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Research article

PRO AND ANTI-INFLAMMATORY EFFECTS OF GRADED PHYSICAL EXERCISE

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ABSTRACT

Background: It is generally believed that exercise is good for health. Exercise can be harmful to immune system depending on type and duration. So it was decided to study the plasma levels of cytokines with increasing severity of exercise. We observed plasma levels of cytokines on performing graded exercise. Cytokines are protein molecules modulating the Immune system. Interferon Gamma and Tumour Necrosis Factor alpha are pro-inflammatory and anti-inflammatory cytokines respectively. **Methods: Study design:** Effect of single bout each of moderate exercise and strenuous exercise and one month of regular moderate exercise on plasma TNF- α and IFN-γ was assessed. Blood samples were drawn from each subject soon after one bout of moderate exercise. Another blood sample was drawn from each of the subjects after one bout of strenuous exercise which was performed on next day. The third blood sample was drawn on last day of one month of regular moderate exercise after performing the exercise. Subjects consisted of 18 healthy volunteers (10 males and 8 females) with mean age, 20.94 years, range, 18-25 years. The sample size was calculated statistically based on a previous study. TNF-α and IFN-γ were estimated by Sandwich ELISA technique. Friedman test was used for analyzing TNF-α and IFN-γ values. **Results:** Mean and SD values of IFN-γ and TNF-α (in pictograms per ml) for baseline (no exercise) was: 54.56 ± 28.54 and 26.17 ± 17.62 respectively, for acute moderate exercise: 28.72 ± 27.57 and 53.83 ± 27.25 respectively, for acute strenuous exercise: 20.36 ± 16.96 and 93.50 ± 5.39 respectively and after one month of regular moderate exercise: 106.33 ± 21.51 and 15.61 ± 8.89 respectively. TNF-α and IFN-γshowed overall significance between different grades of exercise ($p < 0.05$). **Conclusions:** Plasma TNF-α increases with one bout of acute moderate exercise and increases further with one bout of acute strenuous exercise and decreases to below baseline values at the end of one month of regular moderate exercise. IFN-γlevels exhibit opposite behaviour. This shows that regular moderate exercise has beneficial effects on health by way of increasing plasma IFN-γ level and decreasing TNF-α level.

Keywords: Interferon gamma, Tumour Necrosis Factor alpha, Exercise, Inflammation.

INTRODUCTION

Tumour Necrosis Factor alpha (TNF-α) is a pro-inflammatory cytokine and Interferon-Gamma (IFN-γ) is an anti-inflammatory cytokine [1, 2]. Higher levels of inflammatory cytokines like TNF-α and IL-6 is associated with the genesis and complications of several lifestyle disorders[3, 4]. Unaccustomed physical activity can have harmful effects on health[5]. It increases serum IL-6 levels and the hsCRP (highly sensitive C reactive protein) to correlate with increased incidence of cardiovascular diseases[6]. Persisting physical stress increases secretion of IL-6 which in turn leads to premature onset of lifestyle disorders [7]. Moderate exercise performed regularly decreases severity of inflammation in rheumatoid arthritis [8,9]. The performance of immune system improves with daily practice of moderate exercise [10]. Regular moderate exercise improves overall health in all age groups [11, 12].

Several studies have been undertaken to observe the plasma cytokine changes with different modes of exercises like marathon, military training, downhill running on a treadmill, cycling, etc., on different groups of individuals in different parts of the world. Strenuous exercise as in military training and unaccustomed marathon running led to decrease in mucosal immunity. Performance of regular exercise of moderate nature improved the performance of immune system even in the elderly. Moderate exercise performed on a regular basis decreased the levels of IL-6 in patients of Systemic Lupus Erythematosus (SLE) [13, 14, 15, 16]. We undertook this study in order to understand the impact of moderate and strenuous exercise on the plasma levels of IFN-γ and TNF-α in unaccustomed individuals and the benefit of exercise on accustumisation by the same individuals.

MATERIAL AND METHODS

This is a longitudinal study. 18 healthy volunteers, 10 males and 8 females in the age group of 18 to 25 years, with mean BMI of 21.64±1.83 (kg/m^2) not performing any kind of regular exercise were included in this study, after obtaining prior consent. Sample size was calculated for TNF- α and IFN-γ separately, based on a previous study [17]. For IFN-γ, with an effect size of 0.66, power of 80% and significance of 5%, the minimum sample size was estimated to be 15. For TNF- α, with an effect size of 2 and power of 90%, sample size worked out to be 4. However, in view of less sample size obtained on calculation, it was increased to 16. Clearance was obtained from the institutional ethics committee for the study. The approved number of subjects was 20. Two subjects dropped out during the study period and hence only 18 subjects could be included in the study.

Exclusion Criteria: Individuals below and above, the age range of 18 to 25 years, those suffering from any kind of illnesses including chronic disorders and on long term medication and people who smoke, consume alcohol and/or take illicit drugs in any form.

The subjects were made to perform one bout of moderate exercise of 7 minutes (acute moderate exercise), one bout of strenuous exercise of 15 minutes (acute strenuous exercise) and one month of scheduled moderate exercise on a daily basis. That is, each day the subjects would perform one bout of moderate exercise of seven minutes for one month [18]. The sequence of exercise was as follows: The subjects were made to perform acute moderate exercise on the first day. The subjects were made to perform one bout of acute strenuous exercise on the second day. The subjects were made to perform scheduled regular moderate exercise from the third day onwards, for 30 days. The third blood sample was collected soon after performing the bout of moderate exercise on the last day of the one month period. The exercise was performed under supervision. During one month of scheduled moderate exercise, the subjects were made to perform a single bout of moderate exercise daily for 30 days. The exercise was graded as moderate or strenuous based on the rise in heart rate. It was labelled as moderate when the heart rate increased by 50% from resting level and was labelled as strenuous when heart rate increased by 100%[19].

Shuttle Walk Test Protocol: The exercise regime chosen was the standardized 10m Shuttle Walking test regime, described by Glenfield Hospital, Leicester, United Kingdom in collaboration with the department of Physical Education and Sports Science, Loughborough University of Technology, United Kingdom [20, 21, 22, 23]. In this exercise protocol, the subjects walk on a 10 meter plain path at the two ends of which are placed marker cones. The subjects walk between the cones corresponding to the beeps given out by a record player. Subjects have to increase their speed of walking gradually in tandem with the shortening of intervals between the consecutive beeps as time progresses. The level of the shuttle walk regime at which the heart rate increased by 50% of the baseline was chosen as moderate exercise. The level at which the heart rate increased by 100%, i.e. doubled was considered as strenuous exercise. The pulse was counted before and after each bout of exercise to make sure the heart rate had increased by 50% for moderate exercise and 100% for strenuous exercise.

5 ml of the venous blood sample from cubital vein (using vacutainers) just before acute moderate

exercise (baseline) was collected. Another sample was collected immediately after acute moderate exercise on the same day. After performance of acute strenuous exercise on the next day, third sample was obtained. A sample was obtained after one month of scheduled regular moderate exercise on the last day after exercise. Baseline sample just before acute strenuous exercise and just before a performance of exercise on the last day of one month regular moderate exercise was not obtained. The samples were collected between 7 and 8 AM. The blood samples were collected using all aseptic precautions. If the blood could not be obtained at the first prick of the needle, the subject was requested to come on the next day. This is to exclude the possibility of a double prick leading to local inflammation, which in turn leads to a local increase in pro-inflammatory cytokines like TNF-α. The plasma was separated and plasma samples from each individual were aliquoted and stored at - 40^0C till analysis.

Plasma sample was used to estimate the levels of cytokine IFN-γ and TNF-α, by using ELISA (Enzyme linked ImmunoSorbent Assay) method. ELISA was performed using DuoSet ELISA development system as per the manufacturer's instructions (R&D systems, USA).

Estimation of IFN-¥:

Briefly, polystyrene microtiter plates (NUNC, U16 Maxisorp type, Denmark) were coated with monoclonal capture antibody (antihuman IFN-γ) obtained from mouse (R&D systems, USA) and incubated at 4°C overnight. The following day, the plates were blocked and then incubated for 2 hours with plasma. This was followed by addition of corresponding biotinylated detection antibody obtained from goat (R&D systems, USA) and incubated for 2 hours. Strepatavidin, horseradish peroxidise conjugate and then, 3,3', 5,5'-tetramethylbenzidine substrate (Bangalore Genie, India) followed this incubation. The reaction was stopped using 2 N sulphuric acid and optical density (O.D) reading was taken at 450nm (Organon Teknika Microwell system, Reader 230s, Germany). All the experiments were conducted in duplicates. A standard curve was obtained based on the standards provided by the manufacturer. The results were expressed as concentration of cytokines (in pg/ml) read from the standard curve (concentration in range: minimum of 5 pg/ml, to maximum of 150 pg/ml).

Estimation of TNF-α:

Polystyrene microtiter plates (NUNC, U16 Maxisorp type, Denmark) were coated with monoclonal capture antibody (antihuman TNF- α) obtained from mouse (R&D systems, USA) and incubated at 4°C overnight. The following day, the plates were blocked and then incubated for 2 hours with plasma. This was followed by addition of corresponding biotinylated detection antibody obtained from goat (R&D systems, USA) and incubated for 2 hours. Strepatavidin, horseradish peroxidise conjugate and then, 3,3', 5,5'- tetramethylbenzidine substrate (Bangalore Genie, India) followed this incubation. The reaction was stopped using 2 N sulphuric acid and optical density (O.D) reading was taken at 450nm (Organon Teknika Microwell system, Reader 230s, Germany). All the experiments were conducted in duplicates. A standard curve was obtained based on the standards provided by the manufacturer. The results were expressed as concentration of cytokines (in pg/ml) read from the standard curve (concentration in range: minimum of 5 pg/ml, to maximum of 100 pg/ml) [24].

Statistical Analysis: The statistical analysis was carried out using SPSS software version 18.0 (SPSS Inc. Chicago, USA). The variables in the data was summarized as Mean ± SD. Friedman test has been used for analyzing the differences in TNF-α and IFN-γ values in-between the different grades of exercise in the group. Pearsons correlation coefficient was used to find the correlation between TNFα values and BMI. Spearman's correlation was used to find the correlation between IFN-γ values and TNF-α value after different grades of exercise.

RESULTS

18 healthy volunteers in the age group 18 to 25 (mean: 20.94) were taken for the study. TNF- α and IFN-γ levels were studied with different grades of exercises.

Changes in IFN-¥: There was a significant fall in the levels of this cytokine with both acute moderate exercise (p=0. 004) and acute strenuous exercise (p=0. 001) compared to baseline values. There was a significant drop in its levels after acute strenuous exercise when compared to moderate exercise (p=0.033). The rise of IFN-γ after one month of regular moderate exercise was also significant compared to baseline value (p=0.001). That is, the IFN-γ level shot up after the bout of moderate exercise on the last day of one month of regular moderate exercise regime (Figures: 1 & 2).

Changes in TNF-α: There was a significant increase in the levels of this cytokine with both acute moderate exercise (p=0.003) and acute strenuous exercise (p=0.005) compared to baseline value. There was a significant rise in its levels after acute strenuous exercise when compared to moderate exercise (p=0.043). The fall of TNF- α after one month of regular moderate exercise was also significant compared to baseline value (p=0.001). That is, the TNF- α level decreased to below baseline level after the bout of moderate exercise on the last day of one month of regular moderate exercise regime (Figures: 1 & 2).

It was found that a significant positive correlation existed between TNF-α at baseline, TNF-α after one bout of moderate exercise, TNF-α after one bout of strenuous exercise and BMI (r = 0.62,0.76,0.50) ($p<0.05$) . Whereas there was a negative correlation between TNF-α level at end of one month of moderate exercise and BMI (r = -0.34). However this was not statistically significant (p=0.149).

We found that there was a significant negative correlation between the IFN-γ values and TNF-α values during the one month of regular moderate exercise(r= -0.530)(p=0.024) (Figure 3).

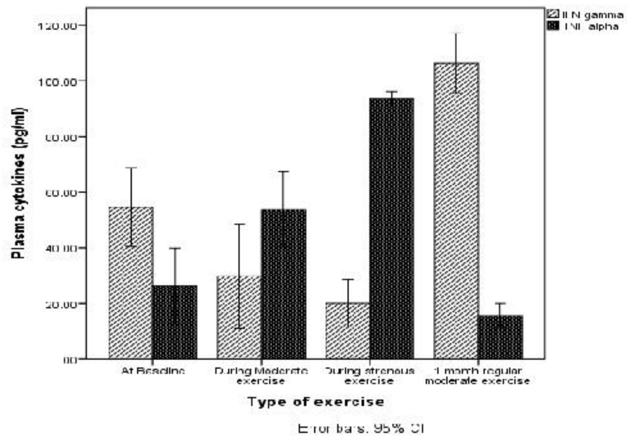

Fig 1: Changes in the in IFN-¥ and TNF- α level (pg/ml) with different grades of exercise.

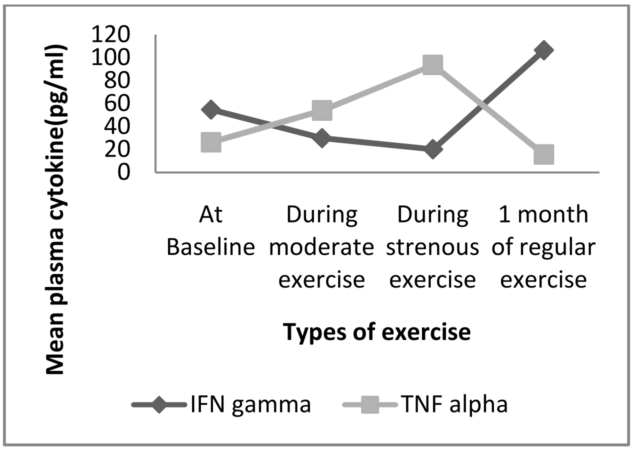

Fig 2: Changes in the in IFN-¥ and TNF- α level (pg/ml) with different grades of exercise.

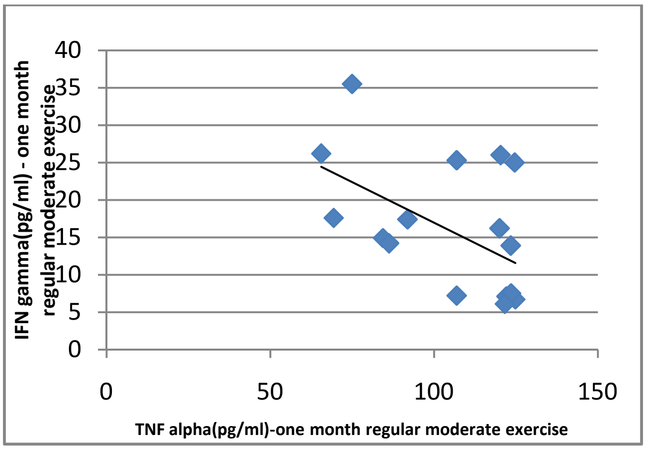

Fig 3: Correlation between IFN-¥ and TNF-α levels (pg/ml) after one month or regular moderate exercise.

DISCUSSION

Sudden bout of physical activity is hazardous to health [25]. The immune system, in many ways, reacts similarly to the sudden bouts of physical activity and physical trauma [26]. Pro-inflammatory cytokines like TNF-α and interleukin-6 are released is response to acute and strenuous exercise[27,28]. Prolonged strenuous exercise decreases the percentage of T cells in circulation[29]. Regular practice of moderate exercise inversely correlates with levels of pro-inflammatory cytokines in coronary heart disease patients retarding the process of atherosclerosis [30]. Therefore, increased levels of pro-inflammatory cytokines like interleukin-6 and tumour necrosis factor alpha are deleterious to health [31].

TNF-α has pro-inflammatory properties and IFN-γ has anti-inflammatory properties. In this study that IFN-γ levels decreased significantly after a bout of moderate exercise and there was a further significant decrease following a bout of strenuous exercise. It increased significantly compared to baseline levels after one month of scheduled regular moderate exercise done on a daily basis; that is, IFN-γ levels shot up after the single bout of moderate exercise on the last day of one month of scheduled moderate exercise when compared to a single bout of moderate exercise without accustumisation to regular moderate exercise, in the same individuals. The TNF-α levels increased after a bout of moderate exercise and there was a further significant increase following a bout of strenuous exercise and decreased significantly compared to baseline levels when compared with one month of scheduled regular moderate exercise done on a daily basis; that is, TNF-α levels decreased to below baseline level after the single bout of moderate exercise on the last day of one month of scheduled moderate exercise when compared to single bout of moderate exercise without accustumisation to regular moderate exercise, in the same individuals. Therefore, in the individuals who adhere to regular moderate exercise, the sudden fall in the anti-inflammatory cytokine and rise in pro-inflammatory cytokine may not occur if such individuals were to get involved in bouts of unaccustomed physical activity. It may induce a 'buffering capacity' or an 'adaptive cytokine response'. This may be beneficial during sudden bouts of physical activity in normal course of life to tolerate those physical stresses better.

Regular moderate exercise is beneficial for maintaining good health and improving the immune status [6, 7, 8, 10, 11]. Since this study shows a rise in IFN-γ and a fall in TNF-α level with regular moderate exercise, a rise in the plasma levels of IFN-γ and a fall in TNF-α level should also be beneficial for maintaining health and immunity. IFN-γ is an anti inflammatory cytokine and TNF-α is pro-inflammatory cytokine, so their altered production leads to unnecessary inflammation and tissue damage [32]. Thus regular moderate exercise seems to modulate their release and alters their levels to the optimum levels necessary for human body to maintain good health.

Mental stress is also known to decrease plasma levels of IFN-γ and increase the level TNF-α [33]. The adaptive cytokine response may also help individuals adhering to regular moderate exercise to cope with bouts of psychological stresses encountered in daily life [34].In these individuals, the levels of IFN-γ may not fall as much as it would decrease in those not performing regular exercise, facing the same level of mental stress, likewise the levels of TNF- α may not rise drastically either [35]. The mechanism behind this is not clearly known till now

Several studies have shown that patients of various diseases and disorders like atherosclerosis, coronary artery disease and diabetes mellitus have elevated levels of TNF- α interleukin-6 (IL-6) and lower levels of IFN-γ[35]. Stress by way of bursts of physical activity in day-to-day life, in such patients increases their levels much further and leads to exacerbation of the disease. It can be postulated that the drastic rise in TNF- α and IL-6 and fall in IFN-γ with bursts of physical activity or with 'acute on chronic infections' tends to flatten if such patients follow a regular moderate exercise regimen.

Certain autoimmune disorders like systemic lupus erythematosus and rheumatoid arthritis are associated with increased plasma levels of pro inflammatory cytokines like TNF- α and IL-6, which increased inflammation. Mast cells release mediators to stimulate T-cells to produce pro-inflammatory cytokines to increase inflammation [36]**.** The anti-inflammatory properties of IFN-γ have been demonstrated both in vitro and in vivo. IFN-γ inhibits integrin mediated adhesion and migration of T-cells in vitro. Flashion et al have demonstrated that when IFN-γ was administered to naïve T-cells and injected to mice, such T-cells did not home in onto the lymph nodes compared to the T-cells not treated with IFN-γ[1]. IFN-γ decreases eosinophil infiltration in a dose dependent manner [37]. Increased levels of TNF-α leads to cachexia, increased levels of C-reactive protein and other acute phase proteins, activates macrophages, increases tumour cytotoxicity, activates neutrophils and increases phagocytosis and induces secretion of other pro-inflammatory cytokines like IL-6 [38]. This study also demonstrates a positive correlation between the pro-inflammatory cytokine TNF-α and BMI at baseline (no exercise), after one bout of moderate exercise and after one bout of strenuous exercise. This may indicate that obesity predisposes to increased levels of pro-inflammatory cytokines. Interestingly, found a negative correlation, though not significant between TNF-α level and BMI at end of one month of regular moderate exercise. This may be because the increase in BMI at end of one month of exercise may be due to increase in the healthy lean body mass and decrease in adiposity [39]. Our study also shows a negative correlation between TNF-α and IFN-γ in all the grades of exercise, but it is statistically significant at the end of one month of regular moderate exercise. This again proves the beneficial effect of regular moderate exercise. Till date very few studies have been undertaken in the same group of human subjects to study the effects of physical stress/exercise on levels of TNF-α and IFN-γ. Regular moderate exercise may benefit patients suffering from inflammatory diseases and auto-immune disorders by bringing down the levels of pro-inflammatory cytokines like TNF-α and increasing the levels of IFN-γ. Since different grades of physical exercise have pro-inflammatory and anti-inflammatory effect, we propose that this study has potential for clinical application.

Limitations of the study: Though the sample size for the present study has been calculated statistically, based on the sample size of a previous study, further research with greater number of samples is needed to throw more light on the pro and anti inflammatory effects of different grades of exercise.

CONCLUSION

Plasma TNF-α increase with one bout of acute moderate exercise and increases further with one bout of acute strenuous exercise and decreases to below baseline values at the end of one month of regular moderate exercise. IFN-γ levels exhibit opposite behaviour. This shows that regular moderate exercise has beneficial effects on health by way of increasing the plasma level of the anti-inflammatory cytokine, IFN-γ and decreasing plasma level of pro-inflammatory cytokine, TNF-α.

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Conflict of Interest: Nil

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