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Review of Research Progress on the Effect of Exercise on Vaccine Immune Response

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Abstract: *Vaccine, as a preventive biological agent, has been widely used. However, due to age, chronic diseases, malnutrition, improper lifestyle and other factors, the immunological efficacy of vaccine is often not up to people's expectations. Research on how to improve vaccine effectiveness has important clinical implications. Exercise, as a behavioral adjuvant, has been shown to play an adjunct role in the immune response to many vaccines. In this paper, the benefits of exercise in different vaccine types are discussed, and the main factors are further analyzed. The results showed that the strengthening effect of exercise might be related to the type of vaccine, and was affected by age, sex and exercise form.*

Keywords: *Exercise; Vaccine; Immune response*

1. Introduction

A vaccine is a biological agent that provides immunity to a specific disease, usually made from a weakened or destroyed pathogen. This agent causes the body's immune system to recognize it, destroy it, and remember it. When the disease-causing agent re-enters the body, the immune system can more easily recognize and destroy it. The administration of vaccines, known as vaccinations, has been extensively studied and proven to be effective. Vaccination is caused by the immune response to antigen exposure and is mediated by antibody titers and/or cells. A successful vaccine elicits a stronger and longer-lasting immune response, thus providing the greatest possible protection against disease. However, due to various factors, the immune effect after vaccination is often not as expected. The most important factor is immune aging, which leads to increased susceptibility to infection, decreased ability to clear pathogens, and decreased response to vaccination[1]. Diseases including poor nutrition, type 2 diabetes, cardiovascular disease, certain cancers, and a number of lifestyle factors such as chronic stress, depression, excessive alcohol consumption, dietary restrictions or weight loss, and smoking have all been shown to contribute to immune aging. Therefore, finding economical, safe, and feasible ways to increase vaccine effectiveness is of great clinical importance.

Increased vaccine effectiveness is often achieved through adjuvants. Vaccine adjuvants typically enhance the vaccine response by stimulating the innate immune system. Many effects of the innate response include a rapid burst of inflammatory cytokines and mobilization and activation of antigen-presenting cells, preparing for the subsequent development of a specific adaptive immune response to the vaccine. However, the development and safety of some new technologies, such as electroporation delivery of DNA vaccines and laser irradiation of vaccine sites, have yet to be proven. A growing number of researchers are focusing on exercise as a low- safety, cost-effective behavioral adjuvant. The features of innate immune system activation are very similar to those associated with acute exercise. In particular, the cytokine interleukin-6 (IL-6) and granulocyte-macrophage colony-stimulating factor (GM-CSF) have been identified as playing key roles in vaccine immune responses. In addition, interleukin-6, which plays a key role in inflammatory responses to stress and acute exercise, has now been shown to play a role in vaccine responses as well[2]. In the study of COVID-19 vaccines, exercise has also been identified as having a potential role in enhancing vaccine immune efficacy[3]. Therefore, it is worth thinking about how exercise, as a vaccine adjuvant, affects the immune response after vaccination.

2. The Effect of Exercise on Different Types of Vaccine Immune Response

2.1. Influenza Vaccine

Influenza is an acute respiratory illness caused by influenza A, B, and C viruses that occur in localized

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outbreaks or seasonal epidemics. Clinical illness has a short incubation period, and manifestations range from asymptomatic to outbreak, depending on the characteristics of the virus and the individual host. Influenza A viruses can also cause sporadic infection or a pandemic on a global scale when a new strain emerges from an animal host in a human population. The most effective way to prevent and control influenza infection is vaccination[4].

Many studies have shown that exercise can enhance the effectiveness of the flu vaccine. Edwards KM[2] et al studied the effect of acute exercise before influenza vaccination on the subsequent antibody response of three virus strains and found that the antibody effect of women at week 4 and 20 was higher than that of the control group. This study suggested that acute exercise could enhance the antibody response to vaccination in women. Based on previous research, the team went on to explore the type and intensity of exercise. By conducting biceps and triceps centrifugation tests before influenza vaccination, we found that centrifugation exercise showed differences between men and women in response to vaccination. In women, centrifugation exercise increased antibody titers and enhanced antibody response. In men, there was no significant change in antibody response, but interferon-gamma response was enhanced, and its cell-mediated response was enhanced[5].Fifty repeated centrifugal exercises at 60%, 85%, and 110% exercise intensities of 1RM for bicep flexion and lateral elevation showed that antibody response after influenza vaccination was independent of exercise intensity[6] .This is consistent with Whitham et al. 's findings that training load had no effect on total IgG measured 14 days after influenza vaccination[7].A study in older adults also showed no significant difference in antibody response to influenza vaccine between moderate intensity training (MT) and high intensity training (IT) [8].In summary, exercise intensity does not seem to affect exercise immune response to influenza vaccine.

2.2. Human Papillomavirus (HPV) Vaccine

HPV is a virus that can cause cervical cancer and other papillomavirus-related diseases and cancers. As reported by the World Health Organization in 2019, cervical cancer is the fourth most common cancer among women, with a global mortality rate of 52%. Faced with the pressure to die from cervical cancer, the World Health Organization has called for 90% of girls under 15 to be fully vaccinated. Almost all cervical cancers are caused by the human papillomavirus, and HPV vaccination is the most effective prevention strategy recommended by the World Health Organization. Could exercise play an adjuvant role in the immune response to HPV vaccination, as it does with the flu vaccine? Bohn-Goldbaum[9] et al tested the effect of an acute exercise session (completing 15 minutes of upper body resistance exercise using elastic resistance bands) prior to HPV vaccination on HPV antibody titers in adolescents. The results showed that acute exercise did not improve the adolescents' immune response to the HPV vaccine series. Although these results are not consistent with what we would expect, since there are few studies on the impact of exercise on HPV vaccines, there may be more perspective in the future as more in-depth studies become available.

2.3. Pneumococcal Vaccine

Pneumococcal vaccination is consistently recommended in Europe for adults who are at high risk of pneumococcal infection due to age, illness, or immunosuppression. Whether exercise can increase the effectiveness of the pneumococcal vaccine is worth investigating. Edwards KM[10] et al found that 15 minutes of arm and shoulder exercise prior to pneumococcal polysaccharide vaccine (PVV) resulted in a significant increase in antibody response, and the increase was only seen in the half-dose group compared to the full dose group. Some researchers have suggested that although planned and supervised interventions are effective, they may be difficult to manage in large populations or for longer periods of time. Therefore, lifestyle-oriented exercise interventions may serve as an alternative form of integrating exercise into daily life. However, Long JE[11] et al found that 16 weeks of exercise in daily living increased subjective and objective exercise levels and quality of life in sedentary middle-aged women, but did not increase antibody response to pneumococcal vaccination; In addition, another trial of brisk walking 45 minutes before vaccination also found that exercise did not affect antibody response to influenza or pneumococcal vaccines[12], which the researchers suggest may be caused by the intensity and/or duration of the intervention, the relatively young population, or the use of vaccines that do not rely on T cells.

2.4. Other Vaccinations

In recent years, in addition to the above few well-studied vaccines, some researchers have turned their

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attention to other vaccines that are less common. Two animal studies showed that exercise had no significant effect on the immune response to rabies vaccine and vaccinia virus (VACV) vaccination. Xia[13] et al showed that exhaustive exercise after rabies vaccine vaccination did not change viral-neutralizing antibody (VNA) titer, antibody subtype, or survival of the deadly rabies virus. Pence BD[14] et al found that 8 weeks of voluntary rotational exercise (VWR) did not reduce vaccinia virus (VACV) mortality or prevent weight loss due to infection, nor did VWR enhance antibody response. Molanouri[15] et al, however, suggested that short-term exercise training enhanced the cell-mediated immune response to HSV-1 vaccine in mice.

It is clear from existing research that the effect of exercise on vaccine-induced immune responses may vary depending on the type of vaccine. To account for this phenomenon, we divided vaccines into thymoid-dependent (TD) and non-thymoid- dependent (TI) categories based on whether T lymphocytes were involved in the immune response. In T-cell-dependent immune responses, immature B cells recognize and process the antigen presented, then interact with helper T cells to mature into plasma cells that secrete antibodies and B cells with long-term memory. In contrast, in non-T-cell-dependent immune responses, the maturation process of B cells does not require interaction with antigen-presenting cells or T cells. Most vaccines, especially those made of soluble proteins, rely on the involvement of T cells. Most studies suggest that exercise enhances vaccine immunity by promoting antigen-specific T cell responses. However, for non-thymus dependent antigens, exercise may not have the desired enhancing effect. This has been validated in previous studies of pneumococcal[11, 12] and vaccinia virus[14] vaccines. However, the study by KATE[16] et al found that exercise enhanced the immune response not only to meningococcal A (a non- thymus dependent antigen), but also to the flu vaccine (a thymus dependent antigen). This suggests that the adjuvant effects of exercise may not be limited to immune responses that require the involvement of T cells. Therefore, the specific mechanism of how exercise affects the immune response of different types of vaccines still needs further in-depth study.

3. The effect of exercise on adverse reactions after vaccination

Vaccination is an act that challenges the body's immune system. Inflammatory markers usually show up within hours after vaccination, a phenomenon that is largely due to a nonspecific innate immune response. These inflammatory mediators not only trigger the body's natural defense mechanisms, but may also cause adverse reactions such as drowsiness, discomfort, and irritability in vaccinated individuals. Pain, swelling and redness, among the adverse reactions associated with vaccinations, often limit people's willingness to get vaccinated. Existing research has shown that exercise plays a role in alleviating the various adverse reactions that occur after vaccination. Two studies in adolescents found that 15 minutes of upper limb exercise before vaccination with the human papillomavirus (HPV) vaccine significantly reduced the amount of tenderness girls felt after the injection, and that such exercise was also associated with fewer days of illness or loss of appetite[17], and less pain during vaccination[18]. Given that women tend to show more significant pain and anxiety responses than men after HPV vaccination, these findings provide a scientific basis for female adolescents to engage in short-term exercise prior to vaccination to relieve discomfort associated with vaccination. In addition, studies by Ushida T[19] and others have confirmed the utility of daily home exercise and activities of daily living (ADL) in alleviating adverse reactions to HPV vaccination in adolescent females. The same evidence has been shown in the elderly. Studies have found that for the elderly, moderate-intensity resistance exercise before influenza vaccination can reduce redness, pain or inflammation at the injection site and reduce adverse reactions to the vaccine compared with no exercise[20]. Another study conducted moderate-intensity resistance exercise and sedentary exercise for 45 minutes respectively before influenza vaccination in elderly people showed that in the first few days after vaccination, people in the exercise group showed fewer adverse reactions after vaccination, such as fever, redness and swelling [21].

Shayea[22] et al also showed that people who walked more than 12,000 steps per day had significantly lower stress levels and sleep disruption, and significantly improved sleep quality, compared with those who walked less than 5,000 steps per day.

These findings not only provide support for the application of exercise intervention in vaccination, but also provide new strategies for improving the acceptance of vaccination and reducing vaccination-related discomfort. However, Lee's[23] study failed to observe the analgesic effect of exercise on improving vaccine-related pain in young people. This may be related to the age and form of exercise inconsistency.

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4. Tnfluencing factors of exercise intervention in vaccine immune response

A series of studies have shown that exercise has a regulatory effect on immune response [24]. Exercise, as an important part of a healthy life, can improve immune efficacy and thus increase the immune response after vaccination[25]. Moreover, the efficacy and specific mechanisms may be related to sex differences, age, autoimmunity, type of vaccine, intensity and type of exercise intervention.

4.1. Age Factors

Many studies have shown that older people tend to have a lower immune response to vaccination than younger people. Exercise training can improve the immune response to influenza virus vaccine in elderly people [26]. Several studies involving older adults have shown that older adults who habitually engage in moderate-intensity physical activity or receive exercise training have a stronger or more durable immune response to vaccination[27-29]. The results of Seevgin's study, which involved 12 weeks of exercise in older adults, also found that engaging in regular light - and moderate- intensity exercise improved post-vaccination antibody responses in older adults compared to no exercise[30]. Aging is associated with a decline in T cell function, and animal studies by Kohut[31] et al have shown that regular moderate exercise can enhance cell-mediated antigen-specific immune response by increasing Th1 cytokine levels and improving Th1/Th2 balance. In addition, another potential factor for exercise to affect vaccine immunity in older adults is that exercise can improve depressive symptoms, positively affect mood, and reduce loneliness in older adults, as there is evidence that immune responses can be behavior-conditioned and that exercise participation affects mental health, and mental health affects vaccine response[32].Based on this, there is a consensus among existing studies that moderate-intensity exercise can improve immune response to vaccination, at least in older adults.

4.2. Gender Factors

Previous studies have revealed gender differences in vaccine antibody responses, finding that men tend to respond more strongly to measles, diphtheria toxoid and neonatal tetanus vaccines than women. Research in recent years has further confirmed that the effects of exercise on vaccine immune response also show gender differences. For example, an acute stress-induced enhancement of antibody response was observed only in women, but not in men[2], or an enhancement of cell-mediated immune response was observed in men, while an enhancement of antibody response was observed in women[5, 16]. One possible explanation is that, compared to women, men may experience more significant muscle damage after acute exercise, manifested by increased plasma creatine kinase activity and increased white blood cell infiltration. Even with similar levels of muscle damage, women show a reduced inflammatory response (characterized by a small increase in white blood cells) [33]. In addition, studies have shown that estrogen increases more in women in response to acute trauma, while androgens increase more after men engage in resistance exercise[34]. These endocrine sex differences may affect the relative TH1/TH2 balance of men and women. In the resting state, the ratio of TH1/TH2 cytokines in stimulated T cells is consistently higher in males than in females[35], and TH1/TH2 balance may be altered to varying degrees by stress-induced changes in male and female endocrine hormones. For example, it has been suggested that estrogen increases the secretion of interleukin-4, a TH2 cytokine and co-inducer of antibody production, which may help enhance humoral immune responses[36]. This may explain why only women showed an increase in humoral immunity with the same acute exercise intervention.

4.3. Forms of Exercise

As mentioned earlier in this article, the inconsistency in the results of some studies may be due to the different forms of exercise selected in different studies. Woods JA[29] et al found that cardiovascular exercise training alone led to a more durable serum protective response in the intervention of moderate-intensity (60%-70% of VO2 Max) cardiovascular exercise, flexibility, and balance training. Other studies have also shown that five months of Tai chi and Qigong training prior to influenza vaccination[28], 10 months of moderate-intensity training[27], and immediate moderate-intensity endurance exercise[37] improved antibody response to influenza vaccination. A Hallam trial showed that exercise with mild to moderate intensity aerobic exercise for 90 minutes after influenza or COVID-19 vaccination found that exercise could consistently increase serum antibodies to each vaccine for 4 weeks after vaccination without increasing its side effects[38]. These studies all suggest that moderate-intensity aerobic endurance exercise training improves immune response to vaccines. At present, there is a relatively consistent view that both chronic and acute exercise interventions can improve immune response to vaccination[39], and

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the mechanism of action of acute exercise has been speculated. Previous studies have suggested that an acute bout of exercise may have a suppressive effect on the immune system, thereby weakening the immune response to infection. In recent years, however, this idea has been questioned. New research suggests that the temporary reduction in the number and function of lymphocytes after exercise is actually a sign of cell mobilization to peripheral tissues, which contributes to the monitoring and regulation of the immune system, rather thansuppressing immune capacity. The "acute stress-induced enhanced immune response" hypothesis proposed by Edwards[40] et al states that T cells are redistributed to peripheral tissues after exercise, followed by the mobilization of new progenitor cells into circulation, which may promote improved immune monitoring function after exercise. Changes such as increased blood perfusion to the muscles, shortened muscle flap, or edema associated with muscle deformation after acute exercise may influence subsequent immune response through a variety of mechanisms. For example, increased tissue perfusion from exercise may promote greater lymph flow to the draining lymph nodes, triggering a more effective immune response. In addition, exercise-induced tissue damage may lead to the local release of inflammatory mediators that activate dendritic cells, which helps dendritic cells migrate to lymph nodes and enhance their antigen presentation [39]. These mechanisms may explain why men exhibit a stronger cell-mediated immune response after performing centrifuge exercise. The effects of chronic exercise, however, remain unclear. However, most of the existing studies focused on the elderly group, and proposed the hypothesis that "exercise creates space". This hypothesis suggests that regular moderate-intensity exercise, lasting several months to several years, may "make room" for new, more fully functioning cells by inducing apoptosis in aging and failing memory cell subpopulations, which may alter the composition of the pool of peripheral cells toward less aging[41]. As for exercise intensity, there are few existing studies. One study reviewed 14 clinical trials and concluded that antibody titer is influenced by many factors, mainly related to age, gender and physical activity intensity, and that moderate exercise intensity is the most beneficial for the increase of antibody titer [42].

Taking the current research results together, there is increasing evidence to support the idea that the enhancement effect of exercise on immunological response after vaccination may be mainly reflected in those individuals or specific antigens with weak initial immune response. For example, while certain vaccines elicit significantly different antibody responses in different sexes, exercise-induced immune response enhancement tends to be more pronounced in those gender groups with weaker responses[2, 5, 16, 37]; Some studies have also found that exercise shows significant enhancement in those strains that are least responsive in the control group [2, 6, 10]; In addition, exercise did not show additional immune-adjuvant effects in older adults who already had higher serum protection levels[43]; And a few studies noted that exercise significantly increased immune response in trials of half-dose vaccination, but not in full-dose vaccination[6, 10]. In addition, animal studies have found that the immune- boosting effects of acute stress or exercise are amplified in animals that take immunosuppressive drugs or are older[44]. This could mean that small changes caused by exercise may be masked for groups or antigens that already have a stronger immune response. Conversely, when individuals or antigens exhibit weaker antibody responses and immune function, exercise's enhanced effect on vaccine immunity is more pronounced.

5. Summary and Prospect

Exercise can enhance the immune response to vaccination, and its specific effect may be related to the type of vaccine, and is affected by age, sex and type of exercise.

The adjuvant effect of exercise is amplified in populations that exhibit a weaker immune response and are at risk for immune impairment. Therefore, the clinical value of exercise as a vaccine adjuvant to enhance vaccination response is considerable, especially in populations at risk of immune decline or impairment and with poor vaccine immune response. In addition, in view of the possible adverse reactions caused by full dose vaccination, half-dose or low-dose vaccination may be considered in future vaccination plans, combined with exercise intervention, in order to achieve better immune effects and reduce adverse reactions. There are some limitations in the existing literature, and there is huge space for research on the mechanism of action of exercise as an immune adjuvant for vaccines, the optimal immune dose, the optimal exercise prescription, the personalized regimen for different vaccines, and the combination of exercise with other adjuvants (such as physical, nutritional, and pharmaceutical), which also provides directions for future research.

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