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STRUCTURED SUMMARY

Introduction

Previous studies have shown that Military Field Training (MFT) has effects on warfighters' hormonal responses, neuromuscular performance and shooting accuracy. The aim of the present study was to investigate the changes in body composition, upper and lower body strength, serum hormone concentrations of testosterone (TES) and cortisol (COR), insulin-like growth factor – 1 (IGF-1) and sex hormone binding globulin (SHBG) and shooting accuracy during prolonged MFT.

Methods

Serum hormone concentrations, isometric strength of the upper and lower extremities and shooting performance were measured four times during the study: before MFT (PRE), after 12 days (MID), at the end of MFT (POST) and after four days recovery (RECO). The study was approved by the Finnish Defence Forces and was granted ethical approval by the Ethical Committee of the University of Jyväskylä.

Results

There was no change in prone shooting score between the measuring points. In the standing position, however, there was a significant ($p \le 0.001$) decrease from PRE 58.2 ± 12.3 points to MID 45.2 ± 10.4 points. Also POST 61.4 ± 10.8 points and RECO 56.8 ± 13.6 points were significantly ($p \le 0.001$) higher than MID 45.2 ± 10.4 points. Serum hormone concentrations of TES and IGF-1 decreased significantly during MFT. In COR and SHBG concentrations significant increases were observed during MFT. Individual changes in lower body strength and changes in shooting standing score between the measurement points (PRE - MID / POST / RECO) correlated significantly (r=0.332, p=0.031; r=0.335, p=0.025; r=0.489, p=0.001, respectively). The similar finding was observed with changes in upper body strength and changes in standing between the PRE

and RECO measurement points (0.339, p=0.010). The changes in COR and the changes in prone shooting showed a positive correlation in all measurement points (r=0.531, p \leq 0.001; r=0.337, p=0.024; r=0.572, p \leq 0.001). The changes in IGF-1 correlated negatively (r=-0.325, p=0.038) with shooting prone between the PRE and MID measurement points. The changes in shooting standing and the changes in TES between PRE and POST correlated negatively (r=-0.378, p=0.010).

Conclusion

In this study we observed a decrease in leg strength from the PRE to MID measurements. When the physical load requirements during the MFT decreased after the MID measurements, leg strength increased. In addition, the shooting score from the standing position decreased from the PRE to MID measurements and improved significantly from the MID to POST measurements. The prone shooting score did not show any significant changes during the study period. Significant positive correlations were found between the changes in standing shooting score and the changes in strength for the legs and upper body. There was a positive correlation between the changes in serum COR concentrations and changes in standing shooting score.

Altogether, the present study showed that the prolonged MFT has adverse effect on the strength levels and the shooting ability in warfighters. This shows that ensuring warfighters get an appropriate amount of rest while performing their duties is important. Shooting from a prone position was not affected by the changing workloads and this result indicated that soldiers should shoot from a prone position, whenever possible, especially when fatigued.

INTRODUCTION

Warfighters are exposed to physical, environmental and mental stressors when training for military operations. These stressors include factors such as physical and cognitive fatigue caused as a consequence of prolonged physical exertion and/or sleep deprivation and insufficient energy and fluid intake. During military field training (MFT) these factors have shown to cause disruptions in hormonal balance^{1,2,3,4}, leading to reduced physical and cognitive performance^{5,6,7,8,9}, extended recovery times¹⁰ and increased susceptibility to infections¹¹. How this kind of environment effects on warfighters' hormonal responses, neuromuscular performance and shooting accuracy and the consequences of these stressors and their influence on health, physical performance level and work capacity of a warfighter are of vital importance to commanders.

Previous studies have examined various biomarkers in warfighters in relation to nutrition status, fluid intake, body composition^{5,12}, prolonged physical exertion, neuromuscular performance^{6,13} and sleep deprivation^{14,15}. Decrements in lower and upper body strength have been demonstrated after a prolonged MFT. The type of loading is a key determinant to which part of the body becomes fatigued ^{2,6,7,13}. In order to carry out daily duties, warfighters must have good muscle strength capability¹⁶. Even in the face of technological developments in the military field, the modern warfighters tasks are, however, physically very demanding. Both lower and upper body strength must be considered: marching long distances require a warfighter to have a strong lower body, while for lifting and carrying heavy equipment, a warfighter must have good upper body strength^{7,17}. The modern warfighter needs power and strength as well as aerobic capacity and muscular endurance. The optimal level of either one is dependent on occupational tasks of a warfighter¹⁸. Multiple studies have also demonstrated that strength training and higher strength levels coincide with lower injury levels, particularly in the lower extremities^{19,20}.

The impact of MFT on hormonal changes is well demonstrated. Cortisol (COR) and sex hormone binding globulin (SHBG) concentrations have been shown to increase during prolonged MFT^{1,3,7,21,22,23}, whereas testosterone (TES) and insulin-like growth factor - 1 (IGF-1) concentrations have been shown to decrease^{1,6,21,24,25,26,27,28} Friedl et al. (2000) found that during US Army Ranger training a warfighter lost 15 % in body mass, 7 % in fat free mass and 65 % of their fat mass. Nindl et al. (2006) studied the effects of short term MFT on hormonal responses. The study showed that there was a 3 % loss in body mass and 24 to 30 % loss in free TES levels. Kyröläinen et al. (2008) found that during the first couple of days of strenuous MFT there was a significant increase in COR levels (32 %) and a decrease in TES levels (27 %). Also, SHBG levels have been found to increase during basic military training²³ and during heavy and strenuous MFT²⁶.

Shooting is one of the most important occupational skills for a warfighter. There is limited information regarding shooting performance and how it is affected by prolonged MFT. It has been shown that shooting performance differs as a result of different loading intensities^{29,30,31,32,33}. Warfighters are required to move on the battlefield, and maximizing shot accuracy in a state of increased heart rate and fatigue³¹. Several factors affect the accuracy of shooting in warfighters. Anxiety has been shown to decrease the accuracy of shooting as well as a negatively impact on decision making³⁴. Fatigue is also a significant factor affecting marksmanship, especially after anaerobic physical strain^{30,31,32}. In addition to anxiety and fatigue, sleep deprivation has shown a detrimental effect on the shooting accuracy. Research on how prolonged MFT in a multistressor environment affects the warfighters shooting performance is lacking³³.

The aim of the present study was to investigate the changes in body composition, upper and lower body strength, serum hormone (TES, COR, SHBG, IGF-1) concentrations and shooting accuracy

during a prolonged MFT. We hypothesized that we would observe declines in all measured variables and the study would provide better understanding of the associations between warfighters physical performance and shooting capability during MFT.

METHODS

Subjects

Sixty-one (n=61) male subjects volunteered for the present study. Each subject (conscript) was a Finnish Army member conducting infantry training, performed during their six-month mandatory service in the Finnish Defence Forces. Based on exit interviews, twelve individuals dropped out due to discomfort of having to give blood samples and unsustained motivation to participate in the study. Forty-nine subjects between 19 to 22 years of age completed the study. The mean (\pm standard deviation) age was 20 \pm 1 years, height of 179 \pm 6 cm, body mass 73.5 \pm 8.7 kg and body fat 12.6 \pm 5.0 %.

All subjects were fully informed of the experimental design and possible risks, and every subject signed an informed consent before the study commenced. The subjects were informed that they could cancel their participation in the present study at any stage if they so wished without any consequences. This study was conducted according to the provisions of the Declaration of Helsinki and was granted ethical approval by the Ethical Committee of the University of Jyväskylä. The study was also approved by the Finnish Defence Forces.

Experimental Design

A week before MFT, all the subjects were tested for their baseline values. The same tests were also performed on the day 12 of MFT, at the end of MFT and after a recovery period of four days. Blood samples, isometric strength of the upper and lower extremities and shooting performance were recorded during the measurement days. The PRE measurement week was a normal training week for the study participants. Duties included lectures in the classroom, rifle maintenance and preparation for MFT. The entire 21-day MFT period, which was divided into three phases, was performed in field conditions. During the first phase (ST) the subjects performed combat drills and live-fire shooting exercises. The goal for each conscript was to improve their combat and shooting skills and advance their weapon handling abilities. In this phase, the aim was not to physically exhaust the conscripts but rather to ensure that each of them maintained a high level of performance by ensuring that they had an appropriate amount of rest and sleep. The normal training day started at 07:00 hours and ended not later than 19:00 hours.

In the second phase (MFT), they practiced moving from their base to their attacking positions. The tasks performed included reconnaissance, combat maneuvers, patrolling and tactical road marches. In the last phase (MFT) they executed combat mission as a part of larger military exercise. The tasks were the same as in the second phase. After the prolonged MFT, the subjects had four days of recovery, two at home and two at the garrison before the final study measurements were taken.

Measurements

Neuromuscular performance

Maximal isometric strength of the upper and lower extremities was measured with dynamometers. The measurements were conducted using a leg and bench press dynamometer manufactured by the University of Jyväskylä, Department of Biology of Physical Activity, Finland. The knee angle was set to 107 degrees ³⁵. During the maximal strength test for upper extremities the equipment was adjusted for each subject so that when in sitting position with their feet flat on the floor their arms were parallel to the floor and the elbow angle was 90 degrees. The test was performed by pushing the bar horizontally. The subjects were given one trial attempt before the two actual test trials were

conducted on both leg extension and bench press. The subjects were instructed to produce maximal force as fast as possible in both leg extension and bench press. On all trials, the testing personnel encouraged them vocally during the maximal effort. The best performance was selected for analysis.

Serum Hormone concentrations

Venous blood samples were drawn four times from the antecubital vein after an overnight fast between 0630 - 0730 to analyze TES, COR, SHBG and IGF-1 (Siemens Immulite 2000 XPI, Siemens Healthcare, USA). Interassay coefficients of variance were 9.4% for TES, 7,6% for COR, 5.6% for SHBG and 6.7% for IGF-1. The samples were centrifuged (Megafire 1.0 R Heraeus, DJB Lab Care, Germany) at 3500 rpm for 10 minutes and frozen and transported to the laboratory for later analysis.

Shooting

The shooting test was performed from both prone and standing positions. First, the conscripts fired ten shots at the target from a prone position and then ten shots from a standing position. The best possible score was 100 points, and the result for each person was given at an accuracy of 0.1 points. The shooting test was performed indoors and the target was ten meters away in both prone and standing positions. The weapon system used (Eko-Aims Oy, Ylämylly, Finland) was similar to the Army assault rifle (RK95, Finland) which the conscripts handled daily. Because the tests were performed indoors the conditions were the same in all measurement periods. The sum of ten shots from both positions was recorded for analysis.

Statistical Analysis

The data was analyzed using IBM SPSS Statistics 22.0 (IBM Corporation, Armonk, NY). Statistical analysis included descriptive statistics, Pearson correlation, and multivariate analysis of variance with repeated measures. Probability adjusted *t* tests were used for pairwise comparisons. A general linear

model, with repeated measures ANOVA was used to analyze the differences between the different measuring points. Bivariate correlation was used for correlation analysis where the changes in the variables between the different time points were tested. The p < 0.05 criterion was used for establishing the statistical significance.

RESULTS

Neuromuscular performance

There was a significant increase ($p \le 0.05$) in isometric leg press force from MID of 3406 ± 923 N to POST 3532 ± 1011 N measurement. No other significant changes were found in leg press. Force of upper body isometric bench press increased significantly ($p \le 0.001$) from PRE of 890 ± 181 N to MID 929 ± 179 N. There was a decline in POST of 900 ± 179 N ($p \le 0.05$) and RECO 873 ± 178 N ($p \le 0.001$) measurements when compared to MID 929 ± 179 N. RECO 873 ± 178 N ($p \le 0.001$) was also significantly lower than POST of 900 ± 179 N measurement. (Table 1)

Shooting

There was no change in prone shooting score between the measuring points. In the standing position however there was significant ($p \le 0.001$) decrease from PRE 58.2 ± 12.3 points to MID 45.2 ± 10.4 points. Also POST of 61.4 ± 10.8 points and RECO of 56.8 ± 13.6 points were significantly ($p \le 0.001$) higher than MID of 45.2 ± 10.4 points. (Table 1)

Serum hormone concentrations

Testosterone

Serum TES concentrations decreased significantly ($p \le 0.001$) from PRE 18.5 ± 4.5 nmol/l to MID 13.8 ± 4.9 nmol/l (-25.0%) and POST 16.0 ± 4.2 nmol/l (-13.0%). The POST value was also significantly ($p \le 0.01$) higher (15.9%) than the MID. RECO 19.9 ± 3.7 nmol/l was significantly ($p \le 0.001$) higher (44.2 %) than MID and POST (24.4 %) and also higher than PRE ($p \le 0.05$) (8.2 %). (Table 2)

Cortisol

There was a significant increase in serum COR concentrations between PRE 301 \pm 86 nmol/l and MID 355 \pm 76 nmol/l (p≤0.05) (17.8 %), POST 396 \pm 69 nmol/l (p≤0.001) (31.3 %) and RECO 385 \pm 85 nmol/l (p≤0.001) (27.8 %). Also POST cortisol was significantly (p≤0.001) higher that of MID (15.9%). (Table 2)

Insulin-like Growth Factor-1

IGF-1showed a significant ($p\leq0.001$) reduction from PRE of 40.6 ± 7.7 nmol/l to MID 32.5 ± 8.9 nmol/l (-20.0 %) and POST 32.5 ± 7.7 nmol/l (-20.0 %) Also a significant increase of the same magnitude ($p\leq0.001$) was observed between RECO of 39.4 ± 7.8 nmol/l and MID (21.2 %) and POST (21.2 %). (Table 2)

Sex Hormone Binding Globulin

There was a significant increase in SHBG from PRE of 30.1 ± 7.6 nmol/l to MID 32.8 ± 7.9 nmol/l (p ≤ 0.01) (9.0 %) and POST of 34.3 ± 9.1 nmol/l (p ≤ 0.001) (14.0 %). A significant (p ≤ 0.001) decline was observed between POST and RECO 31.5 ± 8.1 nmol/l (-8.2 %). (Table 2)

Associations between strength, shooting and serum concentrations

In the present study individual changes in lower body strength and changes in shooting standing score between the measurement points (PRE - MID / POST / RECO) correlated significantly (r=0.332, p=0.031; r=0.335, p=0.025; r=0.489, p=0.001). The same effect was found with changes in upper body strength and changes in shooting standing between PRE and RECO measurement points (0.339, p=0.010). With regard to serum concentrations a negative correlation was observed between the changes in SHBG and changes in IGF-1 in all measurement points (r=-0.310, p=0.043; r=-0.482, p=0.001; r=-0.382, p=0.010). There was also a positive correlation between the changes in SHBG and the change in TES (r=-0.330, p=0.027) when comparing the PRE and RECO measurement points.

The changes in COR correlated negatively with the changes in TES (r=-0.341, p=0.025) and the changes in IGF-1 (r=-0.346, p=0.023) between the PRE and MID measurement points. The changes in COR and the changes in shooting prone showed a positive correlation in all measurement points (r=0.531, p \leq 0.001; r=0.337, p=0.024; r=0.572, p \leq 0.001). The changes in IGF-1 correlated negatively (r=-0.325, p=0.038) with shooting prone between the PRE and MID measurement points. The changes in shooting standing and the changes in TES between PRE and POST correlated negatively (r=-0.378, p=0.010).

DISCUSSION

Our study supports previous investigations and adds to the existing literature on stressors and key military performance measures. The present study showed the decrease in leg strength from the PRE to MID measurements. When the physical load decreased after the MID measurements, the leg strength increased. In addition, the shooting score from the standing position decreased from the PRE to MID measurements and improved significantly from the MID to POST measurements. The shooting prone score did not show any significant changes during the study period. Serum COR and SHBG concentrations increased from PRE to MID and POST. SHBG increased in RECO measurements, but COR did not change. Serum TES and IGF-1 concentrations decreased during MFT and increased in RECO measurements. Significant positive correlations were found between the changes in standing shooting score. All the measured variables except cortisol returned close to the baseline level after the recovery period.

Previous military field exercise studies^{2,6,7,13} have shown that prolonged physical activity and negative energy balance combined with sleep deprivation have negative impact on neuromuscular performance and hormonal balance of a warfighter. In the present study, maximal upper body strength increased significantly from the PRE to MID measurements, but decreased back to PRE levels in the POST and RECO measurements. This was probably partly due to learning, but indicated that upper body strength was not affected by prolonged MFT.

It has been shown that lower body strength is an important factor for warfighters to be successful in their duties^{16,17}. In the previous studies the lower body power has been reported both to either decrease

or increase² after MFT. In the present study, a slight, but not significant, decrease in leg extension values in the MID measurements. This was probably due to the higher loading of the first part of MFT as the four days before the MID measurements were physically the most demanding part of MFT. These findings suggest that lower body strength levels are related to the loads of MFT. There were no further declines after the loading was reduced. This indicates that it is possible to recover physically during the present type of MFT. Kyröläinen et al. (2008) had similar findings with reduced load during prolonged MFT. They showed that a lighter period between two intensive MFT parts can allow strength and hormone levels to recover before the commencing of the second intensive training period.

Serum TES concentration decreased significantly from the PRE to MID (-25.0%) and PRE to POST (-13.0%) measurement. Similar findings have been reported earlier^{1,3,21}. A significant increase was observed between MID to POST (15.9%) and POST to RECO (24.4%) measurements. This was probably due to the amount of physical load during MFT, as it was physically harder in the beginning of MFT.

Serum COR concentration on the other hand, increased during MFT (31.3%) and did not return back to resting levels during the recovery period (27.8%). Friedl et al. (2000) and Nindl et al. (2007) found similar effect with US Army Rangers. Cortisol concentration increased significantly during the study period, but no recovery period was included. Kyröläinen et al. (2008) found that during a 20 day MFT cortisol levels increased by 32 %. COR, unlike TES and strength values did not begin to increase after the MID measurements. The present results showed that despite the loading was reduced in the latter part of MFT, the stress levels were at highest at the end of MFT, when the warfighters' training reached its capstone exercise.

Previous studies have shown that SHBG concentration has increased during strenuous physical training²². In a study with Finnish conscripts, Tanskanen et al. (2011) showed that SHBG values were

elevated during eight weeks of military training. Accordingly, Alemany et al. (2008) have shown an increase in SHBG during MFT. In the present study, SHBG concentrations increased significantly from the PRE values in the MID (9.0%) and POST (14.0%) measurement points, but returned back to the PRE values in the RECO measurements.

IGF-I is one particular biomarker that has demonstrated a positive relationship between circulating levels and aerobic fitness³⁶. Additional biomarkers (e.g. COR, TES, SHBG) have also shown to predict excessive rates of physical performance change. In addition to the ability of biomarkers to predict fitness measures, certain biomarkers that are sensitive to changes in homeostasis may serve as early indicators of stress or overreaching^{3,23,26}. Rosendahl et al. (2002) reported a significant decline in total IGF-1 values after 11 weeks of garrison training. There have also been decreases in IGF-1 values after MFT³⁷ and longer special force training⁶.

In the present study IGF-1 concentration decreased from the PRE to MID measurements by 20.0%. The values stayed the same from MID to POST and returned back to resting levels in the RECO measurements. Similar findings have been reported in earlier studies^{7,28,38}. Even more drastic changes (-62.0%) have been found during special force training⁶. The decrease in IGF-1 concentration is mainly due to physical strain and energy deficit, which has been shown to decrease IGF-1 concentration²¹. This decrease in IGF-1 concentration indicates that warfighters' ability to recovery from physical strain and to repair muscle damage is weakened and can lead to decrease in physical performance. IGF-1 concentration seems to be a good marker to evaluate warfighters' recovery and physical performance.

In previous studies soldiers' shooting performance has mainly been measured after different simulations of military work. These studies have shown that drastic anaerobic work periods can decrease shooting accuracy, but it has been shown to recover quickly³³. Evans et al. (2003) observed

the fatiguing upper body obstacle course decreased shooting accuracy significantly, but it recovered quickly. Load carriage has also been shown to decrease shooting accuracy⁴⁰, although it seems that there is no change before the carried loads of 45% of body weight³⁴. In a study of Tenan et al. (2017) shooting performance was studied during a loaded march with live-fire shooting in the field. They found that load carriage and marching did not affect shooting accuracy, actually the shooting improved with lighter load. In the present study we found that shooting from the prone position did not alter during MFT. Standing shooting was more sensitive to fatigue, but it seemed to decrease only after the first and most physically demanding part of MFT. Declines in lower body strength and hormonal concentrations have been shown to occur during MFT^{6,7}. This might explain the decline in standing shooting score as physical exhaustion causes the heart rate to elevate and influence the shooting mechanisms³³. More research should be done in the future to investigate the interaction between mechanical and physiological effects and differences in the standing and prone shooting positions in soldiers.

The change in standing shooting score correlated positively with the change in lower body strength. The similar correlation was observed between the change in upper body strength and the change in standing shooting only between the PRE and RECO measurements. It seems that muscular strength, especially in the lower body seems to be important for the standing shooting accuracy of a warfighter during MFT. Both lower and upper body strength seems to be important for enhancing the recovery process and thus the standing shooting accuracy in the recovery phase.

In the RECO measurements almost all the measured values were recovered to the PRE measurement values. Serum COR concentration was significantly higher than in the PRE measurements. Also, body weight (BW) and skeletal muscle mass (SMM) were significantly lower than in the PRE measurements, but had almost recovered to the PRE values. It seems like four days is adequate for the warfighter to recover from the physical strain of the present prolonged MFT in all measured variables except for COR concentration.

The present study had some limitations. Participants were representatives of the larger population doing their military service. A number of the subjects in the study represents only a small fraction of the total number of service members. Thus, some caution should be used when extrapolating the physiological data to the general population. Also, the number of dropped subjects in the study might have had an influence on the results, because most of the dropped subjects were among the poorest half with regard to physical fitness. On the other hand, this might also decrease the motivational effect of the results, when the least motivated subjects were dropped out of the study. The present subjects were familiarized with most of the physical tests, but some new tests were implemented (maximal isometric tests), which could have had some influence in the results due to learning effect. Nevertheless, all the measurements were carefully controlled by the trained researchers, and the tests were completed in the same order and same time of day in all the measurement points.

The strength of the present study was that the conscripts performed similar duties during the study period. In addition, there was a daily control of the subjects and the researchers were able to monitor the loading during the whole study period. The MFT lasted for 21 days, which made it more realistic when compared to short (three to five days) MFTs. The physical loading in the latter part of MFT was lower than expected. This may have influenced the observed measures as they (shooting and isometric maximal strength) did not decline after the MID measurements as expected based on prior studies.

The present study showed that the prolonged MFT has adverse effect on the strength levels and the shooting ability in warfighters. Therefore, to ensure that warfighters get an appropriate amount of rest, while performing their duties is important. Shooting from a prone position was not affected by the changing loads and this result indicated that soldiers should shoot from a prone position, whenever possible, especially when fatigued.

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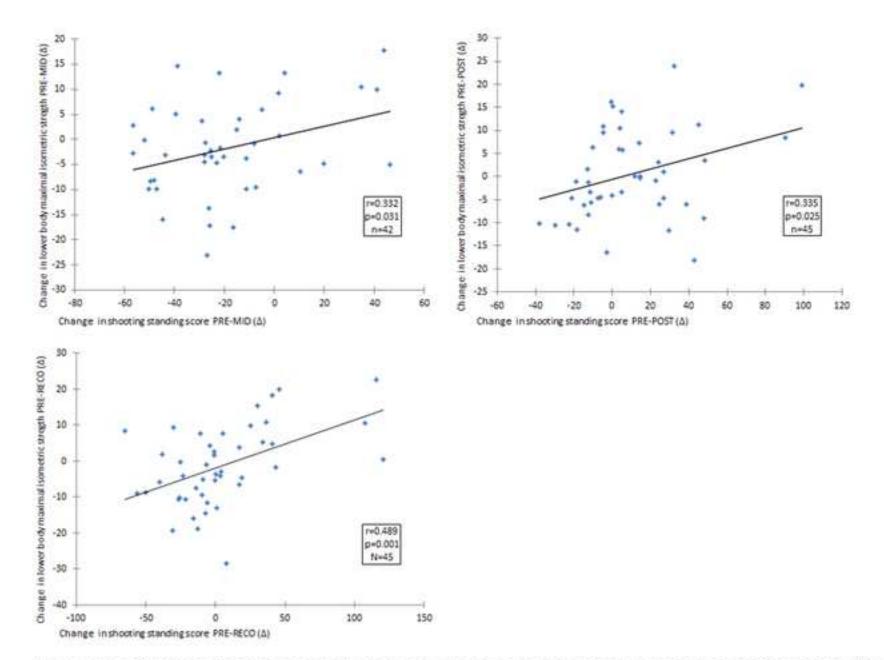


Figure 1. Correlations between the lower body maximal isometric strength and shooting standing score between the PRE-MID, PRE-POST and PRE-RECO measurement points

Abbreviations: PRE, Before training measurements; POST, Post training measurements; RECO, Recovery measurements

Isometric strength	PRE	MID		POST		RECO	
Bench Press (N)	890±181	929±179	***	900±179	Ť	873±178	*†††‡‡‡
Leg Press (N)	3495±931	3406±923	-	3532±1011	Ť	3424±913	-
Shooting	PRE	MID		POST		RECO	
Prone (Points)	84.3±11.7	85.5±9.1	-	84.8±11.5	-	87.2±11.0	-

Table 1. Mean (±SD) values of isometric strength and shooting tests during MFT (*,†,‡ = p<0.05, ***,†††,‡‡‡ = p<0.001; *, *** = compared to PRE values, ††† = compared to MID values, ‡, ‡‡‡ = compared to POST values)

Abbreviations: PRE, Before training measurements; POST, Post training measurements; RECO, Recovery measurements

Hormones	PRE	MID		POST		RECO	
TES (nmol/l)	18.4±4.5	13.8±4.9	***	16.0±4.2	***††	19.9±3.7	*†††‡‡‡
COR (nmol/l)	301±86	355±76	*	396±69	***††	385±85	***
IGF-1 (nmol/l)	40.6±7.7	32.5 ± 8.9	***	32.5±7.7	***	39.4±7.8	****
SHBG (pmol/l)	30.1±7.6	32.8±7.9	**	34.3±9.1	***	31.5±8.1	***

Table 2. Mean (±SD) serum hormone concentrations and SHBG concentrations during MFT (* = p<0.05, **,†† = p<0.01, ***,†††,‡‡‡ = p<0.001; *, ** , *** = compared to PRE values, †, ††, ††† = compared to MID values, ‡, ‡‡ = compared to POST values)

Abbreviations: PRE, Before training measurements; POST, Post training measurements; RECO, Recovery measurements; TES, Testosterone; COR, Cortisol; IGF-1, Insulin-like growth factor 1; SHBG, Sex hormone-binding globulin