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Original article

## Exercise-induced downregulation of serum interleukin-6 and tumor necrosis factor-alpha in Egyptian handball players

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## ABSTRACT

Muscles of candidates work at various grades of intensity during handball exercises according to the pace of exercise. The movement pattern involves large number of contractions, feints, dodges and numerous changes in movements, all of which are highly responsible for changes in trainer's organs, including the immune system. In this study, inflammatory mediators involving interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- $\alpha$ ) in serum of 18 Egyptian male handball players, selected from Tanta club handball under 21 year's old team, were analyzed. The analysis was established on samples collected just before and immediately after intermediate reasonable exercise via enzyme linked immunosorbent assay (ELISA). Moreover, white blood cells (WBCs) count and other hematological markers including hemoglobin %, hematocrit value, and platelet count were assessed. Our results demonstrated a significant decrease in the levels of IL-6 and TNF- $\alpha$  after exercise compared to those before exercise. This was coupled with an increase in WBCs and platelets count. It is also noteworthy that there was a significant positive correlation between serum levels of IL-6 and TNF- $\alpha$  in the study subjects coupled with a significant negative correlation between IL-6 and WBCs after the exercise. Therefore, it is concluded that intermediate reasonable exercises result in decreased levels of IL-6 and TNF- $\alpha$ , which result in decreasing of the inflammation and help in healing and rapid recovery of muscles of the candidates.

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## 1. Introduction

The concept of immune modulation as a reaction to physical exercising is not new, however, the data elucidating the underlying mechanisms of these changes are still insufficient. The profitable effect of regular intermediate reasonable physical exercising on immune system is well confirmed especially in sedentary subjects (Petersen and Pedersen 2005). On the contrary, unreasonable long term and/or very strong physical exercises have harmful effects on

the immunity of candidates (Collinson, 2017; Córdova et al., 2010). The immunosuppression brought about by physical exercises usually persists for 3–72 h beyond exercise according to the measured parameter (Kostrzewa-Nowak et al., 2015; Parisotto et al., 2003). On the other hand, acclimation of muscles due to exercises and cardiopulmonary capability are mainly dependable on local and systemic inflammation (Guarner and Rubio-Ruiz, 2015; Mikkelsen et al., 2009; Sultan et al., 2014). Indeed T and B-lymphocytes are crucial ingredients of immune system that represent the cellular and humoral immunity, respectively. It is well-established that there is a link between humoral and cellular immune response (Cabrera-Ortega et al., 2017; Kostrzewa-Nowak et al., 2019). T cells are the responsible for interleukins production including interleukin-6 (IL-6). In addition, they are charged for the production of signaling molecules including tumor necrosis factor alpha (TNF- $\alpha$ ); a well-known universal marker of inflammation, and hematopoietic granulocyte macrophage colony-stimulating factor (Carbo et al., 2013; Peters and Yosef, 2014). Therefore, the existence of T cells producing IL-6 and TNF- $\alpha$  in peripheral blood is

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related to chronic inflammation and autoimmune diseases (Korn et al., 2007; McGeachy and Cua, 2007; Peters and Yosef, 2014). Increasing literature data showed that the degree of exercise controls the levels of produced inflammatory mediators including IL-6 and TNF- $\alpha$  that might be beneficial in healing and recovery of muscles or devastating (Ghafourian et al., 2016; Nieman, 1997; Petersen and Pedersen, 2005).

Two main contradicting effects of IL-6 have been outlined in literature. IL-6 is related to insulin resistance and obesity (Pedersen and Febbraio 2008). On the other hand, IL-6 has an insulin-like effect on glucose metabolism, downregulates TNF- $\alpha$ , and provokes the production of other anti-inflammatory cytokines including IL-1ra and IL-10 in the circulation (Kaur et al. 2006). On the other side, TNF- $\alpha$  triggers the production of several immune system molecules, including IL-1 and IL-6 (Grohmann et al., 2005; Kaur et al., 2006). TNF- $\alpha$  decreases glutathione peroxidase, catalase, and superoxide dismutase as well as increases lipid peroxidation and intracellular reactive oxygen species in heart muscles (Kaur et al. 2006). As for skeletal muscles, TNF- $\alpha$  might lead to reduction in muscle mass via promotion of myofiber atrophy and inhibition of muscle cell differentiation (Jejurikar et al., 2006; Saini et al., 2012). Also, TNF- $\alpha$  is associated with large depletions in the glutamine and other amino acids both in the circulation and from skeletal muscle stores (Watford 2015). Exercise has biphasic roles according to the exercise intensity that may be either downregulation of inflammatory mediators in case of intermediate reasonable exercise or upregulation in case of unreasonable exercise (Halson 2014).

One of the sports that requires rapid pace, physical strength and different paces of exercising is handball (Achenbach et al., 2018; Wagner et al., 2017). During this sport, muscles of candidates excessively contract and function at extreme intensity. The participants usually exhibit large number of movement changes, feints and dodges (Achenbach et al., 2018; Wagner et al., 2017). It is well established that homeostasis disorders are common among athletes due to hard exercise programs that are established during the season. In addition, muscle injury stimulated during either hard exercises or competitions leads to liberation of different myocellular enzymes and inflammatory mediators into blood plasma of the participants (Fatouros and Jamurtas, 2016; Ghafourian et al., 2016; Malm et al., 2000; Ziemann et al., 2013). Therefore, there is no wonder that many physiotherapists recommend intermediate reasonable exercise programs to help healing and recovery of the muscles of candidates (Steinacker et al. 2004).

In Egypt, although handball is very popular sport and Egypt is one of the leaders in this game that won many world trophies, still there is a lack of data describing the impact of intermediate reasonable exercise on inflammatory mediators including IL-6 and TNF- $\alpha$  among handball players. The rationale for the research was chosen after extensive search in literature. IL-6 and TNF- $\alpha$  are the most commonly measured pro-/anti-inflammatory cytokines in serum or plasma being frequently used as biomarkers of inflammation and known to stimulate C-reactive protein (CRP) release from the liver (Pepys and Hirschfield 2003). IL-6 and TNF- $\alpha$  are also frequently linked to increased incidence of disease (Pai et al. 2004), physical frailty or muscle wasting (Saidenberg-Kermanac'h et al., 2004; Schaap et al., 2006), and early death (Bruunsgaard 2002). Therefore, to better understand the mechanism of biological adaption of the immune system to physical effort among Egyptian handball players, we studied the impact of intermediate reasonable exercising on the levels of inflammatory mediators in candidates. To achieve this aim the levels of IL-6 and TNF- $\alpha$  as well as other hematological and immune markers including WBCs, RBCs, hemoglobin, platelets and hematocrit were

assessed in blood withdrawn from candidates before and after intermediate reasonable exercise.

## 2. Materials & methods

### 2.1. Subjects

The present study was carried out on 18 handball male players selected from Tanta club handball under 21 year's old team. All procedures were approved by Research Ethics Committee of Faculty of Pharmacy, Mansoura University (Code: 2020-88). Subjects selected were healthy and showing no symptoms of viral or bacterial infections at the time of samples collection. In addition, all test subjects had no history of major disorders that would affect basal levels of inflammatory markers like cardiovascular or neurological disorders. The test subjects represented a homogenous group with mean age of  $19.22 \pm 0.25$  years and mean body mass index of  $23.89 \pm 3.26$  kg/m<sup>2</sup>.

### 2.2. Samples collection

Blood samples were collected by clean venipuncture from test subjects just before daily usual handball exercise. One ml of blood was mixed with EDTA, while 3 ml of blood were allowed to clot for 15 min at room temperature and centrifuged for 10 min at 600g to isolate serum. Isolated serum was aliquoted and stored at  $-80$  °C till analysis. The same procedure was repeated after 1.5 h of intermediate reasonable exercise to collect whole blood and serum samples. Samples after exercise were collected within no more than 5 min of the end of physical exercise.

The intensity of exercise is assessed by the physical load planner in case of professional sportive teams (Halson 2014). During the competition period, the exercise load is distributed according to the schedule of matches. Exercise may be either intermediate reasonable or of higher intensity relative to the effort exerted by the players on the match day. The effort exerted in the match day is considered to be the maximum load (100%). Intensity of the exercise is reduced in the first exercise after the match, and then it gradually increases till reaching the peak on match day. In our study, since this was the second exercise after the match, the intensity of the exercise ranged between 60 and 70% including jogging, passing the ball while standing or while jogging and ball shooting for 1.5 h, which is intermediate reasonable exercise.

### 2.3. Blood picture and ELISA assay

Whole blood samples collected before and after exercise were subjected for blood picture analysis using hematology analyzer (D-Cell 60, Diagon®Ltd, Hungary). Data obtained included total WBCs count per microliter, differential ratio of WBCs subtypes (lymphocytes, monocytes, neutrophils, and eosinophils), RBCs count (million/ $\mu$ l), hemoglobin concentration (gm/dl), hematocrite value (%), and platelets count per microliter. On the other hand, serum samples were used to measure IL-6 using commercially available ELISA kit (D6050, R&D Systems, Inc., Minnesota, USA) according to the manufacturer's instructions. Also, TNF- $\alpha$  levels were analyzed in serum samples using commercially available ELISA kit (MBs2502004, My BioSource, San Diego, CA, USA) according to the manufacturer's instructions.

### 2.4. Statistical analysis

Data were expressed as mean  $\pm$  SEM. Paired *t*-test was used to compare between data obtained before and after exercise. For correlation studies, Pearson correlation was applied. Statistical

calculations were done using the computer software IBM SPSS version 25 (Chicago, IL, USA) and Microsoft Excel (Microsoft®OfficeExcel®2013). Statistical significance was set at  $P < 0.05$ .

### 3. Results

#### 3.1. Exercise-induced downregulation of IL-6 & TNF- $\alpha$

Serum levels of IL-6 decreased from  $104.55 \pm 2.93$  (Pg/ml) before exercise to  $55.57 \pm 3.06$  (Pg/ml) after exercise with highly significant difference ( $P < 0.001$ ). Also, exercise decreased serum levels of TNF- $\alpha$  from  $92.31 \pm 3.63$  (Pg/ml) before exercise to  $34.02 \pm 1.86$  (Pg/ml) after exercise with highly significant difference ( $P < 0.001$ ) (Fig. 1A). Moreover, there was a very significant positive correlation between IL-6 and TNF- $\alpha$  serum levels ( $r = 0.85$ ,  $P < 0.01$ ) (Fig. 3A).

#### 3.2. Exercise increases total WBCs count with no change in WBC subtypes ratios

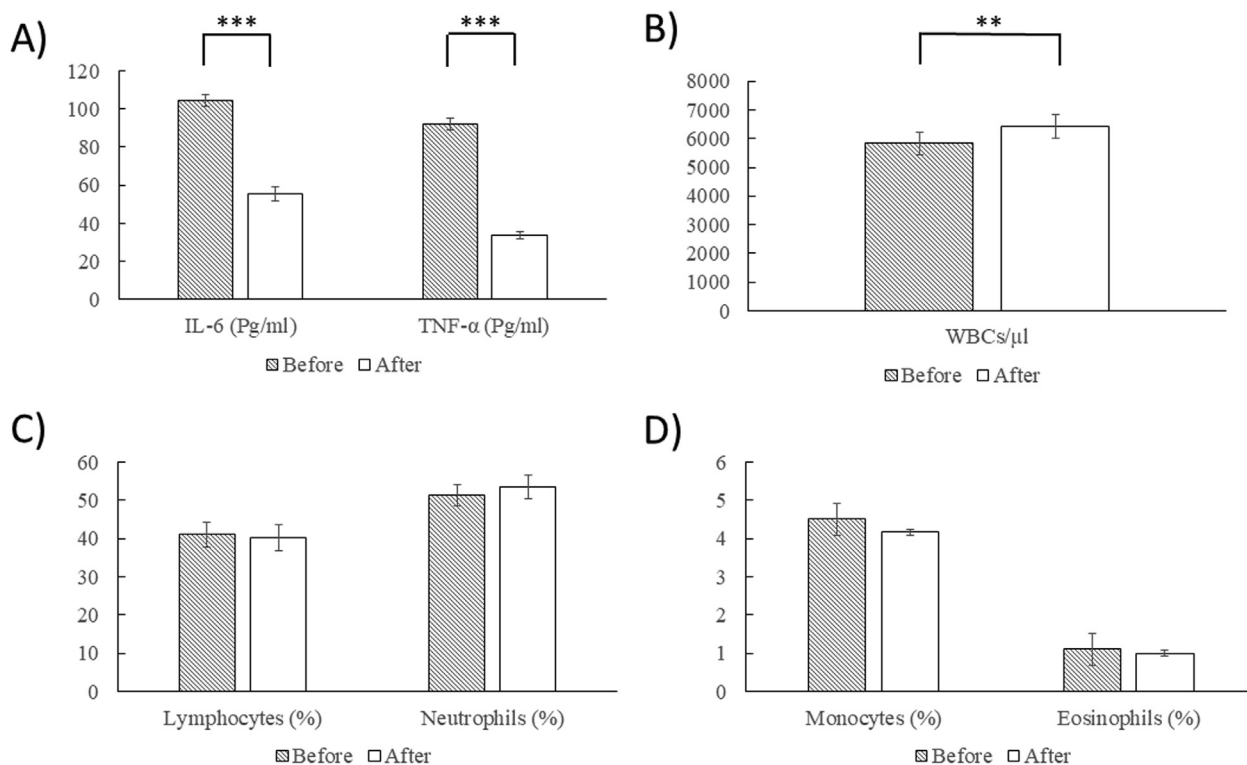
Total WBCs count increased from  $5833.33 \pm 404.55$  before exercise to  $6438.88 \pm 414.79$  after exercise with very significant difference ( $P < 0.01$ ) (Fig. 1B). However, our results showed a slight insignificant increase in neutrophils percentage and a decrease in monocytes percentage after exercise compared to those before exercise (Fig. 1C and 1D). Also, there was no significant changes in RBCs count, hemoglobin percentage, or hematocrite value after exercise (Fig. 2A and 2B). Nonetheless, there was a very significant increase in platelets count after exercise ( $P < 0.01$ ) (Fig. 2C).

#### 3.3. Correlation of TNF- $\alpha$ with monocyte percentage and IL-6 with total WBCs count

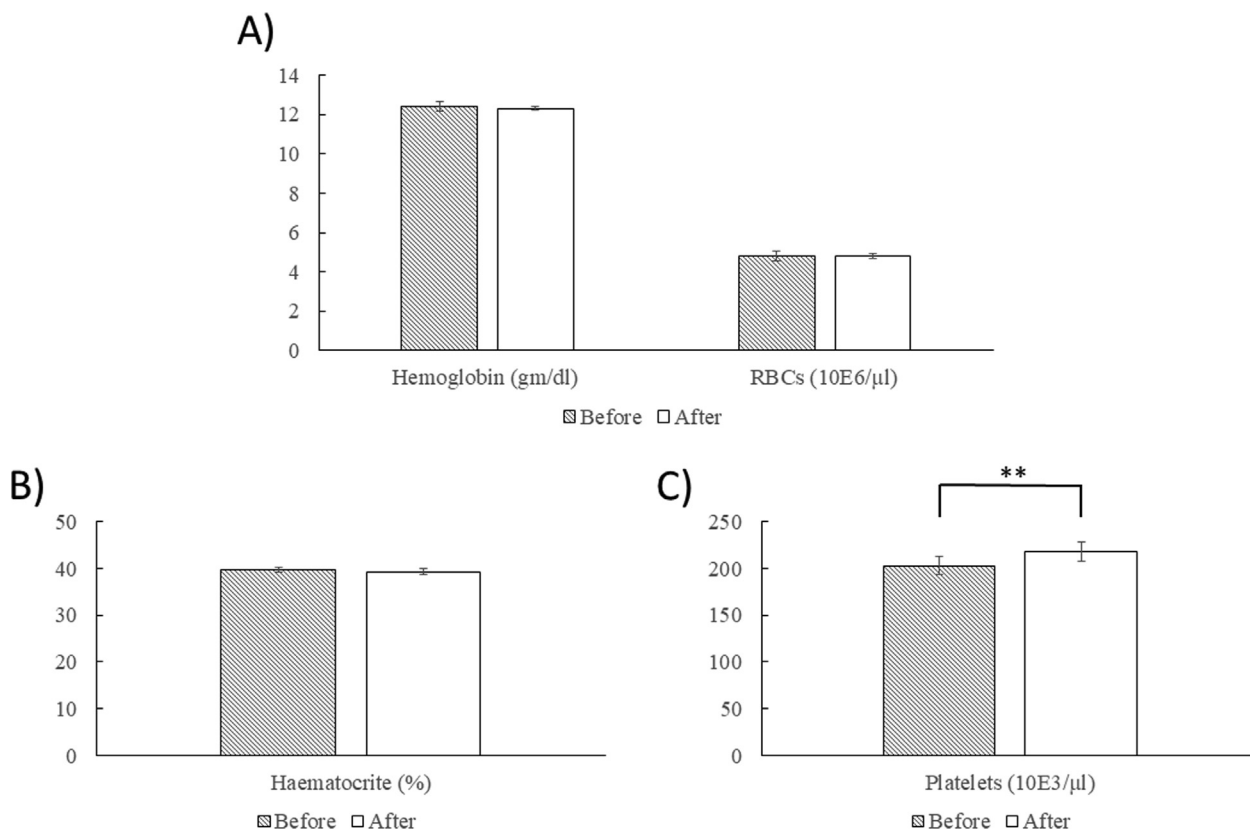
Correlation studies showed no significant correlations between IL-6 or TNF- $\alpha$  with any of blood picture results. However, TNF- $\alpha$  showed a significant negative correlation with monocytes percentage in test subjects before exercise only ( $r = -0.42$ ,  $P < 0.05$ ) (Fig. 3B) and Table 1. Moreover, IL-6 showed a significant negative correlation with WBCs count in test subjects after exercise only ( $r = -0.43$ ,  $P < 0.05$ ) (Fig. 3C) and Table 1.

### 4. Discussion

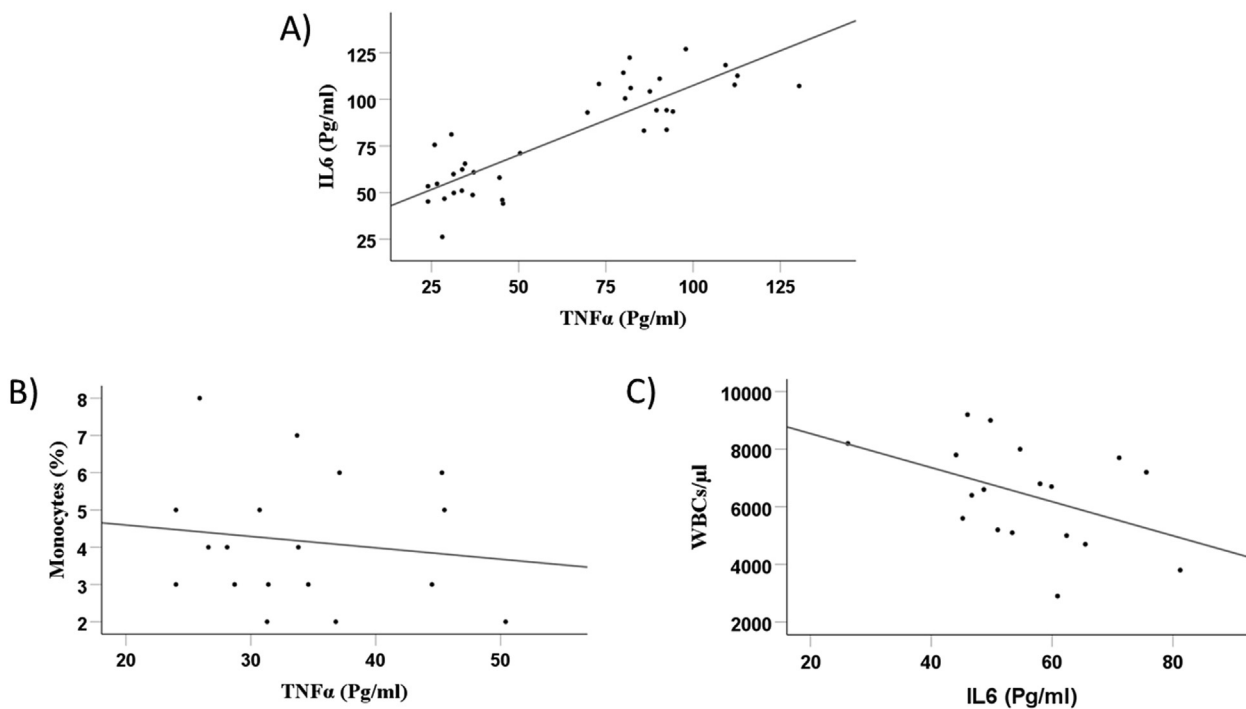
Among known cytokines, IL-6 and TNF- $\alpha$  are important mediators of the changes that occur in immune and musculoskeletal systems (Machado et al. 2014). They have a crucial role as pro-inflammatory cytokines, which mediate the processes of inflammation (Pandiyam and Zhu, 2015). They can however cause undesirable exorbitance of inflammation when produced in excess (Spoto et al. 2014). This situation is harmful especially when it is accompanied with chronic diseases that are characterized by existence of certain degree of inflammation (Siebert et al. 2015). In the present study, the measured levels of IL-6 and TNF- $\alpha$  in serum of candidates decreased significantly after intermediate reasonable exercise compared to those before exercise. It is reported that the levels of these cytokines can significantly decrease with different types of exercises such as cycling, swimming, handball, downhill running, athletics, etc. relying on the pace of exercise (Walsh et al. 2011). Exercise promotes skeletal muscles vasodilation (Xiang et al. 2005). Also, reasonable intermediate exercise loads decrease leptin levels in serum (Xiang et al. 2005). Leptin is a



**Fig. 1.** Levels of biomarkers before and 5 min after exercise in handball players. **A)** Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- $\alpha$ ); (\*\*\*): Significant difference  $P < 0.001$ . **B)** Total white blood cell count; (\*\*): Significant difference  $P < 0.01$ . **C)** Lymphocytes percentage and neutrophils percentage of total white blood cell count. **D)** Monocytes percentage and eosinophils percentage of total white blood cell count.



**Fig. 2.** Hematological biomarkers before and 5 min after exercise in handball players. **A)** Hemoglobin concentration (gm/dl) & red blood cell count (RBCs) (million/μl). **B)** Hematocrite value (%). **C)** Platelets count (1000/μl); (\*\*): Significant difference  $P < 0.01$ .



**Fig. 3.** Scatter-dot graphs showing significant correlations. **A)** Significant positive correlation between interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- $\alpha$ ) in the study subjects; (Pearson correlation coefficient ( $r$ ) = 0.85,  $P < 0.01$ ). **B)** Significant negative correlation between monocytes percentage and tumor necrosis factor-alpha (TNF- $\alpha$ ) in subjects before exercise; (Pearson correlation coefficient ( $r$ ) = -0.42,  $P < 0.05$ ). **C)** Significant negative correlation between interleukin-6 (IL-6) and total white blood cells count (WBCs) in the study subjects after exercise; (Pearson correlation coefficient ( $r$ ) = -0.43,  $P < 0.05$ ).

**Table 1**

Pearson correlation coefficient (2-tailed) of interleukin-6 (IL-6) & tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) with white blood cells (WBCs) differential ratio, red blood cells (RBCs), and platelets. (\*): Significant correlation ( $P < 0.05$ ).

Groups	Parameters	W.BC.s/ $\mu$ l	Lymphocytes (%)	Monocytes (%)	Neutrophils (%)	Eosinophils (%)	R.B.Cs (10E6/ $\mu$ l)	Platelets (10E3/ $\mu$ l)
Before exercise	IL-6 (Pg/ml)	0.09	0.20	-0.23	-0.16	-0.11	0.26	0.15
	TNF- $\alpha$ (Pg/ml)	-0.00	-0.05	-0.42*	0.119	-0.49*	-0.44*	-0.12
After exercise	IL-6 (Pg/ml)	-0.43*	0.05	0.10	-0.07	0.00	-0.13	-0.17
	TNF- $\alpha$ (Pg/ml)	0.23	-0.29	-0.13	0.30	0.01	0.17	-0.14

well-known adipocytokine known to elevate mRNA and protein expression of IL-6 resulting in inducing the inflammation (Tazawa et al. 2019). Moreover, it is reported that there is a positive correlation between leptin and TNF- $\alpha$  (Sun et al. 2005). Thus, in our study we suggest that reasonable exercise has decreased leptin levels leading to decreased levels of IL-6 and TNF- $\alpha$ . Whether, reasonable exercise-mediated downregulation of IL-6 and TNF- $\alpha$  occurs through direct muscle activity, an alteration in the hormonal milieu, or both is unknown. In our study the pace of exercise was reasonable intermediate and did not involve excessive efforts, which explains the lower levels of IL-6 and TNF- $\alpha$  after exercise than those before exercise. Our results are in agreement with Xiang et al. who reported that application of moderate regular exercise to obese Zucker rats causes significant decrease in IL-6 levels in comparison to obese sedentary rats (Xiang et al. 2005). Moreover, Keller et al. depicted the impact of exercise in normalization of TNF- $\alpha$  levels in mice. They speculated that IL-6 may mediate this effect (Keller et al. 2004). In addition, Faldt et al. hypothesized that IL-6 establishes its action through the reduction of body fat mass and stimulation of energy expenditure. Furthermore, it was demonstrated that deficiency of IL-6 in mice resulted in reduction of endurance and energy disbursement throughout exercise (Fäldt et al. 2004). On the other hand, it is reported that odd whimsical exercise results in an extreme increase in the plasma levels of IL-6 (Peake et al. 2005). Whimsical laborious exercise results in disruption of the myofibers through increased expression of IL-6. Therefore, there is a correlation between the increased level of IL-6 and the degree of muscle damage brought about by laborious exercise (Tomiyama et al. 2004). Thus, it is well documented that when released in the optimum levels, IL-6 may help in healing of tissue trauma (Blair et al., 1992; Filteau et al., 1992). Carrying out regular moderate exercises is helpful in maintaining the optimum levels of IL-6 and keeping good health. In addition, muscle atrophy is induced as a result of increased levels of IL-6 and TNF- $\alpha$  (Franceschi and Campisi, 2014; Haddad et al., 2005). Several biological impacts including lipolysis induction and cortisol stimulation take place during exercise as a result of IL-6 production (Pedersen and Febbraio 2008). Moreover, the beneficial effects of regular moderate exercise is well documented in chronic diseases like type 2 diabetes mellitus and cardiovascular diseases with low-grade inflammation (Shephard and Shek 1997). Patients suffering from chronic diseases exhibit high levels of plasma IL-6 and TNF- $\alpha$  in comparison to normal individuals (Franceschi and Campisi 2014). Regular exercise and diet control can help to decrease the inflammation in these patients via decreasing IL-6 and TNF- $\alpha$ . On the other hand, the levels of IL-6 and TNF- $\alpha$  increase when the same patients carry out whimsical laborious exercise leading to the worsening of the disease (Nicklas et al. 2005). In addition, previous studies established on healthy older males indicated that levels of IL-6 significantly decreased after moderate regular exercise. Therefore, it can be concluded that moderate regular exercise might play a crucial role during the aging process through maintaining homeostasis of inflammatory markers (Jankord and Jemiolo 2004).

To investigate the impact of IL-6 and TNF- $\alpha$  expression on WBCs and other hematological markers, we performed correlation stud-

ies between serum IL-6 and TNF- $\alpha$ . According to our results, there was a positive correlation between serum IL-6 and TNF- $\alpha$  levels. This was coupled with significant increase in levels of WBCs in candidates after exercise compared to those before exercise as well as negative correlation between IL-6 and WBCs. Moreover, the impact of IL-6 on hematological markers was demonstrated by the increased count of platelets in candidates after exercise compared to those before exercise. It is well documented that the differentiation of B-lymphocytes and immunoglobulins secretion is stimulated and enhanced by IL-6 (Mauer et al. 2015). IL-6 is a cofactor for thymocytes and hemopoietic colony growth (Platel et al. 1994). Secretion of acute phase proteins such as CRP in hepatocytes is stimulated by IL-6 (Zupke et al. 1998). It also acts as a growth factor for B-lymphocytes (Hunter and Jones 2015). TNF- $\alpha$  is a multifunctional and a pleiotropic stimulator of cellular responses (Kallioli and Ivashkiv 2016). It can act as inducer of cell adhesion molecules and cytokines and regulates the proliferation/differentiation in hemopoietic progenitors and lymphocytes (Dajani et al. 2007). It acts also as a cytolytic factor to certain tumor cells (Balkwill 2006). It is also known to cause insulin resistance (Moller 2000). It is noteworthy that few actions of IL-6 and TNF- $\alpha$  overlap with each other (Steinacker et al. 2004).

## 5. Conclusion

Conclusively, this study is the first report that indicates the decreased levels of IL-6 and TNF- $\alpha$  levels in the Egyptian handball players, who practice intermediate reasonable exercise regimens. The decreased levels of these inflammatory mediators were associated with elevation of WBCs and platelets count. Most interesting is that IL-6 significantly positively correlated with TNF- $\alpha$  in the study subjects, while significantly negatively correlated with WBCs in serum samples collected after exercise. Therefore, intermediate reasonable exercise regimens are highly recommended to protect from injuries as well as to help in the healing and recovery of the candidate's muscles.

## Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

## Acknowledgment

This study was performed at Biochemistry Department, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt, in collaboration with Microbiology and Immunology Department, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt.

## Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

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