another study reported an increase in IL-15[14]. In the study that did not observe increased serum levels immediately after exercise, an increase may have occurred several hours later, but this data was not available. In all of these reports, the secretion dynamics were examined following relatively strenuous exercise, and measurements were performed over a wide time range, from immediately after exercise to several hours later. Further, some of these reports performed measurements using mRNA from skeletal muscle, while others used serum. The present study is different because exercise stimulation was applied to bedridden patients who got nearly no daily exercise. No other studies have examined these subjects. Moreover, there have been no previous studies examining the chronological changes in saliva samples after exercise stimulation. Because bedridden patients generally do not exercise, an exercise intervention in such subjects is a stimulating factor that excludes all other factors. The mechanism by which this is reflected in saliva is unknown. No significant differences were observed between pre-exercise levels and mean values at 0.5, 1, and 3 h after exercise (Table 3). The maximum values obtained after exercise were significantly different from the pre-exercise values (Table 5). This suggests the influence of a number of factors related to exercise stimulation over this period. For the mean values, no individual differences were observed in factors related to the time until expression, such as age, muscle mass, or expression levels of cytokine-associated factors. However, the results revealed individual differences between post-exercise maximum values and pre-exercise values. This suggests that exercise therapy may increase the levels of IL-6, IL-8, and IL-15.

This research indicated that exercise therapy may elevated the levels of IL-6, IL-8, and IL-15 in the saliva of bedridden patients. IL-6 suppresses the production of the inflammatory cytokine TNF-$\alpha$[16]. IL-8 is produced at sites of inflammation and is implicated in neutrophil migration[31]. IL-15 has multifaceted immunological characteristics and has been shown to exert anti-inflammatory actions such as bacterial clearance during infection[32, 33]. Exercise therapy for bedridden patients thus induces the production of cytokines with anti-inflammatory actions, as well as those implicated in bacterial clearance during infection. As the immunocompetence of bedridden patients is known to decline, this indicates the significance of exercise therapy for such patients. *K. pneumoniae* is one of the causative pathogens of aspiration pneumonia[20]. In IL-17RA knockout mice, neutrophil infiltration was delayed in comparison to that in wild-type mice, raising the mortality rate[18] and suggesting that IL-17 may be involved with *K. pneumoniae*. In the present study, we found that exercise therapy elevated the expression of IL-17 in the saliva of bedridden patients, although it is unclear whether this effect was direct or indirect. This suggests that exercise therapy may be an effective stimulation method that helps to prevent aspiration pneumonia and promote spontaneous recovery in bedridden patients.

Because IL-10 and IL-22 have been reported to be expressed in muscles (called myokines), we attempted to measure their levels; however, they were not detected. While sharp increases after marathons have been reported[34], other studies observed nearly no expression. We believe it is more likely that myokines are expressed to maintain homeostasis during the inflammatory response. Another reason that expression was not observed in the present study may be insufficient intensity or duration of stimulation. Moreover, because saliva samples were used, it is possible that the maximum values were not reached within the measurement time frame (3 h post stimulation) owing to a post stimulation time lag.

The mechanism for the elevation of IL expression in saliva seen in this study may include the involvement of myokines, but as this factor was not confirmed directly by muscle biopsy, it cannot be said that elevation was due to skeletal muscle stimulation. The fact that exercise therapy did lead to the elevation of cytokines in bedridden patients, however, does indicate that the effect is of significance.

# REFERENCES

1) Kosaka Y, Nakagawa-Satoh T, Ohrui T, et al.: Survival period after tube feeding in bedridden older patients. Geriatr Gerontol Int, 2012, 12: 317–321. [Medline] [CrossRef]

2) Teramoto S, Fukuchi Y, Sasaki H, et al. Japanese Study Group on Aspiration Pulmonary Disease: High incidence of aspiration pneumonia in community- and hospital-acquired pneumonia in hospitalized patients: a multicenter, prospective study in Japan. J Am Geriatr Soc, 2008, 56: 577–579. [Medline] [CrossRef]

3) Kikuchi R, Watabe N, Konno T, et al.: High incidence of silent aspiration in elderly patients with community-acquired pneumonia. Am J Respir Crit Care Med, 1994, 150: 251–253. [Medline] [CrossRef]

4) Shindo Y, Sato S, Maruyama E, et al.: Health-care-associated pneumonia among hospitalized patients in a Japanese community hospital. Chest, 2009, 135: 633–640. [Medline] [CrossRef]

5) Yoneyama T, Yoshida M, Ohrui T, et al. Oral Care Working Group: Oral care reduces pneumonia in older patients in nursing homes. J Am Geriatr Soc, 2002, 50: 430–433. [Medline] [CrossRef]

6) Maruyama T, Taguchi O, Niederman MS, et al.: Efficacy of 23-valent pneumococcal vaccine in preventing pneumonia and improving survival in nursing home

residents: double blind, randomised and placebo controlled trial. BMJ, 2010, 340: c1004. [Medline] [CrossRef]

7) Butler JC, Breiman RF, Campbell JF, et al.: Pneumococcal polysaccharide vaccine efficacy. An evaluation of current recommendations. JAMA, 1993, 270: 1826–1831. [Medline] [CrossRef]

8) Kohut ML, Boehm GW, Moynihan JA: Moderate exercise is associated with enhanced antigen-specific cytokine, but not IgM antibody production in aged mice. Mech Ageing Dev, 2001, 122: 1135–1150. [Medline] [CrossRef]

9) Crist DM, Mackinnon LT, Thompson RF, et al.: Physical exercise increases natural cellular-mediated tumor cytotoxicity in elderly women. Gerontology, 1989, 35: 66–71. [Medline] [CrossRef]

10) Shore S, Shinkai S, Rhind S, et al.: Immune responses to training: how critical is training volume? J Sports Med Phys Fitness, 1999, 39: 1–11. [Medline]

11) Pedersen BK, Akerström TC, Nielsen AR, et al.: Role of myokines in exercise and metabolism. J Appl Physiol 1985, 2007, 103: 1093–1098. [Medline] [CrossRef]

12) Ostrowski K, Rohde T, Zacho M, et al.: Evidence that interleukin-6 is produced in human skeletal muscle during prolonged running. J Physiol, 1998, 508: 949–953. [Medline] [CrossRef]

13) Akerstrom T, Steensberg A, Keller P, et al.: Exercise induces interleukin-8 expression in human skeletal muscle. J Physiol, 2005, 563: 507–516. [Medline] [CrossRef]

14) Riechman SE, Balasekaran G, Roth SM, et al.: Association of interleukin-15 protein and interleukin-15 receptor genetic variation with resistance exercise training responses. J Appl Physiol 1985, 2004, 97: 2214–2219. [Medline] [CrossRef]

15) Happel KI, Dubin PJ, Zheng M, et al.: Divergent roles of IL-23 and IL-12 in host defense against Klebsiella pneumoniae. J Exp Med, 2005, 202: 761–769. [Medline] [CrossRef]

16) Petersen AM, Pedersen BK: The anti-inflammatory effect of exercise. J Appl Physiol 1985, 2005, 98: 1154–1162. [Medline] [CrossRef]

17) Starkie R, Ostrowski SR, Jauffred S, et al.: Exercise and IL-6 infusion inhibit endotoxin-induced TNF-α production in humans. FASEB J, 2003, 17: 884–886. [Medline]

18) Ye P, Rodriguez FH, Kanaly S, et al.: Requirement of interleukin 17 receptor signaling for lung CXC chemokine and granulocyte colony-stimulating factor expression, neutrophil recruitment, and host defense. J Exp Med, 2001, 194: 519–527. [Medline] [CrossRef]

19) Aujla SJ, Chan YR, Zheng M, et al.: IL-22 mediates mucosal host defense against Gram-negative bacterial pneumonia. Nat Med, 2008, 14: 275–281. [Medline] [CrossRef]

20) Sumi Y, Miura H, Sunakawa M, et al.: Colonization of denture plaque by respiratory pathogens in dependent elderly. Gerodontology, 2002, 19: 25–29. [Medline] [CrossRef]

21) Keller C, Steensberg A, Hansen AK, et al.: Effect of exercise, training, and glycogen availability on IL-6 receptor expression in human skeletal muscle. J Appl Physiol 1985, 2005, 99: 2075–2079. [Medline] [CrossRef]

22) Byrne ML, O'Brien-Simpson NM, Reynolds EC, et al.: Acute phase protein and cytokine levels in serum and saliva: a comparison of detectable levels and correlations in a depressed and healthy adolescent sample. Brain Behav Immun, 2013, 34: 164–175. [Medline] [CrossRef]

23) Pedersen BK, Febbraio MA: Muscle as an endocrine organ: focus on muscle-derived interleukin-6. Physiol Rev, 2008, 88: 1379–1406. [Medline] [CrossRef]

24) Nakamura R: Postural dependence of reaction time in normal subjects and patients with focal brain lesions. Appl Neurophysiol, 1976–1977-1977/1977, 39: 321–325. [Medline]

25) Nakamura R, Hosokawa T, Kitahara T: Reaction time of elbow flexion during passive movements. Scand J Rehabil Med, 1982, 14: 145–148. [Medline]

26) Peterson JM, Pizza FX: Cytokines derived from cultured skeletal muscle cells after mechanical strain promote neutrophil chemotaxis in vitro. J Appl Physiol 1985, 2009, 106: 130–137. [Medline] [CrossRef]

27) Nieman DC, Davis JM, Henson DA, et al.: Carbohydrate ingestion influences skeletal muscle cytokine mRNA and plasma cytokine levels after a 3-h run. J Appl Physiol 1985, 2003, 94: 1917–1925. [Medline] [CrossRef]

28) Pedersen BK, Tvede N, Christensen LD, et al.: Natural killer cell activity in peripheral blood of highly trained and untrained persons. Int J Sports Med, 1989, 10: 129–131. [Medline] [CrossRef]

29) Pedersen BK, Hoffman-Goetz L: Exercise and the immune system: regulation, integration, and adaptation. Physiol Rev, 2000, 80: 1055–1081. [Medline]

30) Ostrowski K, Hermann C, Bangash A, et al.: A trauma-like elevation of plasma cytokines in humans in response to treadmill running. J Physiol, 1998, 513: 889–894. [Medline] [CrossRef]

31) Van Snick J: Interleukin-6: an overview. Annu Rev Immunol, 1990, 8: 253–278. [Medline] [CrossRef]

32) Fehniger TA, Suzuki K, Ponnappan A, et al.: Fatal leukemia in interleukin 15 transgenic mice follows early expansions in natural killer and memory phenotype CD8+ T cells. J Exp Med, 2001, 193: 219–231. [Medline] [CrossRef]

33) Ohteki T, Suzue K, Maki C, et al.: Critical role of IL-15-IL-15R for antigen-presenting cell functions in the innate immune response. Nat Immunol, 2001, 2: 1138–1143. [Medline] [CrossRef]

34) Ostrowski K, Rohde T, Asp S, et al.: Pro- and anti-inflammatory cytokine balance in strenuous exercise in humans. J Physiol, 1999, 515: 287–291. [Medline] [CrossRef]