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Impact of Whole Body Vibration Versus Aerobic Exercise Training in Modulation of Inflammatory Markers in Elderly

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Abstract: Aging is frequently characterized by an increase in systemic inflammation distinguished by elevated levels of pro-inflammatory cytokines. Increased levels of these inflammatory markers have been implicated in the pathogenesis of several diseases, including atherosclerosis, type 2 diabetes and rheumatoid arthritis (RA). The aim of the current study was to investigate the effects of vibration exercise versus aerobic training program on pro-inflammatory cytokines and C-reactive protein (CRP) in elderly. Forty elderly subjects, their age ranged from 60 to 70 years and body mass index (BMI) ranged from 23 to 29 kg/m2. The subjects were divided into two equal groups: group I received vibration exercise. Group II received aerobic exercise training; they did that three times a week for 12-weeks. The mean values of TNF-α, IL-6 and CRP were significantly decreased from 7.86±0.4, 3.19 ±2.4, 18.65±1.9 to 4.23±1.02, 1.82±1.5, 10.76±3.2 respectively, in group I and from7.88±0.4, 3.62 ±8.4, 19.72±2.5 to 5.61±2.4, 1.97±2.03, 12.52±1.99 respectively, in group II Also, there was a significant difference between the groups after treatment on all measured variables. It is suggested that vibration exercise may be more effective and safe to improve anti-inflammatory effect than is aerobic exercise training in elderly subjects.

Key words: Aging · Inflammatory Cytokines · Aerobic Exercise · Vibration Exercise

INTRODUCTION

Elderly are often affected by a "low-grade pro-inflammatory state" characterized by increased levels of cytokines and acute phase proteins (APPs) [1, 2]. Cytokines are intercellular signaling proteins that exert pro- and anti-inflammatory activities through the ligation of specific receptors or stimulating the hepatic production of APPs, such as C-reactive protein (CRP) and fibrinogen [3]. Cytokine signaling pathways are important for numerous physiologic systems beyond immunity. For example, interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) promote lipolysis, accelerate protein catabolism, decrease insulin sensitivity, are essential factors in hematopoiesis and may influence bone and muscle remodeling [4].

Chronic, low-grade inflammation is an independent predictor of several aging-related diseases, including coronary heart disease [5] and stroke [6], diabetes mellitus [7,8], Alzheimer's disease [9] and osteoarthritis [10]. Although several systemic biomarkers are indicative of an up-regulated inflammatory state, C-reactive protein (CRP) and interleukin-6 (IL-6) show the most consistent association with disease and disability in older individuals [11, 12]. Moreover, circulating concentrations of CRP and IL-6 are higher in older persons [13, 14] and there is especially strong evidence that IL-6 (which has been called a ''cytokine for gerontologists''[15,16]) is high with advancing age [17].

Low-grade chronic inflammation is reflected by increased C-reactive protein (CRP) concentrations and increased systemic levels of some cytokines [18, 19]. Several reports investigating various markers of inflammation in different population groups have confirmed an association between low-grade systemic inflammation on one hand and the metabolic syndrome Type 2 diabetes and atherosclerosis on the other [20, 21].

Regular physical activity and/or exercise training are reported to decrease inflammation [22], reduce the risk of disease development [23] and ameliorate the symptoms of

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active disease [24]. In fact, in recent studies from our lab group, physical activity exerted a more potent influence on inflammatory markers than age [25]. The mechanisms responsible for the anti-inflammatory effects of exercise are not clearly defined but could be linked to shifts in monocyte phenotype [26,27]. There is promising evidence that participation in regular physical activity (PA) lowers CRP and IL-6 [28-32]. Observational data in middle-aged and elderly persons have shown an effect of aerobic exercise training on reducing CRP and IL-6 [33-38].

Whole-body vibration (WBV) has become a popular exercise [39]; that generates an oscillating movement on a plate and transmits vertical acceleration to muscle and bone. Its mechanism of stimulating muscle spindles and alpha motor neurons initiates reflex muscle contractions [40, 41]. It has been shown that vibration interventions with low amplitude (0.7 to 14 mm), a moderate frequency (10 to 50 Hz) and short periods of exposure are safe and have beneficial effects on muscular strength and power [42], bone mineral density and body balance in both young healthy and elderly populations [43,44].

There is some contradiction related to exercise effects on plasma CRP and TNF-α levels [45-46]. Lambert et al.[47] evaluated the effects of a 12 wk exercise program on elderly obese subjects, the plasma levels of TNF-α in this population did not change, although CRP values were reduced. Other studies evaluating the effect of exercise on the levels of TNF-α in plasma did not find any difference compared with baseline [48-49], whereas yet other studies have reported increased TNF-α following chronic exercise in patients with multiple sclerosis [50].

Thus, the results of studies on the effects of exercise on inflammatory markers are varied and on the other hand few studies applied on elderly subjects. However, there have been no studies focusing on inflammatory response to vibration exercise. Therefore the purpose of this study was to determine whether 12 weeks of vibration exercise would affect systemic concentrations of C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) in elderly men. The results were compared to a group performing aerobic exercise.

MATERIALS AND METHODS

Subjects Characteristics and General Experimental Design

Study Subjects: Forty elderly men subjects selected from elderly housing with body mass index (BMI) ranged from 23 to 29 kg/m2, non smokers, free from respiratory, kidney, liver, metabolic and neurological disorders as well as chronic inflammatory orthopedic disorders, rheumatoid arthritis or chronic cardiac problems as heart failure, ischemic heart disease and coronary artery by pass graft. Their age ranged from 60-70 years and not involved in any physical therapy program.

Evaluated Parameters

Blood Samples and Biochemical Markers: Blood samples were gathered after 12 to 14 hours of fasting. First, the subjects were required not to perform any physical activity two days before the test. 5 cc of blood was obtained from each subject's left-hand vein in sitting and resting statuses. Samples taken from each subject in clean tubes containing few mg of K2EDTA, centrifuged and plasma was separated and stored frozen at -20° used for estimation of plasma tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and C-reactive protein (CRP). 48 hours after the last training session, the blood samples were obtained for both groups like the first stage [51].

Subjects were randomly divided into two groups: Group I: a vibration exercise group, group II: aerobic exercise group. They trained three sessions / week (i.e. a total of 36 sessions per subject over a 3-month period). All sessions were supervised and participation assessed. All patients were free to withdraw from the study at any time. All participants provided their informed consent after receiving a detailed explanation of the study. If any adverse effects had occurred, the experiment would have been stopped and the Human Subjects Review Board would have been informed. However, no adverse effects occurred and so the data of all the patients were available for analysis. The detailed training regimen was as follows:

Vibration Exercise: Subjects were asked to remain in a standing position on a whole body vibration device. The purpose built device produced a synchronous vibration. All patients were instructed to stand on the vibration platform with their feet shoulder width apart, knees and hips slightly bent and hands by their side to receive maximum vibration exposure, the protocol was performed with patients' shoes removed to prevent any attenuation of vibration that may result from footwear. Subjects exercised on a horizontal swinging platform with amplitude of 2 mm (Vibrogym Professional). Vibration frequency was set to 27Hz from weeks 1 to 9 and to 35 Hz during the last three weeks. It took about 15 minutes to fulfill a training session [52].

Aerobic Exercise Training: The aerobic treadmill-based exercise program was at training heart rate (THR) calculated using Karvonen formula as follow: THR = HR rest + 60% [HR max - HR rest]. After an initial, 5 minute warming up phase performed on the treadmill at low load, the speed was increased to 2 mph for 3 min, then the speed had increased gradually until the subject reached calculated target heart rate (THR), Then the subject walked at the obtained level of speed for 15-20 min and ended with 5-minute cooling down as warming up [53-54].

Statistical Analysis: The mean values of CRP, TNF-α and IL-6 obtained before and after three month in both groups were compared using the paired ''t'' test. Unpaired ''t'' test was used for the comparison between the two groups ($P < 0.05$).

RESULTS

The study involved forty elderly subjects. Their age ranged from 60 to 70 years. The subjects were divided into two equal groups: the first group (I) received vibration exercise. The second group (II) received aerobic exercise three times a week for 12- weeks in order to compare the impact of vibration and aerobic exercise on plasma tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and C-reactive protein (CRP) in elderly subjects. (Table 1) represented non significance difference between both groups. The mean values of TNF-α, IL-6 and CRP were significantly decreased from 7.86±0.4, 3.19 ±2.4, 18.65±1.9 to 4.23±1.02, 1.82±1.5, 10.76±3.2 respectively, in group I and from7.88±0.4, 3.62 ±8.4, 19.72±2.5 to 5.61±2.4, 1.97±2.03, 12.52±1.99 respectively, in group II (Tables 2 and 3). Also, there was a significant difference between the groups after treatment (Table 4). So, it can be concluded that both vibration exercise and aerobic treadmill exercise have a positive effect on pro-inflammatory cytokines and C-reactive protein but vibration exercise training was more effective than aerobic exercise training.

DISCUSSION

The aim of this study was to compare changes in systemic concentrations of CRP, TNF-α and IL-6 after 12 weeks of vibration exercise versus aerobic exercise training in elderly men. The mean values of CRP, TNF-α and IL-6 were significantly decreased in both group I and group II. Also, there was a significant difference between the groups after treatment. This means that in elderly subjects vibration exercise is effective in improving anti-inflammatory effect as well as aerobic treadmill-based exercise program.

CRP is a key inflammatory factor produced by the liver in response to an acute infection or inflammation and its concentration in plasma can increase as much as 1000-fold during injury and infection [55,56]. During regular aerobic exercise, skeletal muscle fibers inhibit the production of the proinflammatory cytokine TNF-alpha

Table 1: Clinical characteristics of study subjects of both groups at baseline

Characteristic	Group I (*n*=20)	Group II (*n*=20)	*P* value
Age, yr	64.55 ± 3.23	64.54 ± 3.27	0.920
Weight, kg	81.2±5.3	79.8±5.6	0.739
BMI, kg/m2	25.7±2.6	26.6±2.1	0.407
TNF-α (pg/mL)	7.86±0.4	7.88±0.4	0.770
IL-6 (pg/mL)	3.19 ±8.4	3.62 ±8.4	0.307
CRP (mg/dl)	18.65±1.9	19.72±2.5	0.964

BMI, body mass index; TNF-α = tumor necrosis factor alpha - IL-6 = interleukin-6 - CRP= C-reactive protein

Table 2: Mean value and significance of TNF-α , IL-6 and CRP in group I before and after vibration exercise

	Mean ±SD			
	Pre-study	Post- study	T-value	P-value
TNF-α (pg/mL)	7.86±0.4	4.23±1.02	4.78	0.002
IL-6 (pg/mL)	3.19 ±2.4	1.82±1.5	7.2	0.004
CRP (mg/dl)	18.65±1.9	10.76±3.2	7.82	0.005

TNF-α = tumor necrosis factor alpha - IL-6 =interleukin-6 - CRP= C-reactive protein

Table 3: Mean value and significance of TNF-α , IL-6 and CRP in group II before and after aerobic exercise

	Mean ±SD			
	Pre-study	Post- study	T-value	P-value
TNF-α (pg/mL)	7.88±0.4	5.61±2.4	4.25	0.02
IL-6 (pg/mL)	3.62 ±8.4	1.97±2.03	5.42	0.05
CRP (mg/dl)	19.72±2.5	12.52±1.99	3.96	0.04

TNF-α = tumor necrosis factor alpha - IL-6 =interleukin-6 - CRP= C-reactive protein.

Table 4: Mean value and significance of TNF-α , IL-6 and CRP in group I and group II after treatment

	Mean ±SD			
	Group I	Group II	T-value	P-value
TNF-α (pg/mL)	4.23±1.02	5.61±2.4	2.96	0.02
IL-6 (pg/mL)	1.82±1.5	1.97±2.03	3.01	0.03
CRP (mg/dl)	10.76±3.2	12.52±1.99	3.89	0.04

TNF-α = tumor necrosis factor alpha - IL-6 =interleukin-6 - CRP= C-reactive protein

and produce several anti-inflammatory cytokines (termed "myokines") that may be involved in mediating the health-beneficial effects of exercise [57]. Additionally, exercise training may reduce mononuclear cell production of pro-inflammatory cytokines by reducing chronic oxidative stress [58].

The anti-inflammatory effects of physical activity are likely to result from multiple mechanisms. Physical activity may simultaneously decrease TNF- α and IL-6. TNF- α induces the production of IL-6, which stimulates the acute-phase response in liver. Moreover, TNF-α may induce down regulation of adiponectin, which regulates glucose and lipid metabolism by targeting the liver and skeletal muscle exerting anti-inflammatory, anti-atherogentic and anti-diabetic effects. Meanwhile, physical activity is associated with the up-regulation of anti-inflammatory cytokines (eg, IL-1ra and IL-10) [30,59,60].

The current study was early supported by Le Maitre et al [61], a study of chronic stable heart failure patients (aged 62 yrs) comparing cycling exercise with electrical stimulation of the quadriceps and gastrocnemius muscles found that only cycling exercise resulted in reductions in sTNFr-II with in significant reduction in Serum CRP and TNF-α in the cycling group. This came in agreement with Goldhammer *et al.* [5] who found large (48%; 7.5 to 3.9 mg/L) reductions in serum CRP in 28 elderly coronary heart disease patients in response to 12 wks of aerobic exercise training as offered in typical Phase II cardiac rehabilitation programs, effects were also seen for IL-1, IL-6 and interferon-γ.

Acute exercise increases muscle production of IL-6 and while IL-6 has been associated with inflammation, it also may have anti-inflammatory properties [62]. Starkie *et al*. [63] reported that exercise and IL-6 infusion could inhibit endotoxin-induced production of TNF-α in humans circumstantially suggesting that IL-6 can act in an anti-inflammatory fashion. As exercise training is the accumulation of many individual acute exercise bouts, such acute increases in IL-6 may contribute to reduced chronic inflammation over the long-term. Another possibility is that regular exercise reduces oxidative stress by up-regulating endogenous anti-oxidant defense systems. Overproduced oxidants like nitric oxide, peroxynitrite and hydroxyl radical during aging are a major causative factor in activation of pro-inflammatory immune cells [64].

These findings are in agreement with Kohut *et al*. [35], showing a significant reduction in serum CRP, IL-6 and IL-18 after 10 months of moderate aerobic exercise compared to the flexibility exercise in low fit older adults aged >64 years whereas TNF-α declined in both groups. As well as Nicklas *et al*.[62] reported that regular aerobic exercise in sedentary, overweight/obese (BMI >28), community-dwelling elderly (70–89 years), even in the absence of weight loss, resulted in a significant 16% and 32% reduction in IL-6, CRP respectively. On the same line; Campbell *et al*. [65] found a significant reduction in CRP in sedentary post-menopausal women aged 60 years after 12 months of moderate intensity exercise when compared to a stretching control group that exhibited no change in CRP.

Another mechanism whereby exercise training might reduce systemic inflammation in the elderly was reported by Tracey [66] as the "cholinergic anti-inflammatory pathway," in which stimulation of the parasympathetic nervous system, via the efferent vagus nerve, inhibits pro-inflammatory cytokine production and protects against systemic inflammation. They described it as a central homeostatic mechanism by which the sympathetic division of the autonomic nervous system stimulates the inflammatory response through the release of epinephrine and nor-epinephrine, while the parasympathetic nervous system works reciprocally to suppress this release of pro-inflammatory cytokine. A primary function of the vagus nerve is to control heart rate, which is typically measured by heart rate recovery (HRR) following exercise and heart rate variability (HRV). A major adaptation to long-term cardiovascular exercise training is a decrease in HRR and HRV. Thus, aerobic exercise training may increase efferent vagus nerve activity and this increased activity may contribute to the anti-inflammatory effect of exercise [67].

The results of our study were in opposite direction to Kapasi *et al.* [68]; they concluded that 32 wks of functionally-oriented endurance and resistance exercise had no effects on serum neopterin or sTNFr-II in 190 frail elderly nursing home patients; as well as Hammett *et al*. [32] have found that 6 months of cardiovascular exercise did not result in changes in total body or trunk fat and had no effect on serum CRP, despite improving cardiovascular fitness. It should be noted though that the baseline CRP in these subjects was quite low (~1.5mg/L). Another contradicts with Beavers et al [69] who found that IL-8 was the only cytokine that was significantly reduced in the exercise group. IL-6sR, IL-1sRII, sTNFr's I & II, IL-15, adiponectin, IL-1ra, IL-2sRα and TNF-α were all not affected. In another contradict Jones *et al*. [70] who conducted a 6-month moderate-intensity aerobic exercise intervention in postmenopausal breast cancer survivors.

No significant effect of exercise was observed on CRP, IL-6, or TNF-α concentration between women randomized to exercise versus usual care. Nevertheless, the difference between the findings of the current study and other researches [32,68-70] can be attributed to the differences between the studied groups, their race, exercise duration, exercise intensity, period and type.

CONCLUSION

In summary, both vibration and aerobic exercise training induced anti-inflammatory effect through reducing pro-inflammatory markers but vibration exercise produced a more significant reduction in CRP, TNF-α and IL-6 as compared to aerobic exercise. Since vibration training is safe, easy to be applicable, low time consuming and effective intervention; may be preferred by elderly as a part of an intended lifestyle modification.

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