

## DISCUSSION

Concept of successful ageing is in first line a preventive approach of care for older people. Declines in skeletal muscle performance and changing body composition with advancing age are hallmark examples of physiological aging process<sup>(178)</sup>.

Chronic low-grade systemic inflammation is a common manifestation of aging. Many mechanisms likely contribute to age-related inflammation<sup>(179)</sup>. Two to four-folds elevations in circulating levels of pro-inflammatory cytokines ;such as interleukin 6 (IL6), tumor necrosis factor (TNF)- $\alpha$ , and acute phase proteins such as C-reactive protein (CRP) and serum amyloid A (SAA), are typical in the elderly when compared to the young, even in the absence of chronic disease<sup>(180)</sup>.

TNF- $\alpha$ , which is one of the main inducers of the acute-phase response, plays an important role in alterations of muscle protein metabolism<sup>(181)</sup>, while CRP is one of several proteins referred as acute phase reactants which is used to monitor changes in inflammation associated with aging. The CRP concentration is thus a very useful non specific biochemical marker of inflammation<sup>(182)</sup>.

Lifestyle intervention such as regular exercise training may provide a low cost and long-term alternative to limit inflammation and slow declines in the elderly. Resistance exercise is recommended to be an important strategy, for the reduction or prevention of functional decline associated with aging<sup>(183)</sup>.

In the present study; we aimed to study the level of TNF- $\alpha$  and CRP before & after programmed resistance exercise in elderly subjects. This study was carried out on 30 healthy elderly subjects, aged 60 years or more ,of both gender and with no history of any systemic metabolic diseases.

We found in our study that, after exposure of the subjects to four weeks of programmed resistance exercise training, there were a significant decreased in both TNF – alpha level and serum CRP level measured ( $p=0.036$  and  $p=0.009$ ) respectively when compared to the previous starting level measured before the exercise in the same individuals. Which demonstrate that RET represents a low cost strategies that reduces age-related inflammation by decreasing the inflammatory markers and so may improves the quality of life in older adults.

In partial agreement with this study, Ogawa et al<sup>(184)</sup> studied twenty-one elderly women with mean age  $85 \pm 4.5$  years old, who had participated resistance exercise training sessions at least once per week for 12 weeks. The exercise program involved low-intensity resistance exercise. The duration of each exercise session was approximately 40 minutes consisting; of foot press, front traction, vertical traction, and shoulder press performed on Kinesis devices. Circulating levels of C-reactive protein (CRP) and tumor necrosis factor (TNF- $\alpha$ ) were measured before and after the exercise training. Ogawa, et al found that RET induced reduction significantly in CRP level( $P < .05$ ) while non significant changes in TNF- $\alpha$  level. These results suggest that even low-intensity exercise is beneficial for sedentary elderly as it induced a reduction in inflammatory markers and cytokines levels .

Also in a partial agreement with the current study, a cohort study of 3289 older Chinese with average age 60 years old, had participated in a population-based cross-sectional survey. Yu et al<sup>(185)</sup> found that higher levels of physical activity, assessed with the International Physical Activity Questionnaire, were related to lower levels of high-sensitivity CRP but not TNF- $\alpha$ . As plasma concentrations of hs C-reactive protein were 1.58, 1.74, and 1.27 mg/L among individuals with low, medium, and high levels of total physical activity, respectively. The inverse association between physical activity and hsCRP remained statistically significant ( $P=0.0138$ ). Moreover being physically active is associated with a better profile of inflammatory factors.

However, similarly consistent with Griewe et al<sup>(186)</sup>, studied the TNF- $\alpha$  level in muscles of eight elderly subjects ( $81\pm 1$  year old) underwent skeletal muscle biopsies before and after 12 weeks of resistance exercise program. They found that muscle TNF- $\alpha$  mRNA and protein levels decreased after RET and muscle protein synthesis rate was inversely related to levels of TNF- $\alpha$  protein. These data suggest that TNF- $\alpha$  contributes to age-associated muscle wasting and that resistance exercise may attenuate this process by suppressing skeletal muscle TNF- $\alpha$  expression.

This is consistent with the study of Elosua et al<sup>(187)</sup>, in which 1004 persons aged 65 years or more, participants in a cross-sectional population-based study performed a 400 meter walking test to assess physical performance. Compared to sedentary men, men practicing light and moderate-high physical activity had a significantly lower C-reactive protein (CRP) ( $p=0.025$  and  $p=0.001$ ) respectively, whereas only those men participated in moderate-high physical activity had a significantly lower TNF- $\alpha$  ( $p=0.030$ ). In women, those practicing light and moderate-high physical activity had only significantly lower CRP ( $p=0.020$ ), but TNF- $\alpha$  level was no longer significant. Moreover, as regard to gender and types of exercise; CRP level decreased in both gender while TNF- $\alpha$  decreased in men only with moderate to high exercise.

Another study was done by Geffken et al<sup>(188)</sup>, 5888 elderly aged 65 years or older; expected to remain in the area for 3 years as data obtained in 1989–1990 and 1992–1993 revealed that C-reactive protein was significantly correlated inversely ( $p=0.001$ ) when measured before and after self-reported long term physical activity, suggesting that increasing exercise is associated with reduction of inflammation in elderly.

Similarly, Taaffe et al<sup>(189)</sup> reported that CRP levels in the MacArthur cohort of high-functioning elderly persons were related to physical activity and walking speed, over seven years in those surviving and able to undergo testing so moderate physical activity may be beneficial in attenuating chronic inflammation. As CRP was reduced as moderate and strenuous physical activity had increased in 880 healthy elderly aged 70 to 79 years old.

This is consistent with Campbell et al<sup>(190)</sup> study which had examined the effects of twelve months of moderate intensity exercise for 5 days/week against a stretching control group in 115 overweight or obese sedentary post-menopausal women aged 50 to 75 years. In agreement with this study, they found that exercisers realized a significant reduction in CRP levels at 12<sup>th</sup> month, but not third month, of intervention when compared to the control group that exhibited no change in CRP. These findings support the role of exercise in modulating inflammatory processes that are related to increased risk of chronic disease among obese women.

The study of successful aging of Reuben et al<sup>(191)</sup> support this current study as they found that among 870 persons aged 70 to 79, individuals with higher levels of recreational activity had significantly lower CRP and IL-6 levels. Moreover the association between high levels of recreational activity and lower levels of the inflammatory markers IL-6 and CRP suggests a mechanism for its protective effect and supports interventions that increase physical activity in older persons. High levels of house/yard work and recreational activity were independently associated with lower risk of high CRP.

This is consistent with McFarlin et al<sup>(192)</sup> study, which revealed that acute exercise or a physically active lifestyle may possess anti-inflammatory properties. As hsCRP measured in elderly 60 to 80 years after a modified Balke submaximal treadmill test in previously inactive elderly (PI) and a control group of physically active (PA) elderly who maintained normal activity. Older participants had significantly higher hsCRP than young participants ( $p < 0.05$ ). Data collapsed across both groups; revealed that hs-CRP levels were significantly lower in active compared to inactive participants ( $p < 0.05$ ).

Also, Shahram et al<sup>(193)</sup>, studied 30 male subjects aged 60 to 70 years randomly assigned to one of three groups: endurance training, resistance training and control group, three days a week for 8 weeks at a definite intensity and distance. Before and after results showed that endurance and resistance training caused a significant decrease ( $p = 0.002$ ) in the serum CRP level. Therefore this support our study that resistance training caused a decrease in the inflammatory markers.

Similarly, Moreno et al<sup>(194)</sup>, studied serum CRP level in a group of 120 sedentary older Latino adults, with high rates of sedentary lifestyle, before and after physical activity. They found that the increased physical activity was associated with improvements in inflammatory markers. Moreover changing in self-reported physical activity level correlated inversely with decreasing in serum CRP level ( $p = 0.03$ ).

Similarly this is consistent with the study of Kohut et al<sup>(195)</sup>, in which sedentary low fit older adults aged 64 years or more, were randomized to moderate aerobic exercise training ( $n=48$ ) (CARDIO) and a flexibility with strength/resistance exercise group (FLEX) ( $n=49$ ) (3 times/week, 30–45min/day) for 10 months. The CARDIO group resulted in significant reductions in serum CRP compared to the FLEX group ( $p < 0.05$ ), whereas TNF- $\alpha$  levels declined in both groups ( $p = 0.001$ ). With the same regimen Vieira et al<sup>(196)</sup> study, had studied for ten months 127 elderly aged from 60 to 83 years, were randomized to two groups; a FLEX group ( $n=61$ ) where they participated in 3 times/week, 20-75min per day during which they performed flexibility and resistance exercises and a CARDIO group ( $n=66$ ) where they participated in 3 sessions/week (45- 60 min/session). As both studies revealed that aerobic exercises intervention could significantly reducing serum inflammatory mediators more than resistance exercises.

In partial agreement and with direct comparison between the effects of aerobic versus resistance training, 45 sedentary elderly aged more than 64 years participated in the study of Martins et al<sup>(197)</sup> and were randomly assigned to two exercise intervention groups and a non-exercising control group. The participants assigned to the exercising groups followed 16 weeks (45 min, 3 times/week) based either on aerobic training or resistance (strength) training through (elastic bands) followed by a further 16 weeks off-training period. High-sensitivity CRP concentrations were maintained throughout the study for the C (control) group, while in the resistance training group was statistically significant

decreased by 11% and 39% at 16<sup>th</sup> and 32<sup>th</sup> weeks, respectively. The hs-CRP concentrations decreased by 10% at 16<sup>th</sup> weeks and 51% at 32<sup>th</sup> weeks for the AT group.

Similarly, elevation of inflammatory cytokine levels in plasma is associated with reduction of physical performance and independence in the elderly. This was the conclusion of Pereira et al<sup>(198)</sup> study included 451 elderly women aged 65 years or older. Subjects were allocated to muscle strengthening exercise (resistance) and aerobic exercise groups. Both protocols lasted 10 weeks and included 30 sessions performed three times per week. There was a significant correlation between TNF- $\alpha$  levels and the effect of exercise on physical performance in elderly women regardless the exercise type, as TNF- $\alpha$  was decreased significantly ( $p=0.001$ ).

Also this is consistent with Nicklas BJ et al<sup>(199)</sup> study, levels of TNF- $\alpha$  were measured before and after 18 months of randomized controlled physical exercise involving; walking distance, stair-climb time and weight lifting for three days/week, in 214 elderly  $\geq 60$  years, with **kneeosteoarthritis**. In response to exercise, there were significant interaction between TNF- $\alpha$  and exercise training on 6<sup>th</sup> month changes in stair climbing time ( $p=0.007$ ), and on 18<sup>th</sup> month ( $p=0.01$ ).

In agreement with the results of the current study, but with exception of chronic diseases existence, (InCHIANTI) study which had performed on 1020 participants aged between 65 and 102 years, randomly selected with **chronic diseases**. Matteo Cesari et al<sup>(200)</sup>, found that inflammation, measured with high levels of CRP, is significantly associated with poor physical performance and muscle strength in older persons. The physical performance was assessed using: walking speed, the chair-stand test, the standing balance test and hand-grip strength. Serum levels of CRP and TNF $\alpha$ , after adjustment for demographics, chronic conditions, medication use, and other biological variables, were significantly correlated inversely with physical performance.

In contrast to the current work, Beavers et al<sup>(201)</sup>, found that nor CRP ( $p=0.1$ ) nor TNF- $\alpha$  ( $p=0.11$ ) levels had changed, when measured among group of 368 elderly with mean age  $76.4 \pm 4.1$  years, after 12 months of moderate intensity resistance training (150 min/week). IL8 was the only cytokine that significantly reduced in the exercised group. Moreover, Beavers study results did not strongly support the notion that long-term exercise can affect the panel of inflammatory biomarkers.

This is inconsistent with, Kapasi et al<sup>(202)</sup> study which had found that 32 weeks of functionally endurance and resistance exercise (every 2 hrs/day for 5 days/week) which improved functional measures did not bring about beneficial or detrimental effects on immune parameters and had no effects on TNF level measured in the 8<sup>th</sup> and 32<sup>th</sup> weeks in 190 elderly nursing home patients aged above 80 years. Furthermore, data suggested that the antiinflammatory response induced by 32 weeks of resistance training was not sufficient to reducing chronic activation of the TNF system.

Another study was done and disagreed with this study, Hammett et al<sup>(203)</sup>, have recruited 30 healthy elderly subjects aged from 60 to 85 years, after six months of regular resistance exercise. The level of CRP ( $p=0.3$ ) did not have any significant change despite of a significant improvement in their cardiorespiratory fitness. Alternatively, the cumulative effect of exercise may influence serum CRP levels over the course of many years, and although not by shorter term changes in exercise levels.

## *Discussion*

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By changing the type of exercise and by stabilizing the gender, Rahimi et al<sup>(204)</sup> had studied 30 old women aged between 60 to 80 years, categorized in two different groups: control and experimental groups. The latter group included 15 women, who participated in aerobic exercise for eight weeks; three sessions a week for half an hour per session. In contrast, after the two months there were no significant changes between serum CRP level before and after exercise ( $p=0.55$ ).

## SUMMARY

Aging can be defined as a complex mechanism of progressive and irreversible process occurring to molecules, cells and the whole organism ending with death. Better understanding of molecular and cellular mechanisms of aging can hold out some hope in finding feasible solutions to slow down the aging process.

The molecular inflammatory theory of aging has been proposed implicating reactive oxygen and nitrogen species and proinflammatory molecules as key players in the aging process. Increases in oxidative stress with aging may also contribute to the development of chronic inflammation and diseases.

A low-level increase in the systemic concentrations of the pro-inflammatory cytokines such as *tumor necrosis factor (TNF)- $\alpha$*  and acute phase proteins such as *C-reactive protein (CRP)*; is defined as LOW-GRADE INFLAMMATION which is related to atherosclerosis and also related to insulin resistance. The strong association between low-grade elevations in these circulating inflammatory mediators and high morbidity risk independently of pre-existing morbidity, suggests that these cytokines exaggerate pathological processes or act as very sensitive markers of subclinical disorders in elderly populations.

Lifestyle interventions such as *exercise training and dietary modifications* may provide a low cost and long-term alternative to limit inflammation and slow declines in the elderly. Regular physical activity is recommended, and generally considered to be an important strategy, for the reduction or prevention of functional decline with aging. In addition, physical activity reduces the risk of disease and has a beneficial effect on the impact of a large number of chronic diseases and the functional consequences and multimorbidity.

### **In this study, we aimed to:**

Study the level of TNF- $\alpha$  and CRP before & after programmed resistance exercise in elderly subjects.

### **The study was conducted on:**

A total of thirty elderly individuals aged 60 years or more and of both gender, with no history of any systemic metabolic diseases as diabetes, nor hypertension, nor hepatic nor renal diseases. The selected subjects were attended at the Department of Physical Medicine, Rheumatology & Rehabilitation in El Hadara Alexandria University Hospital.

### **All subjects enrolled in the study were subjected to the followings:**

Taking full medical history, also complete clinical examination and electrocardiogram (ECG) were done for each subject before starting the resistance exercise training.

**Laboratory investigations done for the studied individuals included:**

- *Routine laboratory investigations*: complete blood picture ,random blood sugar(RBS), and renal function tests [ blood urea ,serum creatinine and assessment of glomerular filtration rate (GFR) by Modification of Diet in Renal Diseases (MDRD)].
- *Spec.fic inflammatory markers*: (were measured twice before and after resistance exercise)
  1. Tumor necrosis factor –alpha (TNF-  $\alpha$ ).
  2. C-Reactive protein(CRP).

**Resistance exercise training:**

All elderly in the study were subjected to exercise sessions done three times per week for four weeks. The exercise program was involved low-intensity RET which had be performed on Kinesis device for both upper and lower limbs; involved: a warm-up period (5 min), a cool-down period (5 min) and specific resistance training period (30 min) inbetween that consisted of :

- Resistance training for dorsiflexors (a cable is attached to the foot from the floor, and the thigh is raised).
- Front traction (a horizontally drawn cable is grasped and stretched forward).
- Vertical traction (a cable is grasped from above and stretched downward).

**The followings results were found:**

- After exposure of the subjects to four weeks of programmed RET ,there were a statistically significant decrease in both TNF –alpha level and serum CRP level when compared to the previous starting level measured before the exercise in the same individuals.

**From the previous results, we can reach the conclusion that:**

- There were a negative correlation between TNF-alpha & CRP level and the resistance exercise training.
- Resistance exercise represents a low cost strategies that may reduces age-related inflammation by decreasing the inflammatory markers and so may improves the quality of life in older adults.

## CONCLUSIONS

**From the previous discussion, it can be concluded that:**

- Chronic low-grade systemic inflammation is a common manifestation of aging.
- Increasing in oxidative stress associated with aging may also contribute to the development of chronic inflammation and diseases.
- Elevations in circulating levels of pro-inflammatory cytokines :such as *tumor necrosis factor (TNF)- $\alpha$* , and acute phase proteins such as *C-reactive protein (CRP)* were typical in elderly , even in the absence of chronic disease.
- Exercise has a beneficial effect ,as evidence by a statistically significant decrease in CRP and TNF- $\alpha$  after one month resistance exercise training in both gender .
- Most of the studies in the literature have concluded that maintenance of moderate but regular physical activity is associated with a reduction in total morbidity among older people.